Chiral Nucleophilic Catalysts: Applications in the Synthesis of 3,3-Disubstituted Oxindoles and Parallel Kinetic Resolution

by

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Psalm 29:2

Ascribe to the Lord the glory due his name;
Worship the Lord in the splendor of his holiness.

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Abstract

The enantioselective nucleophile-catalyzed rearrangements of oxindole-derived enol acetates and enol carbonates to quaternary carbon containing 3,3-disubstituted oxindoles have been developed. A strong dependence of the reaction rate on the oxindole protecting group was demonstrated. Using achiral DMAP, oxindole-derived enol acetates and enol carbonates protected with amides or sulfonamides rearrange to the 3,3-disubstitituted oxindoles within 20 min with low catalyst loading. In contrast, only partial conversion is observed for alkyl and carbamate protected oxindoles in 5 h. Taking advantage of this enhanced reactivity allowed for the highly enantioselective (>85% ee) rearrangement of enol acetates derived from amide protected oxindoles within a few hours with the readily available chiral amino alcohol-derived catalyst (AcOLeDMAP). The enol carbonates of amide protected oxindoles were also very reactive, but the chiral catalyst AcOLeDMAP decomposed over the course of the reaction. Replacement of the acetyl protecting group at oxygen on the catalyst by benzyl circumvented this problem, thereby allowing the development of highly enantioselective rearrangements of enol carbonates as well (>90% ee). The acetyl and carboxyl rearrangement reactions displayed complementary enantiofacial preference, so both enantiomers of the 3,3-disubstituted oxindoles can be obtained using a single enantiomer of the catalysts.

A dual catalytic homogeneous parallel kinetic resolution (PKR) of racemic alcohols with achiral acyl donors and two chiral catalysts has been developed. A complementary anhydride selectivity of phosphine and DMAP catalysts was found. Using a mixture of aromatic and aliphatic anhydrides, phosphine catalysts selectively promoted the formation of aromatic esters while DMAP catalysts selectively promoted the formation of aliphatic esters. The use of two chiral catalysts, AcOLeDMAP and chiral phosphine *P*-aryl-2-phophabicyclo[3.3.0]octane

(PhPBO), in parallel lead to the resolution of racemic alcohols to form two distinct enantioenriched esters (75% ee and 88% ee).

Chapter 1

Chiral Nucleophilic Acyl Transfer Catalysts

I. Introduction.

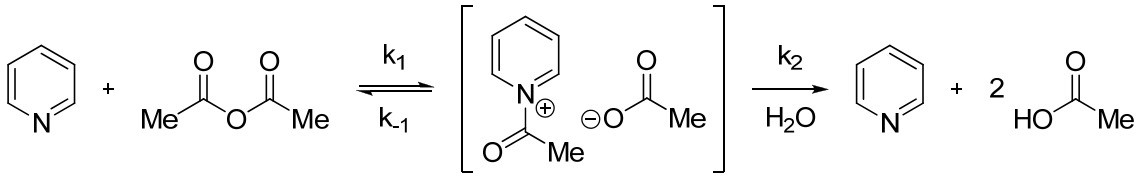
In the following literature review, topics relevant to chiral nucleophilic catalysts will be discussed. The concept of nucleophilic mechanisms related to catalytic acylation reactions will be introduced. This will be followed by a description of kinetic resolutions for the synthesis of enantiomerically enriched organic molecules. Next, an evalution of the current status of the field of chiral nucleophilic catalysts will be presented concluding with the chiral nucleophilic catalysts developed in the Vedejs group.

II. Nucleophilic catalysis.

Bases catalyze organic reactions by three types of mechanisms: specific base, general base and nucleophilic catalysis. In *specific-base-catalyzed* reactions, the catalyst is the anion of the solvent and is involved in a pre-equilibrium step prior to the rate determining step. *General-base-catalyzed* reactions involve abstraction of a proton during the rate-determining step. Any base present in the system can function as a general base, not just the solvent anion. In contrast to specific or general bases, *nucleophilic catalysts* do not abstract protons. Instead, a nucleophilic catalyst enhances the reactivity of a reactant by donating its electron pair to an electrophile other than a proton. Since the electrophile in a nucleophilic catalysis mechanism is larger than a proton, the catalyst nucleophilicity is sensitive to the steric bulk and the polarizability of the nucleophilic atom.[1]

The acceleration effect of pyridine in acylation reactions has been known for over a century[2] and acetic anhydride in pyridine has been a common synthetic procedure for the acylation of alcohols since the early 1900's. The role of the pyridine in the acylation was believed to be general-base catalysis, but it was not until the 1950's that investigations into the mechanism of this acylation were conducted. In 1953, Gold and coworkers published a series of papers on the kinetics and mechanism of the pyridine catalyzed hydrolysis of acetic anhydride.[3] In the initial report, pyridine was found to catalyze the hydrolysis 30,000 times faster than acetate anion even though pyridine and acetate have similar pK_a values. In addition, the more basic 2-picoline and 2,6-lutidine are both catalytically inactive. The independence of the catalytic ability on basicity and the sensitivity towards steric hinderance around the pyridine nitrogen support a nucleophilic mechanism over a general base mechanism. The authors propose that the mechanism occurs with nucleophilic displacement of acetate from acetic anhydride to form acetylpyridinium acetate (**1A**) followed by hydrolysis of this intermediate to form acetic acid and regenerate the pyridine catalyst. A common ion affect in the presence of added acetate anion in addition to a KIE of 5 for the solvent H_2O led the authors to suggest that formation of intermediate **1A** is reversible, followed by slow decomposition of **1A** to products. Unfortunately, all attempts to detect the proposed intermediate were unsuccessful, which the authors attribute to a low equilibrium concentration of the intermediate. A similar intermediate was proposed by Koshland in the hydrolysis of acyl phosphates,[4] but later isotopic labeling experiments indicated that the hydrolysis occurrs by P-O bond cleavage and not C-O bond cleavage as was originally thought, so the acylated pyrdinium is not an intermediate.[5]

Scheme 1-1. Hydrolysis of Acetic Anhydride Catalyzed by Pyridine.



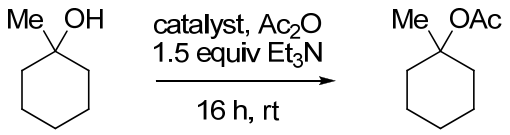
1A

$K_{eq} = k_1/k_{-1}$

The elusive acylpyridinium intermediate was later detected by Fersht and Jencks in 1969.[6] Using a stop-flow technique, acetic anhydride and pyridine were mixed, and two absorbance maxima at λ_{max} = 275 nm ($\varepsilon = 4.3 \times 10^3$) and 225 nm ($\varepsilon = 3.9 \times 10^3$) corresponding to acyl pyridinium acetate **1A** were observed. The appearance and disappearance of the intermediate was followed spectrophotometrically to determine the rate constants for the hydrolysis: k_1 = 84 $M^{-1}sec^{-1}$; k_{-1} = 910 $M^{-1}s^{-1}$; k_2 = 6.9 s^{-1} where k_2 is the hydrolysis of the acyl pyridinium cation by water (Scheme 1-1). The intermediate **1A** is short-lived with the measured $t_{1/2}$ of <100 msec. Addition of substituted anilines to these acylation conditions readily affords the acylated anilines with rate constants of 82 and 86 $M^{-1}sec^{-1}$ for toluidine and anisidine, respectively. These rate constants are identical to the value of k_1 indicating that the rate determining step of the acylation of anilines with pyridine is formation of the intermediate **1A**. On the other hand, the rate determining step for the pyridine-catalyzed hydrolysis of acetic anhydride with water is the second step. The rate constants for the Ac_2O hydrolysis catalyzed by several 3 and 4 substituted pyridines were also determined (Table 1-1). The K_{eq} increased as the pyridines became more basic and the formation of the intermediate (k_1) became favored over the reverse reaction (k_{-1}). The increase in K_{eq} is significantly greater than the decrease in k_2, so the more basic pyridines are more efficient catalysts for the hydrolysis of Ac_2O.

Table 1-1. Rate Constants for the Hydrolysis of Ac_2O Catalyzed by Substituted Pyridines.

Catalyst	pK_a	k_1	k_{-1}	K_{eq}	k_2
Pyridine	5.51	84	910	0.092	6.9
4-Picoline	6.33	490	262	1.86	2.3
3,4-Lutidine	6.79	1160	120	9.67	1.5
4-Methoxypyridine	6.82	935	30	31.2	0.4

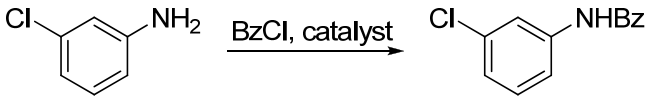


(1)

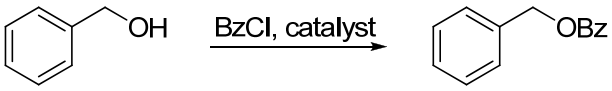
Catalyst: pyridine >5%
DMAP (4 mol%) 86%

Both Litvinenko and Steglich independently reported a dramatic increase in the rate of pyridine catalyzed acylation reactions using 4-dimethylaminopyridine (DMAP) in the late 1960's.[7] In 1969, Steglich reported the ability of DMAP to catalyze difficult acylations.[8] Hindered tertiary

alcohols, such as methylcyclohexanol are not acylated with acetic anhydride in the presence of stoichiometric pyridine (equation 1). In contrast, treatment of methylcyclohexanol with just 4 mol% DMAP and 1 equivalent of triethylamine resulted in 86% acyation after 16 h (equation 1). The stoichiometric triethylamine is required to prevent catalyst deactivation by the acid by-product. Prior to this work by Steglich, Litvinenko published a systematic study on the effect of pyridine substitutents on the rate of the benzoylation of anilines and, subsequently, the same effect on the benzoylation of alcohols (equations 2 and 3).[9] As shown earlier by Gold, substitution at the 2-position of the pyridine dramatically decreases the rate of catalysis (Table 1-2, entries 3 and 7). In addition, electron withdrawing substituents decrease the rate of catalysis (entry 2) while electron donating substituents increase the rate (entries 6, 8, and 9). This effect is most dramatically demonstrated with DMAP which catalyzes the benzoylations 3-4 orders of magnitude faster than does pyridine (entry 11). The dramatic increase in rate is not directly correlated to the increase in basicity since triethylamine is essentially catalytically inactive in the benzoylations despite being more basic than DMAP (entry 12). However, an increase in basicity of unhindered pyridines does correlate to an increase in reaction rate.



(2)



(3)

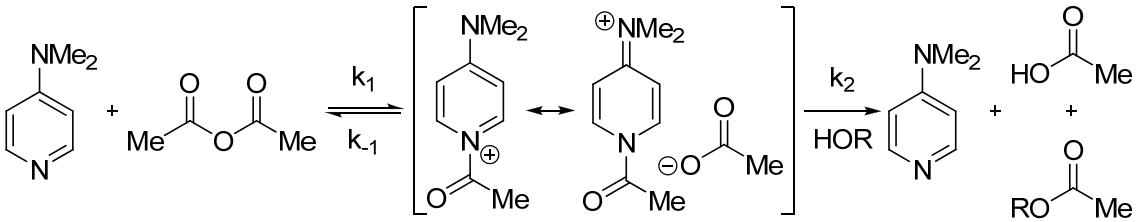
Table 1-2. Relative Rates of Acylations Catalyzed by Substituted Pyridines.

entry	catalyst	pK_a	*m*-chloroaniline	benzyl alcohol
1	none	--	1	1
2	3-cyanopyridine	1.39	14	12
3	quinoline	4.87	138	545
4	pyridine	5.23	568	9.29×10^3
5	isoquinoline	5.40	2.62×10^3	3.39×10^3
6	3-methylpyridine	5.63	1.12×10^3	2.29×10^4
7	2-methylpyridine	5.96	29	435
8	4-methylpyridine	6.02	2.96×10^3	3.98×10^4
9	4-phenoxypyridine	6.25	4.80×10^3	7.98×10^4
10	2,6-lutidine	6.72	8	115
11	4-dimethylaminopyridine	9.70	3.14×10^6	3.45×10^8
12	triethylamine	10.65	21	--

The remarkable catalytic activity of DMAP over pyridine is attributed to the resonance effect of the dialkylamino group.[7a] This resonance increases the nucleophilicity of the pyridine nitrogen and therefore the rate of k_1 is increased. In addition, the resonance stabilizes the intermediate ion pair **2A**. The more stable ion pair **2A** is less reactive than intermediate **1A**, so the increase in relative rate of DMAP over pyridine is due to the increase in concentration of the intermediate **2A** (~5-10%) compared to the negligible concentration of **1A** in non-polar solvents. Computational calculations by Zipse show that an increase in the stability of the acyl pyridinium salt leads to an increase in the rate of catalyzed acylations as expected. However, this effect levels off with much more stable acyl pyridinium cations due to an increase in the energy required for the subsequent rate-determining step.[10]

The search for more reactive pyridines has only revealed a few structures with higher catalytic activity than DMAP. These pyridines contain 4-amino substituents with increased resonance donation into the pyridine ring (Scheme 1-3). Pyrrolopyridine (PPY) is ~2.4 times more reactive than DMAP due to the increased electron availability of the pyrrolidine lone pair (Table 1-3, entry 2).[7a] Similarly, conformationally restricted pyridines **3A** and **3B** are more reactive than DMAP because the amino substituent is held in a conformation favorable for resonance with the pyridine ring (entries 3 and 4).[11] Recently, **3C** was reported to have similar reactivity to PPY, but it requires a 5 step synthesis.[12] Although these derivatives are more reactive, DMAP remains the catalyst of choice for standard acylations due to its ready availability.

Scheme 1-2. Hydrolysis of Acetic Anhydride Catalyzed by Dimethylaminopyridine (DMAP).



Scheme 1-3. Relative Rates of Catalysis of 4-Aminopyridine Derivatives.

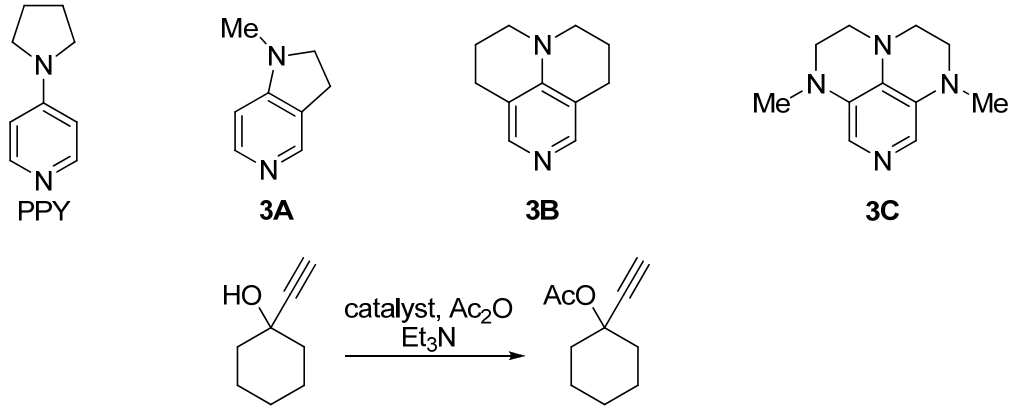


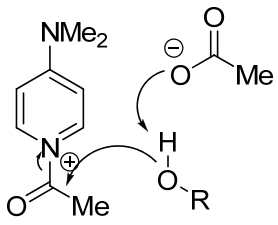
Table 1-3. Relative Rates of Catalysis of 4-Aminopyridine Derivatives.

entry	catalyst	relative rate
1	DMAP	1
2	PPY	2.4
3	**3A**	2
4	**3B**	6

The nature of the acyl donor also has a significant effect on the rate of DMAP-catalyzed acylations.[7a] Acetyl chloride and DMAP quantitatively form an ion pair analogous to **2A** in non-polar solvents, while acetic anhydride and DMAP only form 5-10% of ion pair **2A**. However, this increase in concentration does not lead to a corresponding increase in the rate of acylations. Despite the large differences in concentration of ion pair **2A**, the DMAP catalyzed acylation of ethynylcyclohexanol with Ac_2O is three fold faster than with AcCl. The increased reactivity with Ac_2O, is attributed to general base catalysis by the anion of the ion pair in the rate-determining decomposition to form acylated products (Figure 1-1). The more basic acetate anion is a better general base than the chloride anion, and therefore increases the rate of acylation by deprotonating the incoming nucleophile in the rate determining step. This conclusion is also supported by the fact that DMAP catalyzed acylations occur more rapidly in non-polar solvents than in polar solvents despite the lower concentration of the intermediate **2A** because the tighter ion pair in non-polar solvents facilitates this general base catalysis. Recent computational calculations and kinetics experiments by Zipse show that the reaction is first order in DMAP, alcohol and anhydride and zero order in the auxillary base, triethylamine. These results confirm

that neither the triethylamine nor a second equivalent of DMAP are not involved in the rate-determining acylation step, and therefore, the acetate is the most likely base.[13]

Figure 1-1. General Base Catalysis by Acetate in DMAP-Catalyzed Acylation Reactions.



f1A

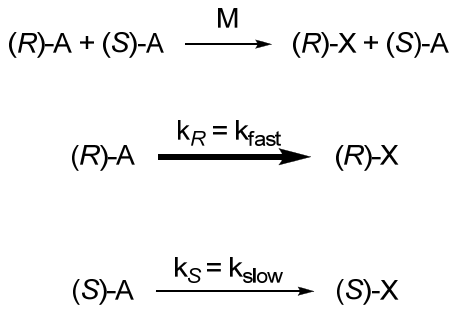
In addition to DMAP, several other nucleophilic organic molecules are used for acyl transfer reactions. Other nucleophilic amines have been used such as *N*-methylimidazole (NMI)[14] and diazabicyclo[2.2.2]octane (DABCO).[15] In addition to nucleophilic amines, nucleophilic phosphines such as Bu_3P[16] and $P(MeNCH_2CH_2)_3N$[17] are also effective acylation catalysts. Recently, *N*-heterocyclic carbenes have been shown to be effective for trans-esterifications.[18] Many of these nucleophilic moieties have been incorporated in chiral catalysts developed for acylation reactions (*vide infra*).

III. Kinetic Resolutions.

Since kinetic resolutions are one of the most common applications of chiral nucleophilic catalysts, an explanation of the principles involved will be presented here. Kinetic resolutions are the oldest synthetic method for the isolation of highly enantiomerically enriched substrates.[19] In 1996, IUPAC defined kinetic resolution as "the achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.)."[20] This scenario is depicted graphically in Figure 1-2: a racemic mixture of (*R*)-A and (*S*)-A is treated with chiral agent M and (*R*)-A and (*S*)-A are converted to products at different rates k_R (k_{fast}) and k_S (k_{slow}). The unequal rates of reaction are a result of the different energies of the two diastereomeric transition states formed between the chiral agent and the two enantiomers. When $k_{fast}>>>k_{slow}$, only the (*R*) enantiomer reacts, and the resolution stops at 50%

conversion when all of (*R*)-A is converted to (*R*)-X. Although some enzymes reach this level of selectivity, most synthetic chiral agents do not. Instead, at partial conversion of a typical resolution, the product X is obtained enriched in the (*R*) enantiomer while the starting material is recovered enriched in the (*S*) enantiomer. Over the course of the resolution, the enantiomeric excess of the starting material increases as the more reactive enantiomer (*R*) is converted to product. When all of the more reactive enantiomer is converted to product, the remaining starting material is recovered in >99.9% ee, but a sacrifice is made in terms of the yield. This high enantiopurity of the recovered starting material is one of the benefits of kinetic resolutions over most asymmetric syntheses which rarely reach the level of enantioselectivity required to produce material in >99.9% ee.

Figure 1-2. General Kinetic Resolution Scheme.



The comparison of the enantioselectivity of kinetic resolutions is made difficult by the changing enantiomeric excesses of the starting material and product over the course of the reaction, so Kagan developed an expression for comparing the effectiveness of kinetic resolutions: **s** = selectivity factor.[16a] The selectivity factor is defined as **s** = k_{fast}/k_{slow} for kinetic resolutions that are first-order in substrate, have no non-linear effects, and are homogeneous. Defining k_{fast} and k_{slow} in terms of the conversion (C) and enantiomeric excess of the starting material (ee) and product (ee') allows the selectivity factor to be expressed in terms that can be measured in the laboratory (equations 4 and 5). Further expansion of these equations by Ismagilov to account for resolutions using a chiral agent of <99% ee are shown equations 6 and 7 where ee_R = enantiomeric excess of the chiral agent.[21]

$$\mathbf{s} = \frac{\ln([1 - C][1 - ee])}{\ln([1 - C][1 + ee])} \quad (4)$$

$$\mathbf{s} = \frac{\ln([1 - C][1 + ee'])}{\ln([1 - C][1 - ee'])} \quad (5)$$

$$\mathbf{s} = \frac{(1 + ee_R)\ln([1 - C][1 - ee]) - (1 - ee_R)\ln([1 - C][1 + ee])}{(1 + ee_R)\ln([1 - C][1 + ee]) - (1 - ee_R)\ln([1 - C][1 - ee])} \quad (6)$$

$$\mathbf{s} = \frac{(1 + ee_R)\ln([1 - C][1 + ee']) - (1 - ee_R)\ln([1 - C][1 - ee'])}{(1 + ee_R)\ln([1 - C][1 - ee']) - (1 - ee_R)\ln([1 - C][1 + ee'])} \quad (7)$$

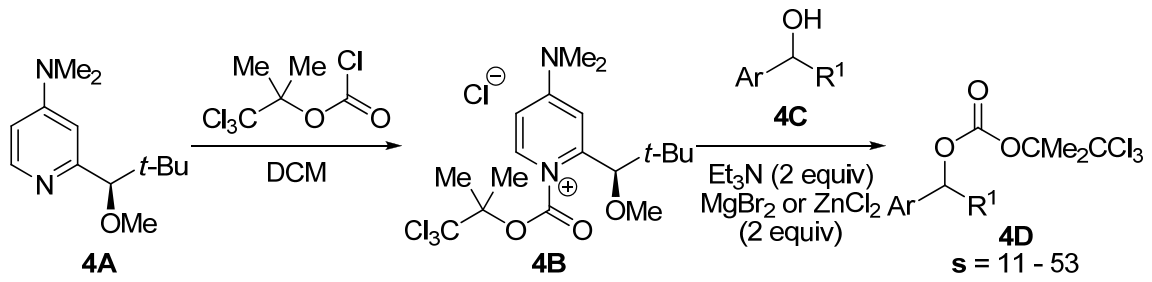
IV. Asymmetric Nucleophile Catalyzed Acyl Transfer Reactions.

The enantioselective small organic molecule catalyzed acyl transfer reactions were first reported in the 1930's. In a series of papers by Wegler, racemic alcohols were treated with brucine, strychnine and other chiral tertiary amines in the presence of acyl donors such as Ac_2O and BzCl.[22] At partial conversion, the products and recovered starting materials were both found to be optically active. Although the optical purities of these products were not determined at the time, subsequent analysis of the results by Spivey indicated that at least one of the resolutions occurred with **s** ~ 3.5.[25a] Over the next 70 years, studies using other naturally occurring chiral amine nucleophiles were met with modest success.[23]

The field of asymmetric acyl transfer reactions flourished with the introduction of specifically designed chiral nucleophiles. The first highly enantioselective entry into this field was reported in 1996 by Vedejs and Chen.[24] Based on the high catalytic activity of DMAP, it was envisioned that a chiral DMAP derivative would be an effective acylation agent. Therefore, 2-substituted DMAP **4A** was synthesized enantioselectively in 3 steps from DMAP. Unfortunately, **4A** does not turn over in the acylation, so acyl pyridinium **4B** has to be pre-formed and used stoichiometrically. In addition, acyl transfer from **4B** to alcohols only occurs in the presence of triethylamine and a Lewis acid. Despite these requirements, DMAP **4B** demonstrates high levels of enantioselectivity in the kinetic resolution of benzylic alcohols **4C**. This example highlights one

of the challenges involved in designing a chiral DMAP catalyst. Although substitution at the 2-position of DMAP brings the chirality close to the active site in the acyl transfer reactions, it decreases the nucleophilicity and impedes catalytic turnover.

Scheme 1-4. Kinetic Resolution of Benzylic Alcohols with Chiral DMAP analog **4A**.



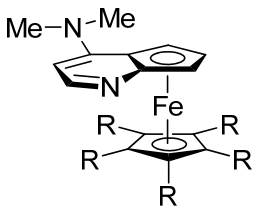
The rapid growth of the field of asymmetric acyl transfer reactions over the last decade has resulted in well over 100 publications and many reviews.[25] Therefore, what is presented here is an overview of the field focusing on the most effective catalysts and those catalysts with interesting design strategies. The development of chiral nucleophilic catalysts in the Vedejs group will be reserved for the following section.

A series of pyridine-derived planar-chiral catalysts developed by Fu and co-workers were first reported in 1996.[26] In contrast to the work by Vedejs and Chen, 2-substituted dimethylaminopyridines **5A** and **5B** are catalytically active. The increased reactivity of these pyridines is due to 1) the compact 2-substituent and 2) the electron-rich FeCp* fragment enhancing the nucleophilicity of the catalyst. However for several applications (*vide infra*), the dimethylaminopyridine-based catalysts **5A** and **5B** are still not nucleophilic enough. So, several new catalysts based on the more nucleophilic pyrrolidinopyridine were developed (**5C** – **5E**). Originally, catalysts **5A** – **5E** were synthesized in 2-3% yield by a 7-step synthesis followed by resolution of the enantiomers by HPLC on chiral support. Recently, a new 7-step synthesis was reported in which the catalysts **5B** and **5C** were both obtained in 25-30% overall yield, and the final enantiomers were resolved by classical resolution.[27] Catalysts **5B** and **5C** are now commercially-available from Strem for $35/100 mg (pricing as of June 2007).

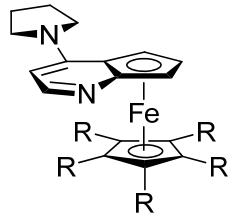
These catalysts were used in the kinetic resolution of several classes of alcohols and amines. The more hindered pentaphenyl DMAP catalyst **5B** is the most effective catalyst of this

series for the resolutions of benzylic alcohols **5F**,[28] propargylic alcohols **5G**,[29] and allylic alcohols **5H**[30] with good to excellent selectivity factors although the reaction times are long. The kinetic resolution of amines stands as an even greater challenge for asymmetric nucleophilic catalysis due to the significant background reaction of amines with the acyl donor. In order to prevent this background reaction, Fu and coworkers employed hindered *O*-acylated azlactones **5K** and **5L** as acyl donors since they only react with the pyridine catalysts and not the amines.[31] The use of the less reactive azlactones **5K** and **5L** as acyl donors requires the more reactive pyrrolidinopyridine derived catalyst **5C** – **5E**. Catalyst **5C** resolves benzylic amines **5I** with good enantioselectivity at low temperature, but minimal selectivity is observed for the resolution of indolines **5J**. The penta-aryl catalysts **5D** and **5E** are more selective with the more hindered penta(dimethylphenyl) catalyst **5E** proving to be the most selective, but again the reaction times were long.

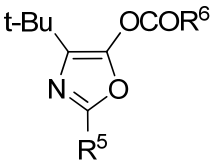
Scheme 1-5. Kinetic Resolutions Catalyzed by Planar-Chiral Pyridines.



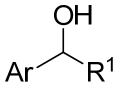
5A, R = Me
5B, R = Ph



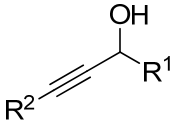
5C, R = Me
5D, R = Ph
5E, R = 3,5-Me_2Ph



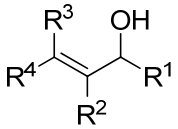
5K: R^5 = 2-Naphthyl, R^6 = OMe
5L: R^5 = Ph, R^6 = Me



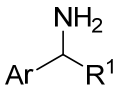
5F
s = 32 - 95 at 0 °C
catalyst: **5B** (1 mol%)
time = 1-5 d
acyl donor: Ac_2O



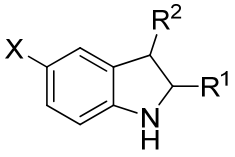
5G
s = 8 - 20 at 0 °C
catalyst: **5B** (1 mol%)
time = 1-20 d
acyl donor: Ac_2O



5H
s = 4.7 - 80 at 0 °C
catalyst: **5B** (1 mol%)
time = 2 d
acyl donor: Ac_2O



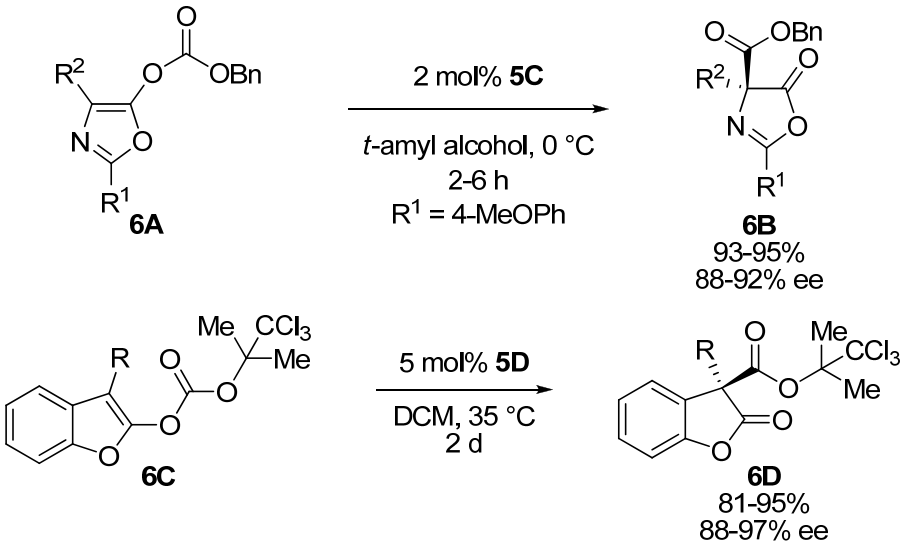
5I
s = 11 - 27 at -50 °C
catalyst: **5C** (10 mol%)
time = 1 d
acyl donor: **5K**



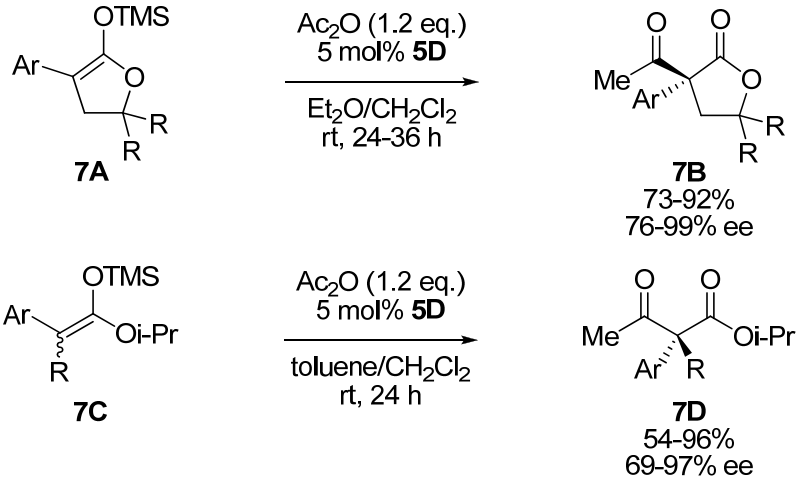
5J
s = 9.5 - 31 at 0 °C
catalyst: **5E** (5 mol%)
t = 2.5-23 d
acyl donor: **5L**

The planar-chiral pyridine catalysts have also been applied to the asymmetric synthesis of all-carbon quaternary centers. Planar-chiral pyridine **5C** catalyzes the rearrangement of benzyl enol carbonates **6A** to *C*-carboxylated azlactones **6B** in high yields and enantioselectivities when R^2 is an α-unbranched alkyl substituent (Scheme 1-6).[32] In this rearrangement, the hindered pentaphenyl ferrocene derived catalyst **5B** is substantially less reactive and enantioselective than either **5A** or **5C**. In addition, while both pentamethylferrocene-derived catalysts **5A** and **5C** afford rearranged products with similar enantioselectivities, **5C** is approximately 4 times as reactive as **5A**. This type of rearrangement is also possible in benzofuranone-derived enol carbonates **6C**.[33] In this system, the rearrangement requires the bulky 2,2,2-trichlorodimethylethoxy migrating group as well as the hindered pentaphenyl catalyst **5D** to achieve high enantioselectivity. However, the rearrangement appears to be slow based on the reported reaction temperature, time and catalyst loading. A discussion of the mechanism of this rearrangement and extension to oxindole-derived substrates is reserved for Chapter 2. Enantioenriched quaternary centers are also synthesized from the acylation of enol silanes.[34] Enol silanes **7A** and **7C** are treated with Ac_2O and planar chiral catalyst **5D** to afford 1,3-dicarbonyls products **7B** and **7D** in 68-97% ee (Scheme 1-7).

Scheme 1-6. Planar-Chiral Nucleophile Catalyzed Rearrangement of *O*-Carboxylated Heterocycles.



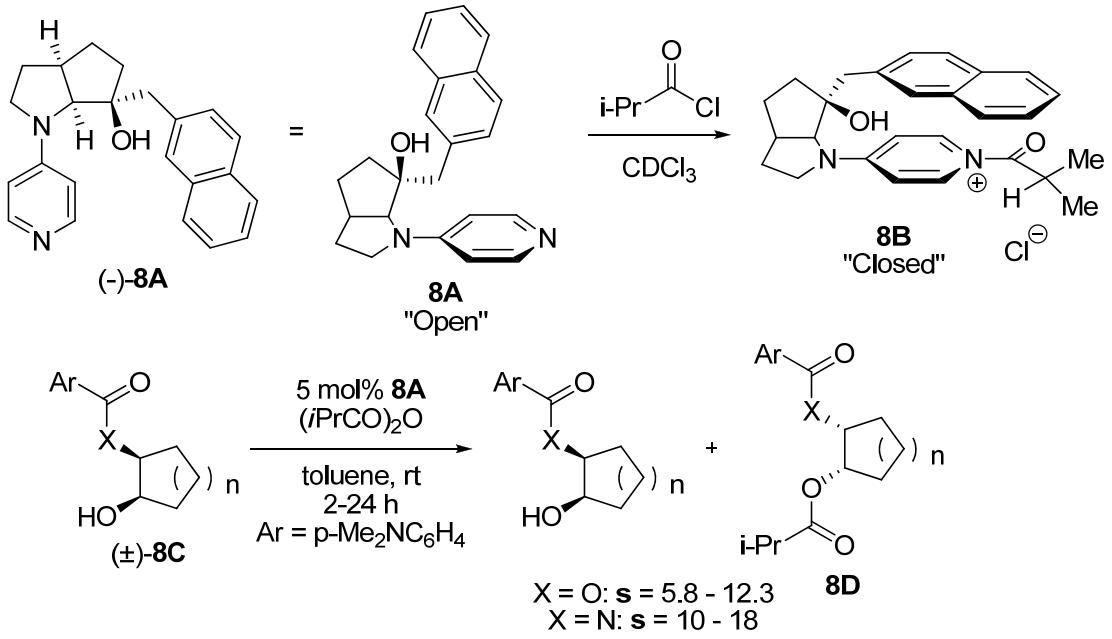
Scheme 1-7. Planar-Chiral Nucleophile Catalyzed Acylation of Enol Silanes.



Planar-chiral catalysts **5A** – **5E** have also been used for dynamic kinetic resolutions of azlactones,[35] [2+2] cycloadditions of ketenes and imines[36] or aldehydes,[37] [3+2]-cycloadditions of α,β-unsaturated acid fluorides and alkenes,[38] additions of phenols[39] and amines[40] to ketenes, and the α-chlorination of ketenes.[41] Despite the variety of uses reported for the planar-chiral catalysts, they have not yet been widely adopted in literature.[42] The limited availability of the catalysts **5A**, **5D** and **5E** may be hindering their wide-spread use.

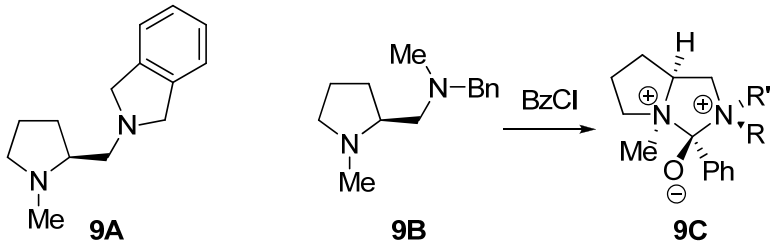
Also in 1997, Fuji developed a new pyrrolidinopyridine derived chiral catalyst **8A**.[43] Catalyst **8A** resolved racemic alcohols **8C** with modest to good selectivity at rt. Although not outstanding, these selectivities are impressive considering the distance between the chiral centers and the active site of the catalysts. The authors propose that a change in the conformation of the catalyst upon acylation brings the naphthyl ring closer to the pyridine active site. NMR studies on the free catalyst **8A** and ion pair **8B** provide evidence for this conformational change. The free catalyst exists in an "open" conformation with free rotation of both the pyridine and the naphthyl groups. In contrast, the ion pair **8B** exhibits differentiated pyridine protons and strong NOE correlations between the naphthyl and pyridine protons, indicating a conformational change that brings the naphthyl and pyridine rings into close proximity. Closed conformation **8B** is proposed to be the active form of the catalyst in the acylation reaction. This catalyst has not yet been used by other chemists, perhaps due to the lengthy synthesis (18% yield over 7 steps) and limited use demonstrated so far.

Scheme 1-8. Fuji's "Induced Fit" Catalyst.



A class of 1,2-diamines derived from proline are also effective acyl transfer catalysts. Diamine catalysts **9A** and **9B**, developed by Oriyama, are readily synthesized in 2 steps from *N-tert*-butoxycarbonylproline and catalyze the benzoylation of alcohols in low catalyst loadings (<1 mol%) at -78 °C within 3 h.[44] Diamine **9B** catalyzes the desymmetrization of meso-diols **9D** in good yield and enantioselectivity. The more rigid diamine **9A** is more enantioselective than diamine **9B** for the kinetic resolution of racemic secondary alcohols **9E** and **9F**, with impressive levels of enantioselection achieved for cyclic secondary alcohols **9F**. Racemic primary alcohols with an α-chiral center are also resolved using catalyst **9B** with modest selectivity factors. These benzoylations are proposed to occur by the formation of a rigid bicyclic complex **9C**, although the exact reaction mechanism is not yet clear. The mechanism was recently called into question by Denmark due to the lack of evidence for the intermediate, and he suggested the benzoylation may occur by general base catalysis.[45] Regardless of the mechanism, these asymmetric benzoylation protocols are starting to be used in the chemical community[46] because of the short synthesis and high selectivity factors for the kinetic resolution of alcohols.

Scheme 1-9. Oriyama's Diamine Catalysts.



9D
catalyst: **9B** (0.5 mol%)
73 - 89%
60 - 97% ee
-78 °C, 3 h

9E
catalyst: **9A** (0.3 mol%)
s = 4 - 20
-78 °C, 3 h

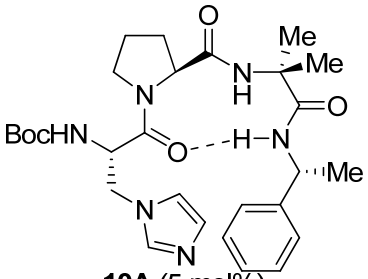
(±)-**9F**
catalyst: **9A** (0.3 mol%)
a: R^1 = Ph: **s** = 37 -160
b: R^1 = Br: **s** = 130 -170
c: R^1 = CO_2R: **s** = 27
-78 °C, 3 h

9G
catalyst: **9B** (0.3 mol%)
s = 2.4 - 16
-78 °C, 3 h

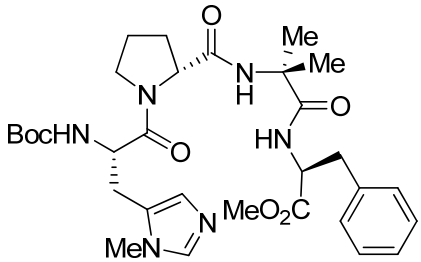
Inspired by nature's acyl transfer catalysts, the class of enzymes called lipases, Miller sought the minimal peptide sequence required for enantioselective acylations. In this quest, Miller designed tripeptide **10A** which incorporated a nucleophilic *N*-alkyl imidazole.[47] Tripeptide **10A** is predisposed for a β-turn in order to bring the two ends of the peptide in close proximity and create the chiral environment around the nucleophilic imidazole. Using catalyst **10A**, moderate levels of enantioselectivy are obtained for the resolution of amino alcohol **10D**. The enantioselectivity is highly dependent on hydrogen-bonding within catalyst **10A** since experiments conducted in $CHCl_3$/*t*-BuOH are unselective supporting the hypothesis that the selectivity arises from an organized peptide conformation. In addition, the resolutions of racemic secondary alcohols lacking a β-amino functionality are unselective with peptide **10A**, suggesting additional hydrogen bonding interactions between catalyst **10A** and the amino alcohol **10D** is necessary for enantioselection. Subseqent library screening of peptide chains led to increased enantioselectivities observed for the resolution of alcohol **10D** using tetrapeptide **10B**[48] and octapeptide **10C**.[49] Octapeptide **10C** exhibits remarkable levels of selectivity with alcohol **10D** and catalyzes the acyl transfer significantly faster than do peptides **10A** and **10D** or *N*-methyl imidazole. This rate acceleration is attributed to a beneficial hydrogen-bonding interaction between the catalyst and fast reacting enantiomer, although the exact nature of this interaction is

not known. Based on the rate acceleration with the more selective peptide catalysts, a fluorescence based screening technique was developed to facilitate library screening.[50] Using this screening method, octapeptide **10E** was found to be highly selective for the kinetic resolutions of racemic secondary alcohols **10G**,[51] and pentapeptide **10F** was discovered as an effective catalyst for the kinetic resolutions of racemic tertiary alcohols **10H**.[52] Additional peptides have been found for the asymmetric phosphorylations and sufinylations of alcohols through library screens.[53] Automated peptide syntheses allow for the ready synthesis of new peptide libraries, and the fluorescence screening technique facilitates the discovery of new catalysts. Like most of the previous catalysts, these peptides have not yet been used in the literature, which may be due to the library screening required to find a catalyst with high selectivity for each new substrate.

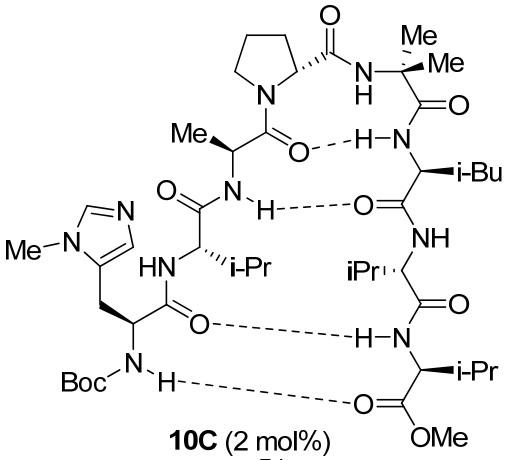
Scheme 1-10. Miller Peptide Catalysts.



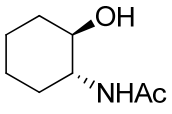
10A (5 mol%)
s = 12.6
0 °C, 48h



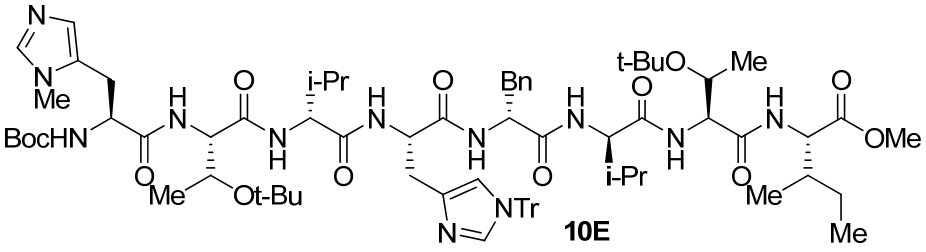
10B (2 mol%)
s = 28
rt, 12 h



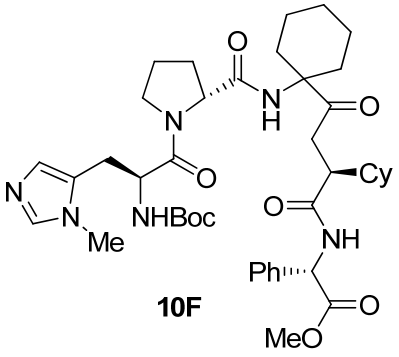
10C (2 mol%)
s = 51
rt, 2 h



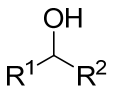
(±)-**10D**



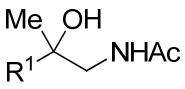
10E



10F



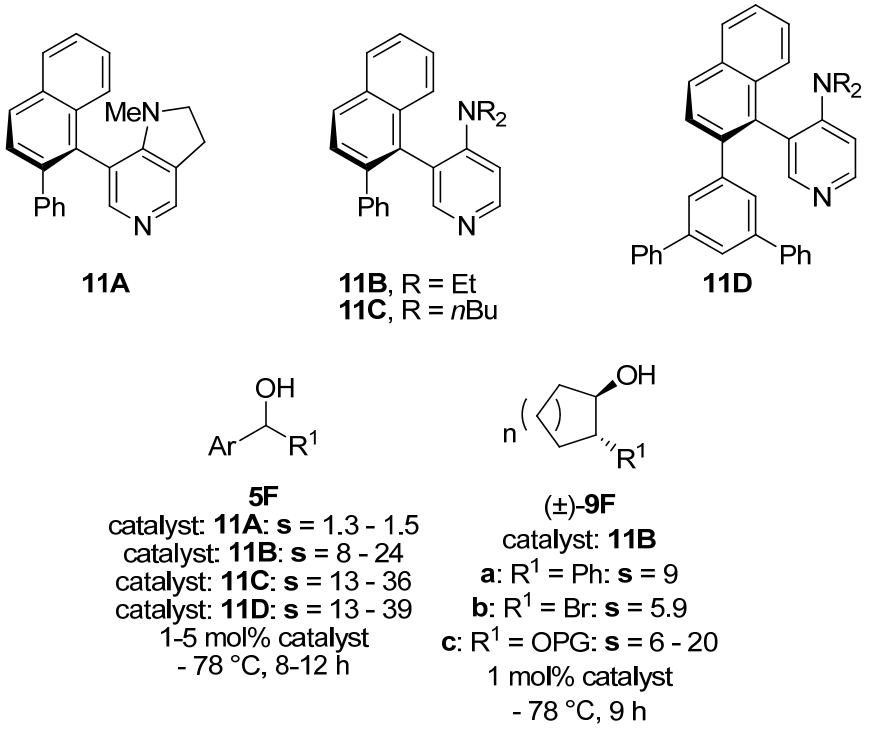
10G
catalyst: **10E** (2.5 mol%)
s = 4 - >50
-65 °C, 24 h



10H
catalyst: **10F** (10 mol%)
s = 9 - >50
rt, 3 d

A series of atropisomeric pyridine derivatives was developed by Spivey.[54] Spivey reasoned that the 3-substitution would not interfere with the nucleophilicity of the pyridines, as the 2-substituents do, while still allowing the chirality to be transferred to the active site. The sterically bulky 3-aryl substitutents of **11A** – **11D** were chosen to increase the rotational barrier between the atropisomers, allowing for separation of the enantiomers. The catalyst **11A** is unselective for the resolution of secondary alcohols **5F**, but an increase in selectivity was observed with the simplified catalyst **11B**.[55] The higher selectivity was attributed to an increase in differentiation of the 3 and 5 positions of the pyridine ring. Catalyst **11B** is also moderately selective for the resolution of a series of cyclic racemic alcohols **9F**.[56] An increase in the steric bulk of either the dialkylamino (**11B**) or the biphenyl substituent (**11D**) led to an increase in selectivity for the resolution of secondary alcohols **5F**.[57] Unfortunately, all of these resolutions must be conducted at -78 °C[58] to achieve good enantioselectivity, and catalysts **11A** – **11D** have not been used yet by other chemists.

Scheme 1-11. Spivey's Atropisomeric Catalysts.



11A

11B, R = Et
11C, R = *n*Bu

11D

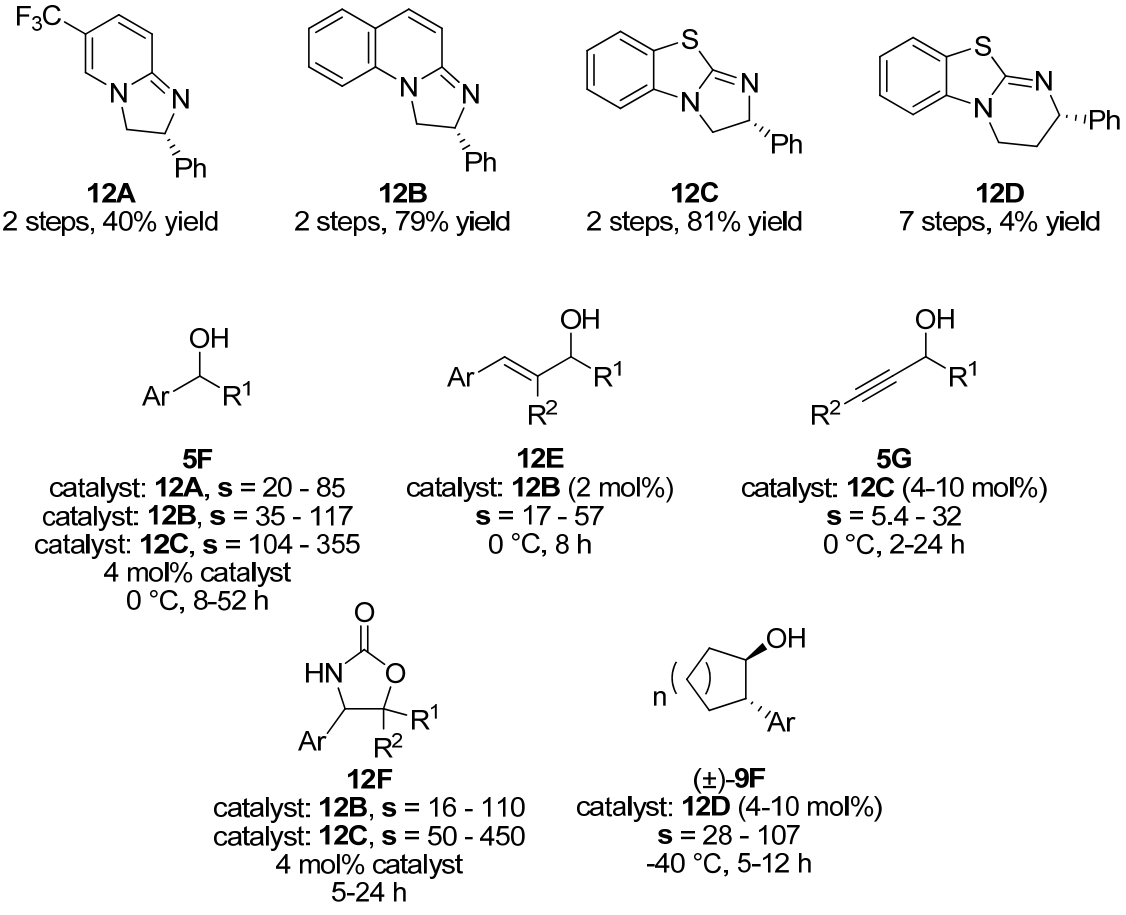
5F
catalyst: **11A**: **s** = 1.3 - 1.5
catalyst: **11B**: **s** = 8 - 24
catalyst: **11C**: **s** = 13 - 36
catalyst: **11D**: **s** = 13 - 39
1-5 mol% catalyst
- 78 °C, 8-12 h

(±)-**9F**
catalyst: **11B**
a: R^1 = Ph: **s** = 9
b: R^1 = Br: **s** = 5.9
c: R^1 = OPG: **s** = 6 - 20
1 mol% catalyst
- 78 °C, 9 h

Recently, several chiral nucleophilic catalysts with a nucleophilic amidine core have been developed by Birman.[59] In contrast to the previously studied pyridine and imidazole nucleophiles,

these amidines (**12A** – **12D**) contain a tetrahedral center adjacent to the nucleophilic nitrogen. The proximity of the stereogenic center and the nucleophilic nitrogen allows for more effective transmittance of the chirality in the enantiodetermining step. Indeed, good to exceptional selectivities are obtained for the resolution of racemic alcohols **5F**, **12E**, **5G** and **9F** and oxazolidines **12F** with low catalysts loadings (2-10 mol%). Notably, benzotetramazole catalyst **12C** resolves secondary benzylic alcohols **5F** and oxazolidines **12F** with exceedingly high levels of enantioselection at rt! Such high levels of selectivity for an acyl transfer resolution have only been observed with enzymes and the chiral phosphine catalysts developed by Daugulis (*vide infra*). The ring expanded catalyst **12D** has recently been reported to be more reactive, but the catalyst synthesis is much longer and lower yielding.[60] These promising catalysts have not yet been adopted in the literature, but the high selectivity and reactivity in addition to the short syntheses leads one to believe they will be used in the future.

Scheme 1-12. Birman's Amidine-Derived Catalysts.

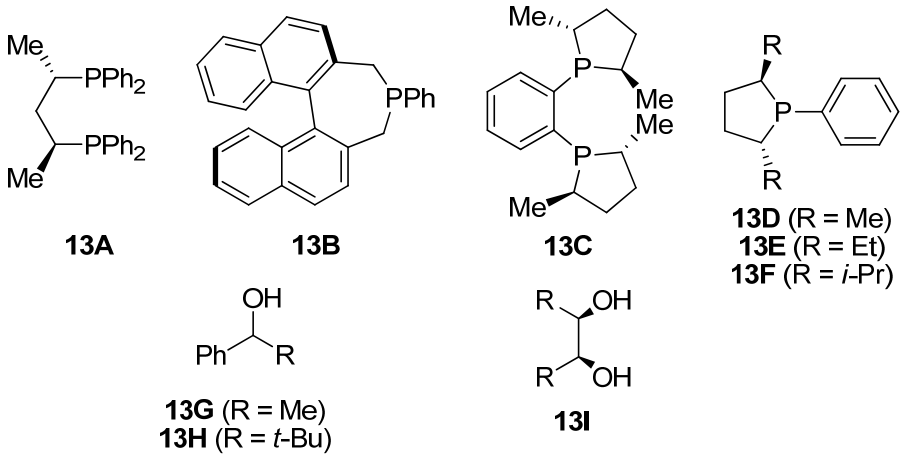


Many additional chiral nucleophilic catalysts have been reported over the last decade.[25] Unfortunately, most of these catalysts display modest levels of enantioselection at best. Overall significant advances have been made in the field of asymmetric nucleophilic catalysis. However, the challenge remains of finding a readily available catalyst that is highly enantioselective for a broad range of substrates and processes.

V. Chiral Nucleophilic Catalysts Developed in the Vedejs Group.

The development of chiral nucleophilic catalysts has been an ongoing effort in the Vedejs group for over a decade. In addition to the chiral 2-substituted DMAP analogs developed by Chen in 1996, the potential of tertiary phosphines as chiral nucleophiles was explored.[61] Several known chiral phosphines were screened for enantioselectivity in the kinetic resolutions of alcohols **13G** and **13H** as well as the desymmetrization of meso-diols **13I**. Chiral phosphines **13A** – **13C** proved either unreactive or unselective in these acyl transfer reactions. The Burk phosphines were modestly more enantioselective, and the unhindered **13D** was the most reactive and selective. Phosphine **13D** catalyzed the resolution of alcohol **13H** with a selectivity factor of **s** = 13, which was the highest achieved with a non-enzymatic acyl transfer catalyst at the time. Unfortunately, this resolution was very slow (16% catalyst loading: 25% conversion over 2 weeks).

Scheme 1-13. Chiral Phosphine Catalysts.



13A **13B** **13C**

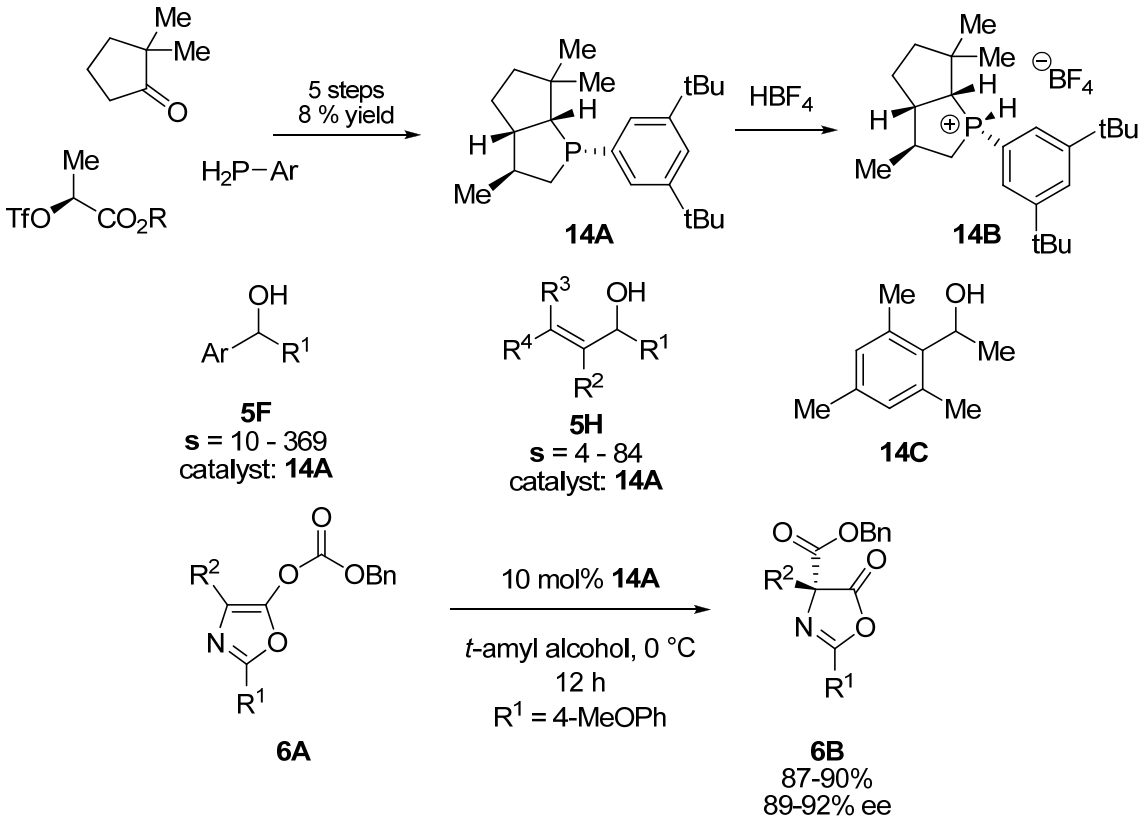
13D (R = Me)
13E (R = Et)
13F (R = *i*-Pr)

13G (R = Me)
13H (R = *t*-Bu)

13I

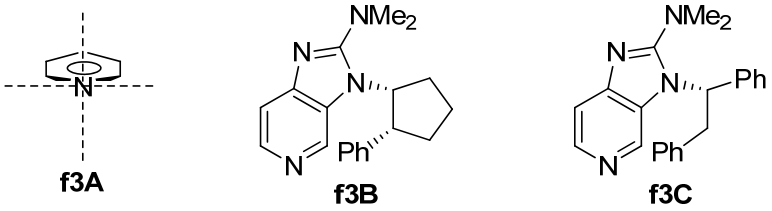
After optimization of the catalyst structure, a new bicyclic phosphine **14A** was found to be both highly reactive and enantioselective.[62] Highly enantiomerically enriched phoshine **14A** (*P*-aryl-2-phophabicyclo[3.3.0]octane, PBO) was synthesized from (*S*)-ethyl lactate in 5 steps. Originally, the air-sensitive phosphine **14A** was protected as the borane complex and released in small batches prior to each use. Subsequently, MacKay found that the phosphine could be protected as the HBF_4 salt **14B** and released *in situ* by triethylamine.[63] This advance facilitates the handling of the phosphine and allows for more precise catalyst loadings. PBO catalyst **14A** resolves both benzylic (**5F**) and allylic (**5H**) alcohols with high selectivity factors. In fact, PBO **14A** catalyzes the resolution of hindered alcohol **14C** with a selectivity factor of **s** = 369-390. This impressive level of selectivity was only seen with enzymatic acyl transfer resolutions at that time. Since then only Birman's amidine catalyst has reached a similar level of enantioselectivity. PBO **14A** also catalyzes the rearrangement of *O*-acylated azlactones to afford quaternary carbon containing azlactones **6B** in 89-92% ee.[64]

Scheme 1-14. Phosphabicyclooctane Catalyst Applications.



In addition to chiral phosphine catalysts, the Vedejs group has developed chiral DMAP catalysts. Due to the lack of catalytic activity of the 2-substituted DMAP analogs synthesized by Chen, the new catalyst design incorporated the chirality at the 3-position of the pyridine ring. The challenge then became inducing chirality at the active site over this distance. In order to desymmetrize the planar pyridine (**f3A**), the strategy was to block either one face of the pyridine ring or one face and one side of the ring. DMAP **f3A** was designed to block one face of the pyridine ring while DMAP **f3B** was designed to block both a side and a face of the DMAP ring. These two 3-substituted DMAP derivatives were enantioselectively synthesized by Harper.[65] Although both **f3B** and **f3C** are catalytically active, the kinetic resolutions of alcohols were minimally selective (**s**<2).

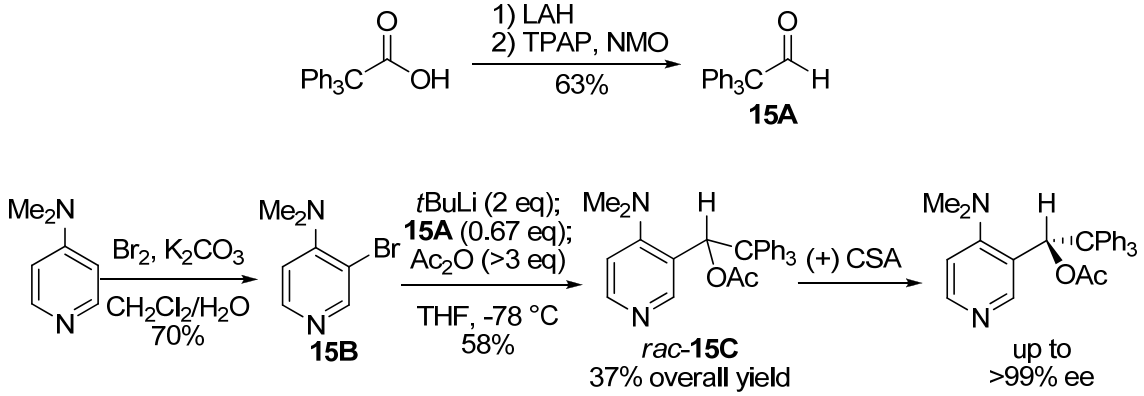
Figure 1-3. Harper's Chiral DMAP Catalysts.



f3A **f3B** **f3C**

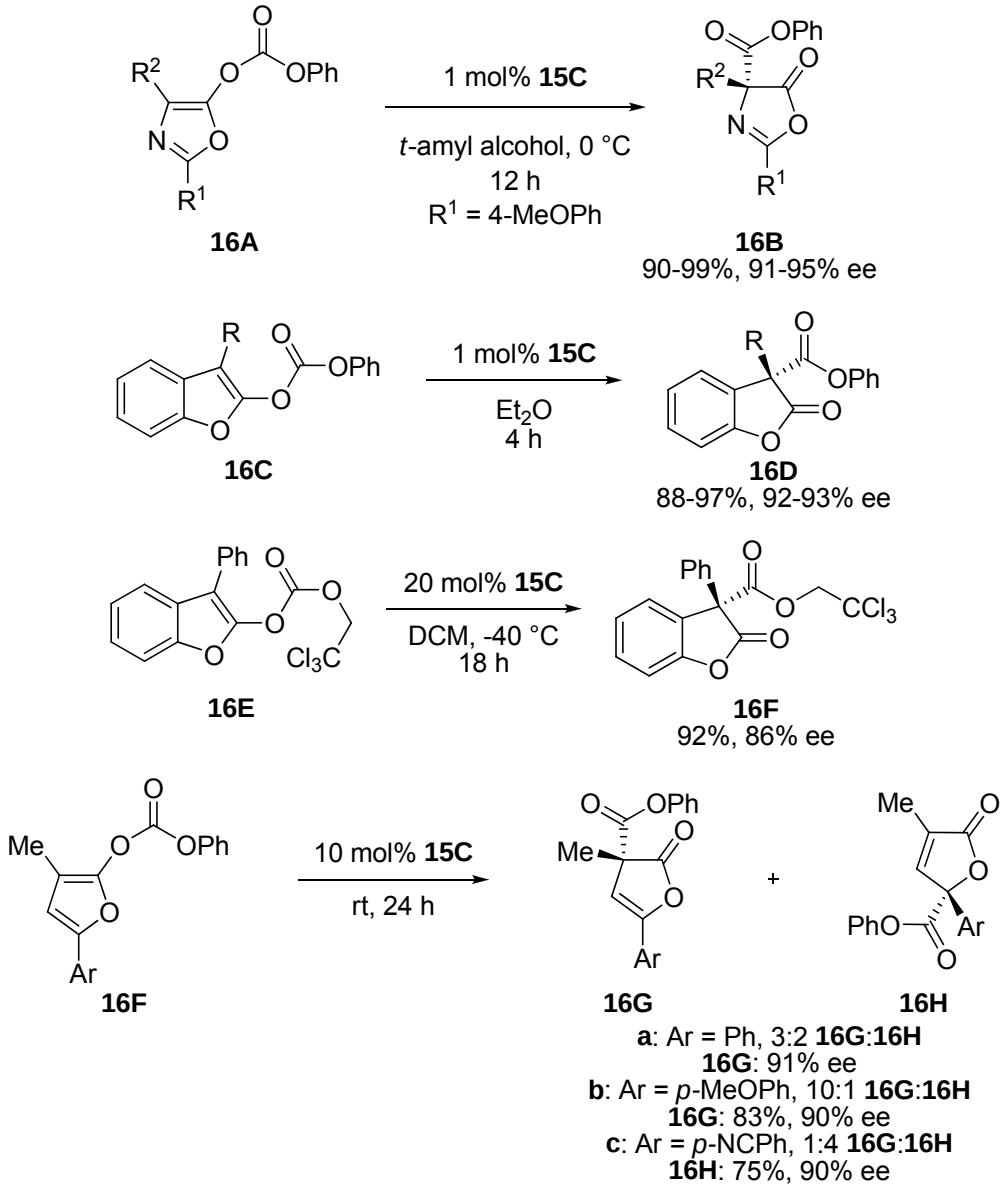
Using this same design strategy of blocking a face and a side, a new DMAP catalyst was developed by Shaw and Vedejs.[64] In this catalyst, the chiral center is located adjacent to the pyridine ring. The favored conformation of this chiral center should place the small hydrogen syn to the dimethylamino group thereby projecting the two substitutents to the opposite faces of the pyridine. In order to differentiate the faces of DMAP **15C**, a sterically bulky trityl group was chosen as one of these substituents. A smaller acetate substituent was chosen to differentiate the two sides of the DMAP catalyst. The synthesis of catalyst **15C** ("TADMAP"; for 2,2,2-Triphenyl-1-Acetoxyethyl-DMAP) starts from the reduction and oxidation of triphenylacetic acid to yield aldehyde **15A**. Then 3-lithiated DMAP was generated from 3-bromoDMAP **15B** and added to the aldehyde **15A**. The resulting lithiated alkoxide was quenched with acetic anhydride to afford TADMAP **15C**. The racemic catalyst **15C** was then resolved by a classical resolution with (+)-CSA to >99% ee. Gram quantities of TADMAP (**15C**) were synthesized by this short route.

Scheme 1-15. Synthesis of TADMAP (**15C**).



Although kinetic resolutions with TADMAP are unselective, the catalyst is highly effective for the synthesis of all-carbon quaternary centers.[64] The rearrangement of **16A** occurs readily in the presence of 1 mol% TADMAP (**15C**). The rearranged product **16B** is isolated in high yield and enantiomeric excess (91 – 95% ee). During the evaluation of the substrate scope, it was found that azlactones with α-unbranched alkyl side chains (**16A**) rearrange readily in 12 h, but an azlactone containing an α-branched alkyl side chain (**16A**, R^2 = *i*-Pr) does not react at all on the same time scale. Furthermore, phenyl substituted azlactone **16A** (R^1 = Ph) rearranged readily, but the rearranged product was obtained in low enantiomeric excess. Benzofuranone-derived enol carbonates **16C** also rearrange in high yield and enantioselectivity (92 – 93% ee) when treated with 1 mol% TADMAP (**15C**) at rt. The phenyl-substituted benzofuranone **16E** is less selective at rt, but after significant substrate and solvent screening, optimized conditions were found that afford rearranged product **16F** in 86% ee with 20 mol% TADMAP (**15C**). TADMAP (**15C**) also catalyzes the rearrangement of enol carbonates derived from furanones. In this case, the nature of the aryl substituent determined the regioselectivity of the rearrangement. If the aryl substituent is electron donating (**16Fb**), the major regioisomer is furanone **16G**. In contrast, if the aryl substitutent is electron withdrawing (**16Fc**), then the major regioisomer is furanone **16H**. Both rearranged products **16Gb** and **16Hc** are obtained in high enantiomeric excess. A discussion of the application of TADMAP **15C** to the rearrangement of oxindole derived enol carbonates is reserved for Chapter 2.

Scheme 1-16. Applications of TADMAP (**15C**).



Although TADMAP was a highly effective catalyst for the enantioselective synthesis of quaternary centers in a variety of heterocycles, the synthesis of the catalyst required a resolution of the final racemic material. Therefore, Shaw developed a new series DMAP-containing chiral catalysts (**17A** – **17G**) derived from the chiral pool according to the same general strategy used for TADMAP.[66] The synthesis commences with nitrogen protection of commercially available amino alcohols, such as **17H**, followed by oxidation of the alcohol to aldehyde **17I**. Cram chelate-

controlled addition of 3-lithiated DMAP to aldehyde **17I** followed by acylation of the resulting alcohol readily yields chiral DMAP **17F**. Structural modifications of these catalysts are easily made by starting with different amino alcohols and nitrogen protecting groups as seen from the other derivatives prepared (**17A** – **17G**). Conformational analysis of catalyst **17B** indicates a strong preference for the two hydrogens to be *syn* thereby placing the bulky DMAP and *i*-Pr substituents *anti* to one another (Figure 1-4, see next page). An initial screening of the catalysts for the kinetic resolution of 1-naphthyl-1-ethanol gave promising results, with catalyst **17F** proving to be the most enantioselective (**s** = 8.9, rt, toluene). On the other hand, only moderate enantioselectivities were found in the rearrangement of *O*-carboxylated azlactones, benzofuranones, and oxindoles using catalysts **17A** – **17G** despite significant substrate and solvent optimization screens. Given the short, enantioselective synthesis of catalysts **17A** – **17G**, we chose to pursue additional applications of these catalysts, as discussed in the chapters that follow.

Scheme 1-16. Synthesis of Amino Alcohol Derived Catalysts.

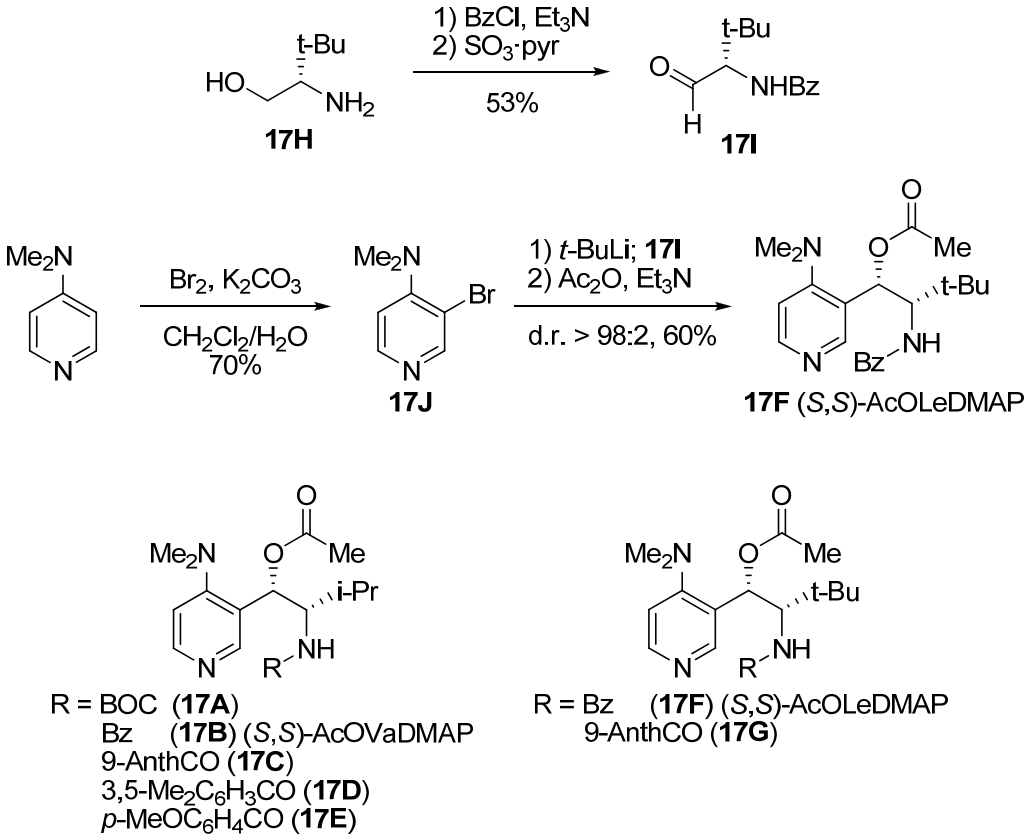
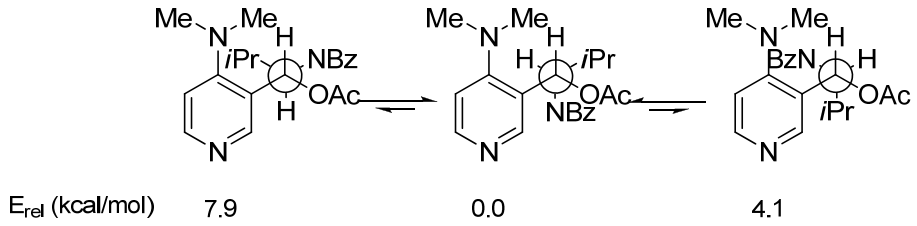


Figure 1-4. Amino Alcohol-Derived Catalyst Side-Chain Conformations.



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Chapter 2

Acetyl and Alkoxycarbonyl Rearrangement Reactions: The Catalytic Enantioselective Synthesis of 3,3-Disubstituted Oxindoles.

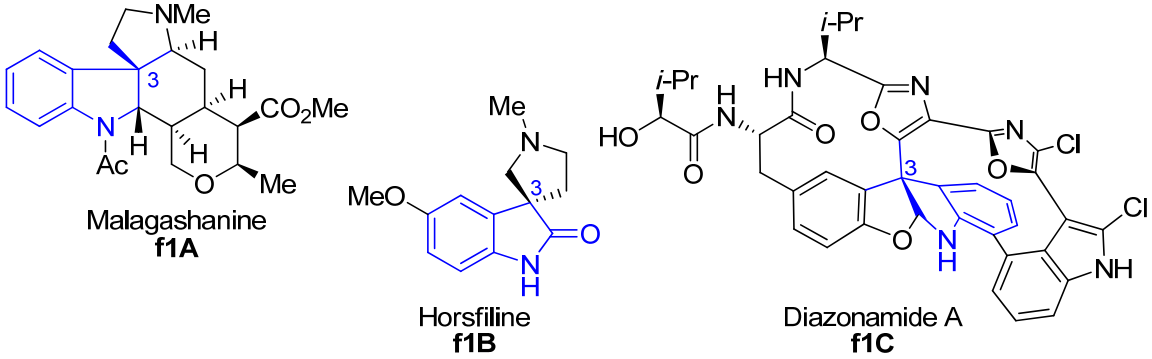
I. Introduction.

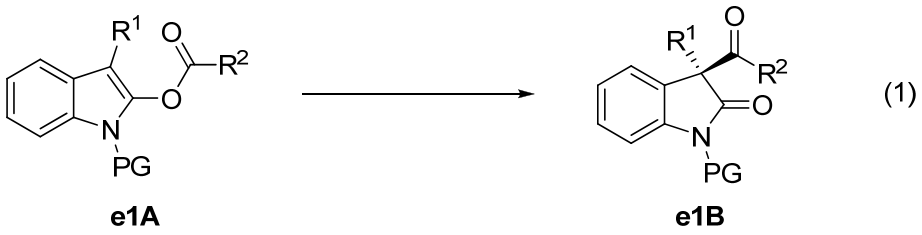
The development of new catalytic methods for the synthesis of enantioenriched chiral centers has been an area of significant research effort and progress in organic synthesis.[1] Many methods are now available for asymmetric reductions and oxidations to generate enantioenriched tertiary centers, and the development of these methods has even led to a Nobel Prize in Chemistry for William S. Knowles, Ryoji Noyori, and K. Barry Sharpless in 2001.[2] In contrast, the catalytic asymmetric synthesis of all-carbon quaternary centers remains a difficult challenge.[3] Carbon-carbon bond formation to generate quaternary centers is disfavored due to the steric repulsion between the carbons of the reaction center. In addition, the stereodifferentiation of the three carbon substituents necessary to form an enantioenriched quaternary carbon is challenging.

Many alkaloid natural products contain a quaternary carbon at *C*-3 of an oxindole or indole as exemplified by Malagashanine,[4] Horsfiline[5] and Diazonamide A[6] (Figure 2-1). The interesting structural motifs and promising biological activities of these alkaloids have inspired the development of asymmetric routes to such quaternary-carbon bearing oxindoles and indoles. In a catalytic manifold, only a single phase-transfer catalyzed alkynylation of an oxindole[7] and few metal-catalyzed syntheses[8,9,10,11] of 3,3-disubstituted oxindoles are known. The chiral-

nucleophile-catalyzed rearrangement of *O*-acetyl or *O*-carboxyl oxindole-derived enolates to *C*-acetyl or *C*-carboxyl oxindoles would be a powerful route to these quaternary carbon containing alkaloids in an enantioenriched fashion (equation 1).

Figure 2-1. Quaternary-Carbon Containing Alkaloid Natural Products.

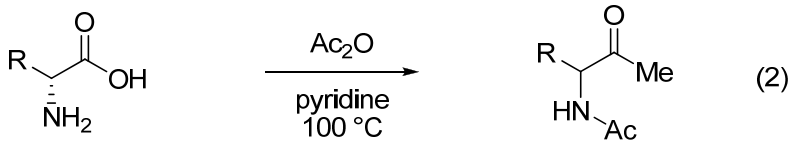




Carboxyl and Acetyl Rearrangement Background.

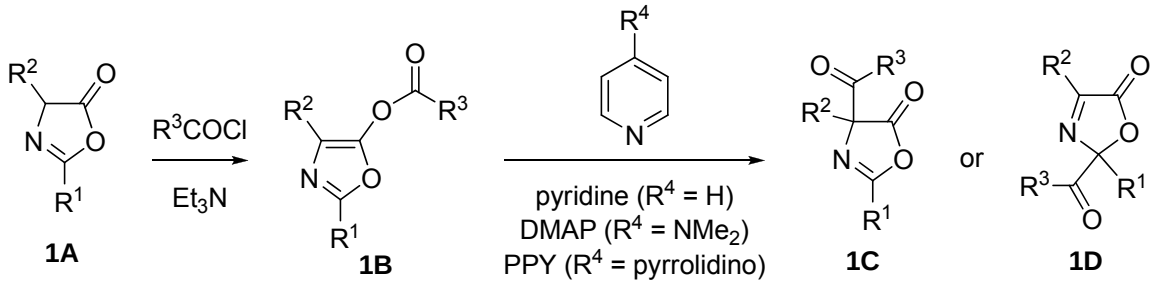
Nucleophile-catalyzed rearrangements of *O*-acetylated or *O*-carboxylated enolates to 1,3-dicarbonyl compounds originated in the studies by Steglich and Höfle into the mechanism of the Dakin-West reaction in 1968.[12] The Dakin-West reaction,[13] the conversion of an amino acid (**e2A**) to an amino ketone (**e2B**) (equation 2), is proposed to proceed via azlactones such as **1A**. While testing the viability of acylating **1A**, Steglich and Höfle found that the proposed intermediate azlactone **1A** is kinetically acylated to afford *O*-acetylated (R^3 = Me) and *O*-carboxylated (R^3 = OMe) azlactones **1B**. Subsequent heating of *O*-acylated azlactones **1B** in pyridine yields the thermodynamically more stable *C*-acylated products **1C** (Scheme 2-1). Under the thermodynamic Dakin-West reaction conditions, these *C*-acylated products are then ring-opened by the carboxylate anion and hydrolyzed to the amino ketones **e2B**. In the absence of carboxylate anions, these quaternary-carbon containing *C*-acylated azlactones **1C** do not ring

open and can be isolated in good yields. The more nucleophilic dimethylaminopyridine (DMAP) or 4-pyrrolodinopyridine (PPY) catalyze the same rearrangement without heating, and complete conversion occurs within minutes at rt to provide *C*-acylated azlactones **1C** in good yields.[14] An unexpected dependence on the electronic nature of R^1 was observed in the regioselectivity of the rearrangement where electron-withdrawing substituents favor the formation of *C*-2 functionalized azlactone **1D** relative to the *C*-4 acylated azlactones **1C** afforded when R^1 is electron donating.



e2A **e2B**

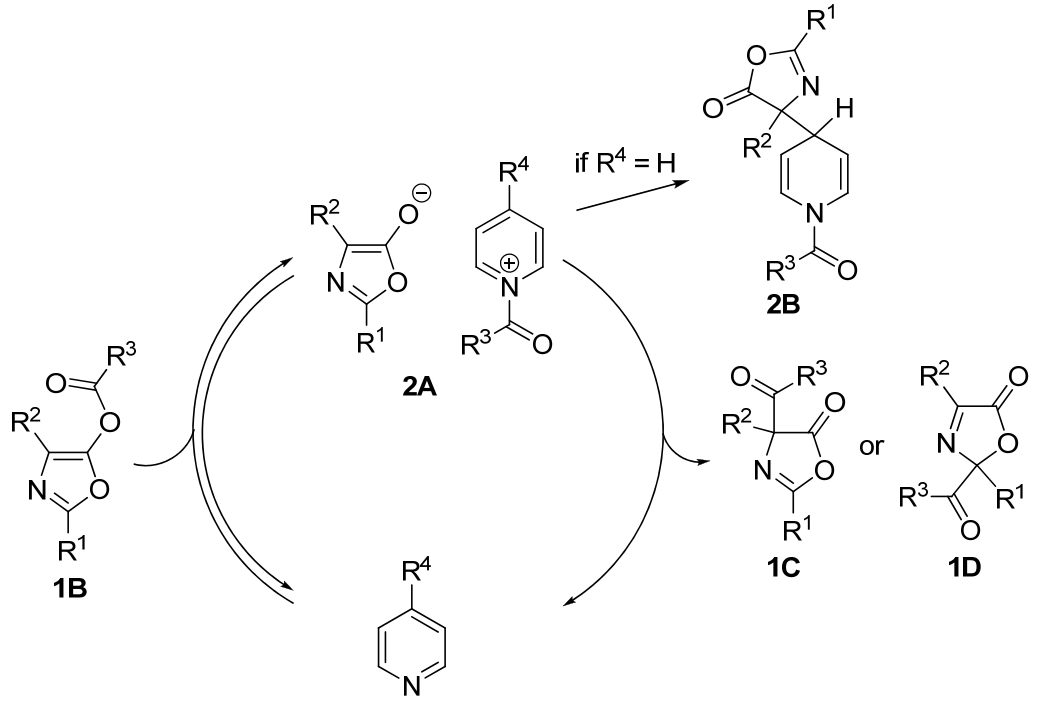
Scheme 2-1. Pyridine Catalyzed Rearrangements of *O*-Acylated Azlactones.



1A **1B** **1C** **1D**

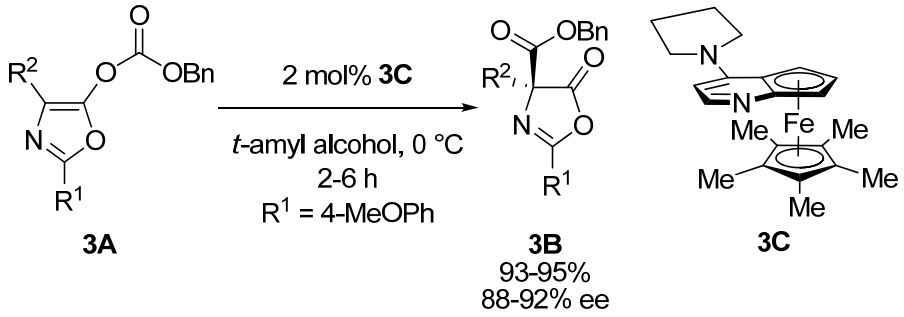
The mechanism for this rearrangement is proposed based on the propensity of pyridine derivatives to act as nucleophiles (Scheme 2-2). Hence, the nucleophilic addition of the pyridine derivative into the carbonyl of **1B** followed by loss of the highly stabilized, aromatic azlactone anion generates ion pair **2A** in analogy to the known acylated pyridinium chlorides.[12b,15] The multidentate azlactone enolate then inserts into the acylated pyridinium salt via either the oxygen anion or the carbon anions, *C*-4 or *C*-2, acting as the nucleophile to give **1B**, **1C** or **1D**, respectively. Support for this mechanism is derived from the isolation a small amount of dihydropyridine **2B** formed upon addition of the azlactone enolate into the 4-position of the acylated pyridinium salt when unsubstituted pyridine was the nucleophile.[12b]

Scheme 2-2. Mechanism of Steglich Rearrangement.

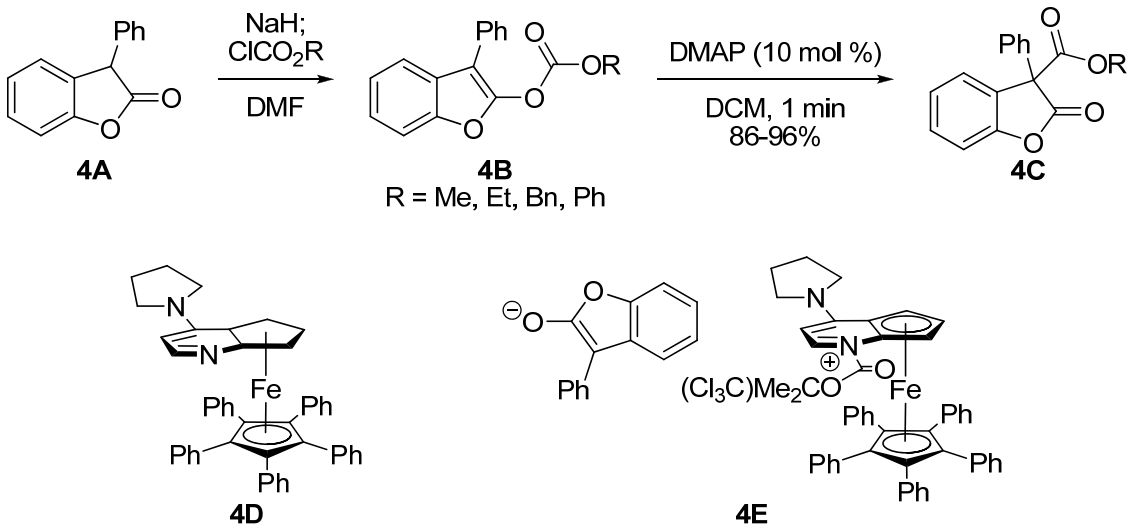


As described in Chapter 1, Fu described the first enantioselective variant of the *O*- to *C*-carboxyl rearrangement with azlactones using planar chiral DMAP catalyst **3C** in 1998.[16] Benzyl enol carbonates **3A** rearrange to *C*-carboxylated azlactones **3B** in high yields and enantioselectivities with a variety of α-unbranched alkyl substituents (R^2, Scheme 2-3). Further mechanistic insights into this variation of the Steglich rearrangement are revealed in the supporting studies. The reaction is zero-order in substrate and first-order in catalyst, and the authors concluded that the resting state of the catalyst is the ion pair (**2A**) proposed by Steglich. In addition, scrambling of the carboxyl migrating groups in both starting material and products occurs when a mixture of two different enol carbonates is used, and the isolation of scrambled starting materials led the authors to propose a reversible first step in the Steglich mechanism. The C–C bond forming step is proposed to be irreversible due to the high enantiomeric excesses of the final products.

Scheme 2-3. Rearrangement of Azlactone-Derived Enol Carbonates with Planar Chiral **3C**.



Scheme 2-4. Nucleophile Catalyzed Benzofuranone Enol Carbonate Rearrangement.

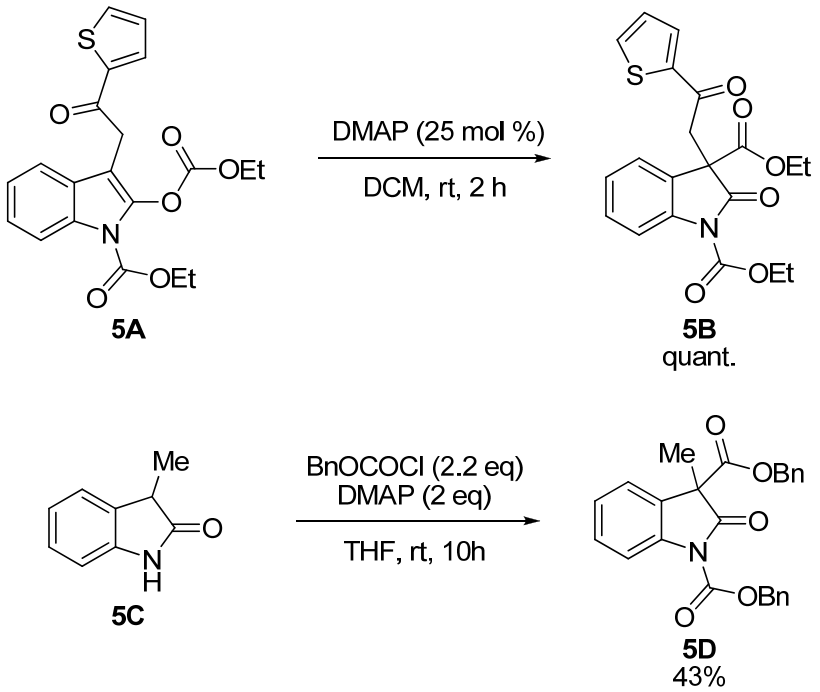


In 1986, Black reported the extension of this type of oxygen-to-carbon alkoxycarbonyl rearrangement reaction to benzofuranone systems.[17] Similar to the azlactone series, under kinetic acylation conditions the benzofuranones **4A** are selectively *O*-carboxylated. Treatment of the *O*-carboxylated benzofuranone **4B** with DMAP (~10 mol%) causes rapid conversion to the *C*-carboxylated benzofuranone **4C** within 2 minutes at rt (Scheme 2-4). A deep blue/purple color is observed during the reaction that fades upon completion of the rearrangement. Interestingly, the highly colored substance forms an air-sensitive crystalline precipitate in hexanes. Although this precipitate could not be characterized, upon dissolution in chloroform the color fades and the only products are the *C*-carboxylated benzofuranone **4C** and DMAP suggesting that the precipitate is

an ion pair analogous to the speculated intermediate **2A**. The precipitate forms in 94% yield based on the molecular weight of the speculated ion pair, indicating that the resting state of the catalyst is the ion pair in this system as well. During later studies by Fu using a planar-chiral pyridine **4D** described in Chapter 1, a similar purple precipitate was isolated, and this time the precipitate could be analyzed by low-resolution X-ray crystallography to assign the structure of the long hypothesized ion pair intermediate (**4E**).[18]

A few scattered reports of the desired oxindole-derived enol carbonate rearrangements have also appeared in the literature. In an initial example by Marchesini, the enol carbonate **5A**, which is formed under kinetic carboxylation conditions, rearranged to the quaternary-carbon containing oxindole **5B** when treated with 25 mol% of DMAP in 2 h (Scheme 2-5).[19] Cohen later reported a related synthesis of *C*,*N*-dicarboxylated oxindole **5D**.[20] Treating 3-methyloxindole (**5C**) with 2.1 equivalents of benzylchloroformate and 2 equivalents of DMAP afforded *C*,*N*-dicarboxylated oxindole **5D** in 43% yield. This reaction presumably proceeds via an enol carbonate similar to **5A** which then rearranges to *C*-carboxylated oxindole **5D**.

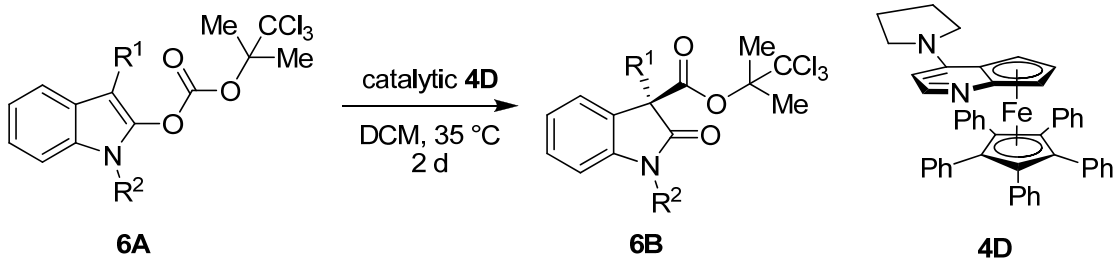
Scheme 2-5. Racemic Rearrangement of Oxindole-Derived Enol Carbonates.



The rearrangement of oxindole-derived enol carbonates is much slower compared to the corresponding azlactone- and benzofuranone-derived enol carbonates. Whereas in the catalyzed rearrangement of azlactone- and benzofuranone-derived enol carbonates the resting state of the catalyst is the ion pair, the resting state of the nucleophile-catalyzed rearrangement of oxindole-derived enol carbonates is the free catalyst. This difference is explained by the difference in the stability of the corresponding ion pairs. The more acidic ester-stabilized aromatic enolates (benzofuranone pK_a = 13.5 in DMSO)[21a] are less basic than the DMAP catalyst (DMAP: pK_a= 10.1 in MeOH, pK_a= 17.3 in $MeNO_2$),[21b,c] so the equilibrium of the starting materials and the intermediate lies towards the ion pair (**2A**). In contrast, the increased pK_a of the amide stabilized enolate (oxindole pK_a = 18.5 in DMSO)[21a] results in a shift of this equilibrium away from the ion pair. Although the ion pair in the oxindole-derived substrate is more reactive due to the increased basicity of the enolate, the decreased concentration decreases the overall rate of rearrangement.

This reduced reactivity is evident when chiral catalysts are applied to the rearrangement of oxindole-derived enol carbonates. The planar chiral pyrrolidinopyridine **4D** catalyzes the rearrangement of enol carbonates **6A** with high enantioselectivity and yield.[18] However, the rearrangements need 2 days in warm dichloromethane with 5-10 mol% catalyst loading even with the enhanced nucleophilicity of the pyrrolidino substituted pyridine **4D**. In addition, to obtain the high stereoselectivity both the sterically bulky 2,2,2-trichloro-1,1-dimethylethyl enol carbonate and pentaphenyl ferrocene-derived catalyst are necessary. Unlike two of Fu's catalysts (**3C** and the dimethylaminopyridine derivative of **4D**), the key catalyst **4D** is not yet commercially available. Furthermore, the published synthesis requires 7 steps and resolution of the product racemate by HPLC on chiral support.[22]

Scheme 2-6. Planar-Chiral Pyridine Catalyzed Rearrangement of Oxindole-Derived Substrates.



6A **6B** **4D**

Table 2-6. Planar-Chiral Pyridine Catalyzed Rearrangement of Oxindole-Derived Substrates.

Entry	Substrate	R^1	R^2	Catalyst loading	ee (%)	Yield (%)
1	**6Aa**	Ph	Me	5 mol%	99	91
2	**6Ab**	2-thienyl	Me	5 mol%	95	81
3	**6Ac**	Bn	Me	10 mol%	94	82
4	**6Ad**	Me	Me	10 mol%	93	72
5	**6Ae**	Ph	Bn	5 mol%	98	88

The decreased reactivity of the oxindole-derived enol carbonates has also been problematic in work done in the Vedejs group by Shaw.[23] With the less reactive dimethylaminopyridine derived TADMAP (2,2,2-triphenyl-1-acetoxyethyl DMAP, **7C**), extraordinarily long reaction times are required for the rearrangement of *N*,*O*-dicarboxylated oxindoles **7Aa** and **7Ab** producing *C*-carboxylated **7Ba** and **7Bb** with modest enantioselectivity (Scheme 2-7, Table 2-7). Changing the protecting group on nitrogen to the strongly electron donating *para*-methoxyphenyl (**7Ac**) similarly results in a slow reaction and modest enantioselectivity. The reaction times are shorter with allyl (**7Ad**) and benzyl (**7Ae**) protected oxindole substrates, but the stereoselectivities are low. The less bulky methyl protected oxindole substrate used by Fu (**6Ad**) allows for rearrangement within 24 hours with 10 mol% catalyst loading, but gives the product in only 39% ee. Introducing an electron-withdrawing nitro group in the oxindole (**7Af**) increases the rate of rearrangement, allowing the reaction to occur at lower temperature at a synthetically useful rate, further increasing the selectivity. However, this structural change limits the scope of the reaction and therefore is not a general solution to the reactivity problem. Modestly improved reactivity was also found with the 3-phenyl substituted oxindole **8A**, resulting from the additional enolate stabilization. Thus, TADMAP (**7C**) catalysis gives full conversion to the rearranged product **8B** within 3 days at room temperature (Scheme 2-8, compare to Table 2-7, entry 2). The reaction proceeds without a substantial decrease in enantioselectivity at 40 °C allowing for complete rearrangement within 18 h to give **8B** with 86% ee.

Scheme 2-7. Rearrangement of 3-Alkyl Substituted Oxindole Substrates with TADMAP (**7C**).

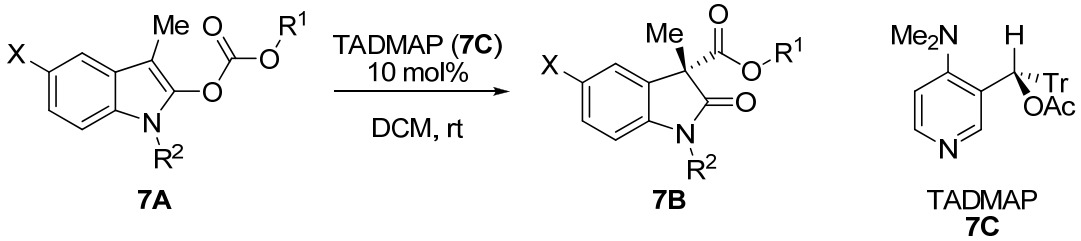
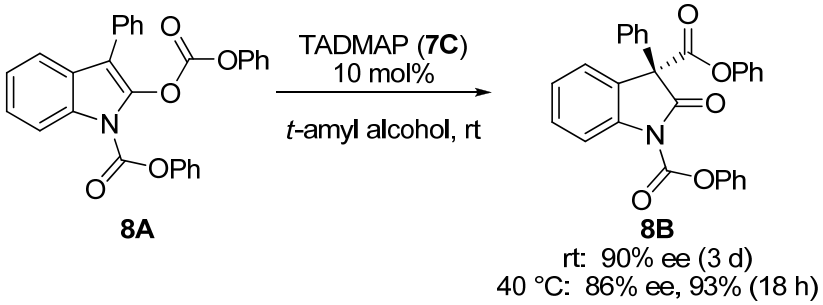


Table 2-7. Rearrangement of 3-Alkyl Substituted Oxindole Substrates with TADMAP (**7C**).

Entry	Substrate	R^1	R^2	X	Time	ee (%)
1	**7Aa**	$C(Me)_2CCl_3$	$CO_2C(Me)_2CCl_3$	H	35 d	57
2	**7Ab**	Ph	CO_2Ph	H	35 d	23
3	**7Ac**	Ph	PMP	H	28 d	48
4	**7Ad**	Ph	Allyl	H	8 d	37
5	**6Ad**	Ph	Bn	H	8 d	7
6	**7Ae**	$C(Me)_2CCl_3$	Me	H	1 d	39
7	**7Af**	$C(Me)_2CCl_3$	Me	NO_2	5 h	65 (75 @ 0 °C)

Scheme 2-8. TADMAP Catalyzed Rearrangements of *C*-Phenyl Substituted Oxindole Substrate.



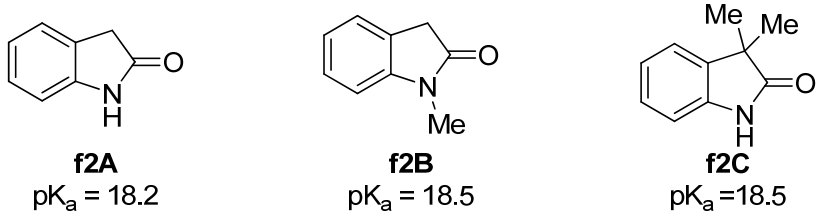
As shown by these examples, the chiral nucleophile-catalyzed rearrangement of the less reactive oxindole substrates requires extended reaction times and occurs with modest enantioselectivity in the 3-methyl series. Therefore, a general synthesis of the 3,3-disubstituted oxindoles in reasonable time frames using a readily available chiral nucleophilic catalyst still remains a problem to be solved. The above results also show that rearrangement rates are problematic. Accordingly, a more reactive oxindole derived substrate was sought before further screening of conditions and catalysts.

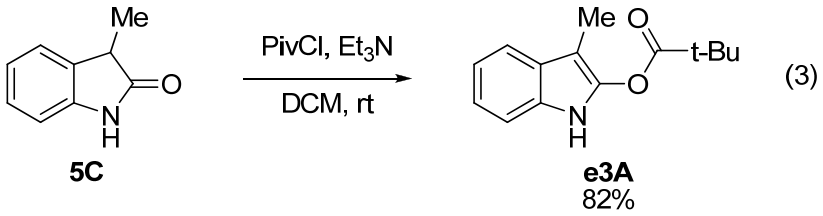
II. Results

Search for a more reactive oxindole-derived enol carbonate.

In order to increase the rate of rearrangement of the oxindole-derived substrates, the previously unstudied enol acetates were targeted in hopes that the higher carbonyl electrophilicity would result in higher reactivity. Ideally, the rearrangement of the oxindole-derived substrates would be carried out without protecting the oxindole nitrogen. Therefore, a route to mono-*O*-acetyl oxindoles was needed. Regioselective functionalization of oxindoles is a challenging task due to the similar pK_a values of the nitrogen and carbon protons determined by Bordwell (Figure 2-2).[21] The identical pK_a values of **f2B** and **f2C** oxindoles indicate that the ionization of oxindoles in organic solvents such as DMSO occurs readily at both nitrogen and carbon, suggesting potentially similar reactivity of nitrogen, oxygen, and carbon in the parent oxindole **f2A**.

Figure 2-2. The pK_a of oxindoles in DMSO.





A survey of the literature revealed a limited number of methods for the generation of the desired oxindole-derived enol esters. Yamada reported in 2002 the selective pivaloylation of oxindole **5C** using PivCl to yield enol ester **e3A** (equation 3).[24] On exposure to triethylamine, acetyl chloride decomposes, so none of the desired acetylated oxindole was obtained. Therefore, the more stable acetic anhydride was used to gain access to the acetylated products. Unfortunately, the lower reactivity of the acetic anhydride resulted in unselective nitrogen, oxygen, and carbon acetylation (Table 2-9, entry 1). A small amount of *N*,*O*-diacetylated oxindole

9B was isolated after chromotagraphy, but none of the desired monoacetylated **9A** was observed in the crude NMR spectrum. It has been shown that acetic anhydride disproportionates in the presence of magnesium bromide to magnesium acetate and acetyl bromide,[25] but when magnesium bromide was added to the acetylation of 3-methyloxindole **5C** with acetic anhydride the amount of carbon and nitrogen acetylated products increased at the expense of oxygen acetylation (Table 2-9, entry 2). Since the reaction with acetic anhydride was not selective for mono-*O*-acetylation, alternative reaction conditions were examined. If an acid chloride is necessary for selective *O*-acylation of oxindoles as suggested by the example by Yamada, then the selective *O*-acetylation requires acetyl chloride. Inoue has reported the selective *O*-acetylation of the highly functionalized oxindole **e4A** using 30 equivalents of acetyl chloride in pyridine (equation 4), but the acetylation of **5C** under these conditions yielded only starting

Scheme 2-9. Acetylation of 3-Methyloxindole (**5C**).

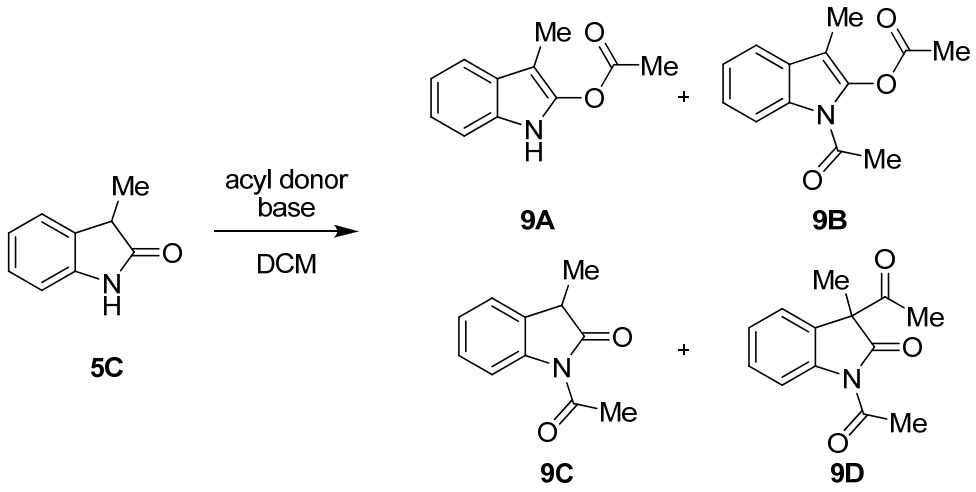
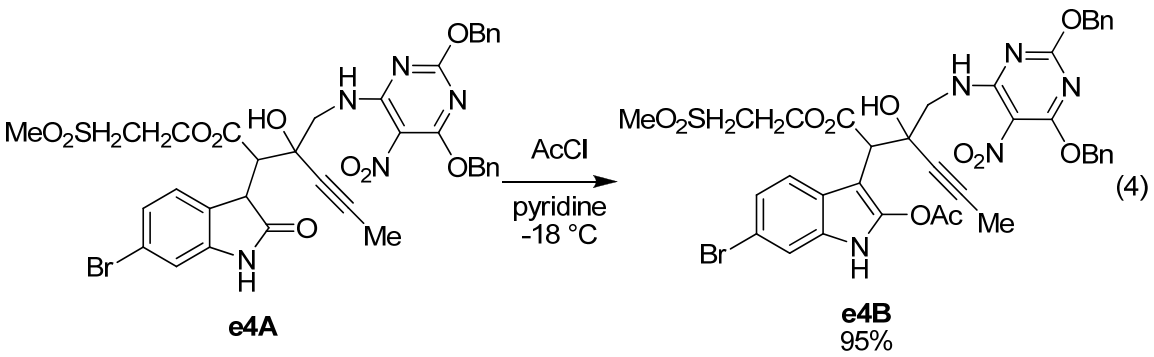


Table 2-9. Acetylation of 3-Methyloxindole (**5C**).

Entry	Acyl donor	Base	Temp.	Time	Product Ratio[a]				
					5C	**9A**	**9B**	**9C**	**9D**
1	Ac_2O	Et_3N	rt	3 h	15	--	43 (19%[b])	19	22
2	Ac_2O, $MgBr_2$	Et_3N	0 °C	2 h	20	--	--	27	53
3	AcCl[c]	pyridine	-10 °C	20 min	>95	--	--	--	--
4	AcCl	2,6-lutidine	0 °C	24 h	--	>95 (81%[b])	--	--	--

[a] percentages by NMR spectroscopy, [b] isolated yield, [c] pyridine as solvent.

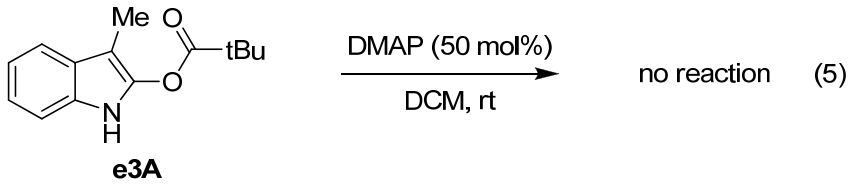
material (Table 2-9, entry 3).[26] Since pyridine is known to form an ion pair with acetyl chloride that is less reactive than the starting acetyl chloride, a hindered weak base which could not form this ion pair should allow for higher reactivity. Indeed using only 2 equivalents of acetyl chloride and 2 equivalents of 2,6-lutidine afforded *O*-acetylated oxindole **9A** as the only product observable by NMR spectroscopy, and **9A** could be isolated in 81% yield. The selective *O*-acetylation under these conditions is likely due to oxindole being acetylated prior to deprotonation since neutral amides are known to be nucleophilic at oxygen. Thus, the key to the selectivity in the acetylation is to use highly reactive acyl donors with hindered weak bases to remove the acid generated in the reaction.



(4)

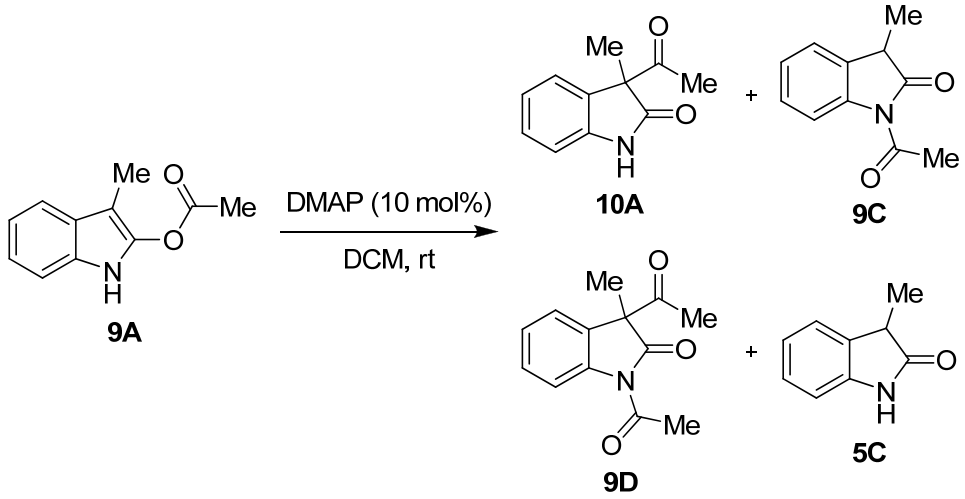
The isolated enol esters **e3A** and **9A** were subjected to DMAP catalysis. Upon treatment of **e3A** with DMAP, no reaction occurred even with 50 mol% catalyst, presumably due to the steric hindrance of the pivaloyl group. DMAP did catalyze the rearrangement of the less hindered enol acetate **9A** (Table 2-10). After 30 minutes, partial conversion to the desired *C*-acetylated **10A** was observed along with significant amounts of *N*,*C*-diacetylated **9D** and deacetylated **5C**. The formation of these latter two products suggests that the intermediate ion pair is capable of dissociating and scrambling as seen with azlactone-derived enol carbonates. Only trace amounts of the starting material remained after 2 h, but oxindoles **10A**, **9C**, and **9D** were formed unselectively. Doubling the reaction time did not significantly affect the ratio of the products formed, but after extended time periods (24 h) the amount of *C*-acetylated product **9A** decreased and *N*-acetylated product **9C** became the major product. This indicates that the reaction may be

reversible, but the reverse reaction does not appear to occur in the time frame of the rearrangement. Unfortunately, the scrambling of the acetyl group between molecules of oxindoles under DMAP catalysis precludes the use of nitrogen-unprotected oxindoles.



e3A

Scheme 2-10. DMAP Catalyzed Rearrangement of Unprotected Enol Acetate **9A**.



9A **10A** **9C** **9D** **5C**

Table 2-10. DMAP Catalyzed Rearrangement of Unprotected Enol Acetate **9A**.

		Product Ratio[a]				
Entry	Time	**9A**	**10A**	**9C**	**9D**	**5C**
1	30 min	36	27	1	17	19
2	1 h	13	31	2	26	29
3	2 h	2	34	3	30	31
4	4.5 h	--	32	3	32	33
5	24 h	--	9	40	23	27

[a] Percentages by ^{1}H NMR spectroscopy

In previous work by Scott Shaw,[23] it was found that the protecting group on the oxindole nitrogen could greatly affect the rate of rearrangement, so methods were examined to find a general preparation of a variety of *N*-substituted derivatives of enol acetate **9A**. Acetyl chloride and triethylamine did not react with the oxindole due to the decomposition of acetyl chloride by triethylamine as seen previously (Table 2-11, entry 1). With acetic anhydride as the acetyl donor,

a small amount of the desired product **9B** was formed but the major product was *N*-acetyl oxindole **9C**[21] that had lost the *O*-acetyl group (Table 2-11, entry 2). A more reactive nucleophile was then generated by deprotonating the nitrogen of indole **9A**. A hindered base was necessary to prevent addition into the electrophilic acetyl group, so indole **9A** was treated with NaHMDS at low temperature. When the resulting anion was quenched with acetyl chloride, the desired *N,O*-diacetylated product was the major product but significant amounts of byproducts **5C**, **9C**, and **9D** were also observed (Table 2-11, entry 3). Generating a more dissociated anion by changing the counterion from sodium to potassium, resulted in an increased selectivity of the reaction yielding *N*,*O*-diacetylated oxindole **9B** in a 4:1 ratio to *C*,*O*-diacetylated oxindole **9D** (Table 2-11, entry 4).[27] When a less reactive electrophile such as acetic anhydride was used, the selectivity again decreased, so very reactive electrophiles are necessary (Table 2-11, entry 5). However this method was suitable for the synthesis of amide-, sulfonamide- and carbamate-protected oxindole-derived enol acetates, and chloroformates in sufficient quantities for testing the rearrangement reactions (Scheme 2-12). Unfortunately, the less reactive alkyl halides were unselective in the alkylation of indole **9A**, so an alternate route was necessary.

Scheme 2-11. Protection of 2-Acetoxyindole **9A**.

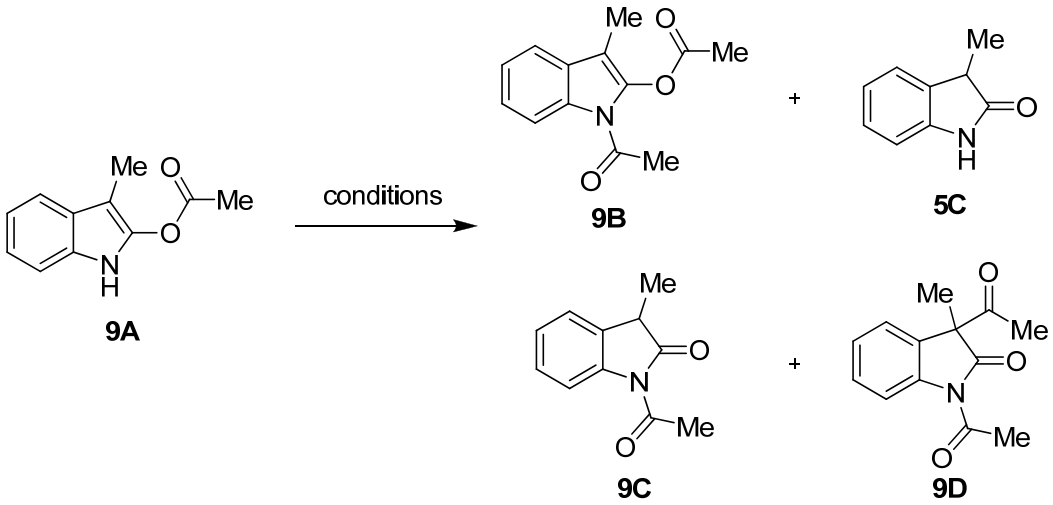
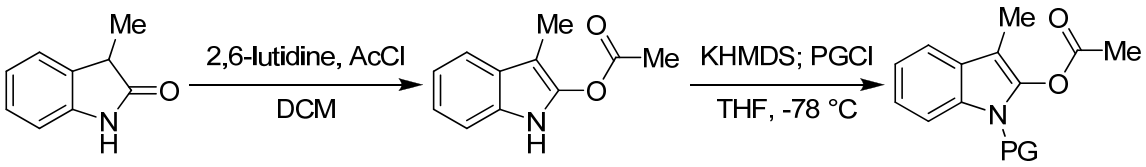


Table 2-11. Protection of 2-acetoxyindole **9A**.

				Product Ratio[a]			
Entry	Acyl Donor	Base	Solvent, Temp	**5C**	**9B**	**9C**	**9D**
1	AcCl	Et_3N	DCM, 0 °C	no reaction			
2	Ac_2O	Et_3N	DCM, 0 °C	--	25	--	75
3	AcCl	NaHMDS	THF, -78 °C	13	47	13	26
4	AcCl	KHMDS	THF, -78 °C	--	81	--	19
5	Ac_2O	KHMDS	THF, -78 °C	--	40	20	40

[a] Percentages by NMR spectroscopy

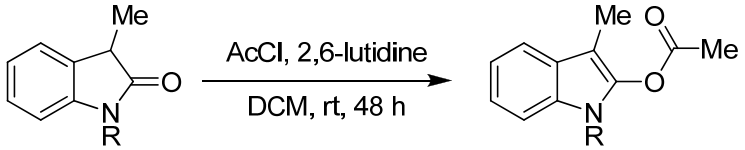
Scheme 2-12. Synthesis of Differentially Protected Oxindole-Derived Enol Acetates.



5C **9A** 81% **9B**

a: PG = Ac (31%)
b: PG = CO_2Me (38%)
c: PG = CBz (36%)
d: PG = BOC (62%)
e: PG = Ts (42%)
f: PG = *p*-Ns (32%)
g: PG = *o*-Ns (28%)
h: PG = $PhCH_2CO$ (27%)
i: PG = Ph_2CHCO (39%)
j: PG = *i*-PrCO (47%)
k: PG = Piv (22%)
l: PG = Bz (55%)

The known *N*-alkyl oxindoles **e6A**[28] and **e6B**[29] could be selectively *O*-acetylated under the same conditions as the free *N*-H oxindoles, albeit with lower reactivity. Although the conversions were low even after 2 days, only *O*-acetylated products and recovered starting materials were observed in the crude reaction mixture by ^{1}H NMR spectroscopy. The desired enol acetates **9Bm** and **9Bn** could be readily isolated from the recovered starting material.



(6)

e6A: R = Bn
e6B: R = Allyl

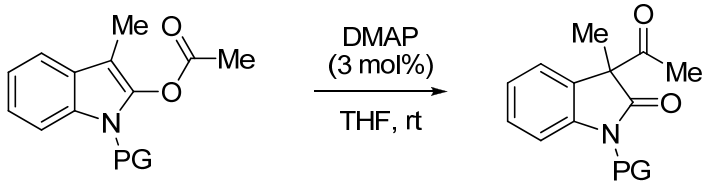
9Bm: R = Bn (42%, 45% conversion)
9Bn: R = Allyl (20%, 34% conversion)

With a variety of protected enol acetates in hand, their reactivity in the DMAP-catalyzed rearrangement was measured. Using 3 mol% DMAP, enol acetates with alkyl- or carbamate-protected nitrogen rearranged slowly (incomplete conversions after 5 hours, Table 2-13, entries 1-5). In the carbamate series, the rate of rearrangement depended on the bulk of the protecting group. The smaller methyl carbamate-protected oxindole **9Bb** gave 78% conversion to **9Db** after

5 hours while only 29% conversion was seen over the same time with the more hindered *t*-butoxycarbonyl (BOC)-protected oxindole **9Dd**.

Moving away from alkyl and carbamate protecting groups that had been studied previously by Shaw, the sulfonamide- and amide-protected oxindoles were examined. Sulfonamide-protected oxindole **9Be** rearranged completely within 50 min under the same reaction conditions (Table 2-13, entry 6). The even more electron-deficient nitro substituted sulfonamides **9Bf** and **9Bg** were still more reactive yielding rearranged oxindoles **9Df** and **9Dg** within 20 min (Table 2-13, entries 7-8). DMAP-catalyzed rearrangement of acetyl protected oxindole **9Ba** was also very fast giving oxindole **9Da** within 20 min. This increased reactivity of the amide-protected oxindoles was seen even with branched amides **9Bh**-**j**. The reactivity dropped off slightly with pivaloyl-protected oxindole **9Bk** although the rate was significantly higher than in the case of carbamates **9Bb**-**d**. On the other hand, the benzoyl protected oxindole **9Bl** was less reactive than the other *N*-acyl analogues.

Scheme 2-13. Effect of Protecting Group on Rate of DMAP Catalyzed Rearrangement.



9B **9D**

Table 2-13. Effect of Protecting Group on Rate of DMAP Catalyzed Rearrangement.

Entry	PG	Time	Result[a]
1	Allyl (**n**)	5 h	73%
2	Bn (**m**)	5 h	89%
3	CO_2Me (**b**)	5 h	78%
4	CBz (**c**)	5 h	68%
5	Boc (**d**)	5 h	29%
6	Ts (**e**)	50 min	>95%
7	*p*-NO_2PhSO_2 (**f**)	20 min	>95%
8	*o*-NO_2PhSO_2 (**g**)	20 min	>95%
9	Ac (**a**)	20 min	>95%
10	$PhCH_2CO$ (**h**)	20 min	>95%
11	Ph_2CHCO (**i**)	20 min	>95%
12	*i*-PrCO (**j**)	20 min	>95%
13	Piv (**k**)	20 min	84%
14	Bz (**l**)	20 min	57%

[a] Percent conversion by NMR spectroscopy

The increased reactivity of the amide- and sulfonamide-protected oxindoles is due to the stabilization of the oxindole enolate by electron withdrawal. Although the carbamate protecting group (**9Ab**-**d**) is also capable of electron withdrawal, the amide resonance contribution would be reduced due to an opposing effect by delocalization involving the carbonyl group and the unshared electrons of the alkoxy substituent. The benzoyl protected oxindole **9Bl** also experiences opposing effects due to electron withdrawal and delocalization, but to a lesser extent in view of the smaller difference in rates of rearrangement (>50% conversion: **9Bb**-5 h, **9Bl**-20 min). The difference in the conjugation of the carbonyl group is evident in the IR stretching frequencies of **9B**. In acetyl-protected **9Ba** the stretch for the amide carbonyl is 1698, but the C=O stretching frequency of carbamate **9Bb** is significantly higher (1737). The amide carbonyl

stretching frequency of benzoyl-protected **9Bl** of 1684 lies between the typical stretch for a benzoyl ketone and a benzoyl amide.

Chiral-nucleophile catalyzed rearrangements of oxindole-derived enol acetates.

With highly reactive oxindole-derived enol acetates in hand, chiral catalysts were screened for their ability to induce the rearrangement enantioselectively. With TADMAP (**7C**), the enantioselectivity of the rearrangment was poor (Table 2-14, entry 1). The readily available BocVADMAP (**14A**)[30] was also poorly selective. However promising selectivities and increased reactivities were seen with benzoyl protected amino alcohol-derived catalysts BzVADMAP (**14B**)[30] and AcOLeDMAP (**14C**).[30] Unfortunately, lowering the reaction temperature to 0 °C only slightly improved the enantioselectivity (Table 2-14, entry 5).

Scheme 2-14. Enantioselective Rearrangement of Enol Acetate **9Ba**.

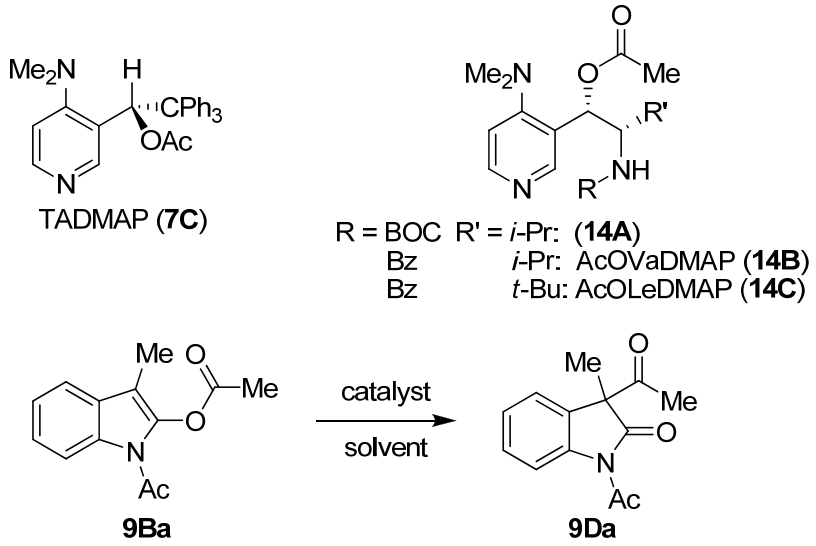


Table 2-14. Enantioselective Rearrangement of Enol Acetate **9Ba**.

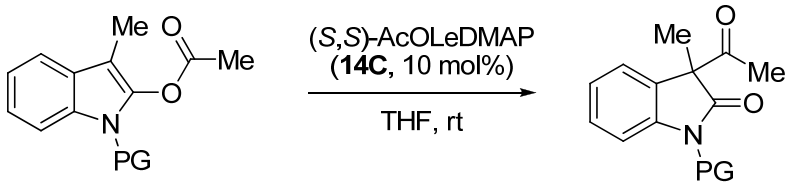
Entry	catalyst (10 mol%)	Solvent	Temp	Time	Yield (%)	ee (%)
1	TADMAP (**7C**)	DCM	rt	3 h	nd[a]	19
2	**14A**	THF	rt	8h	97	27
3	(*S*,*S*)-AcOVaDMAP (**14B**)	THF	rt	4h	93	55
4	(*S*,*S*)-AcOLeDMAP (**14C**)	THF	rt	3.25 h	94	61
5	"	THF	0 °C	4 h	77	68

[a] Not determined

Since the diacetylated oxindole **9Ba** was highly reactive yet only moderately suited for enantioselective acyl migration, other protecting groups were tested with the more selective chiral

catalyst AcOLeDMAP (Table 2-15). The enol acetates with sulfonamide protecting groups (**9Be-g**) were also highly reactive, but the enantioselectivies were moderate (entries 2-4). The branched *iso*butyroyl protected oxindole **9Bj** showed an improved enantioselectivity (77% ee) and better reactivity relative to acetyl-protected oxindole **9Ba** (entry 5). Increasing α-substitution of the protecting group (pivaloyl-protected oxindole **9Bk**) did not enhance the enantioselectivity, but it significantly reduced the reactivity (entry 6). Therefore, amides with steric bulk further away from the reaction center were investigated. With phenylacetyl-protected oxindole **9Bh** similar enantioselectivities and reaction rates to isobutyroyl protected oxindole **9Bj** were seen (entry 7). Fortunately, the addition of a second phenyl on the acetyl protecting group (**9Bi**) increased the enantioselectivity to 86% ee without decreasing the reaction rate so this protecting group was used in further optimizations (entry 8).

Scheme 2-15. AcOLeDMAP-Catalyzed Rearrangement of Differentially Protected Enol Acetates.



9B **9D**

Table 2-15. AcOLeDMAP-Catalyzed Rearrangement of Differentially Protected Enol Acetates.

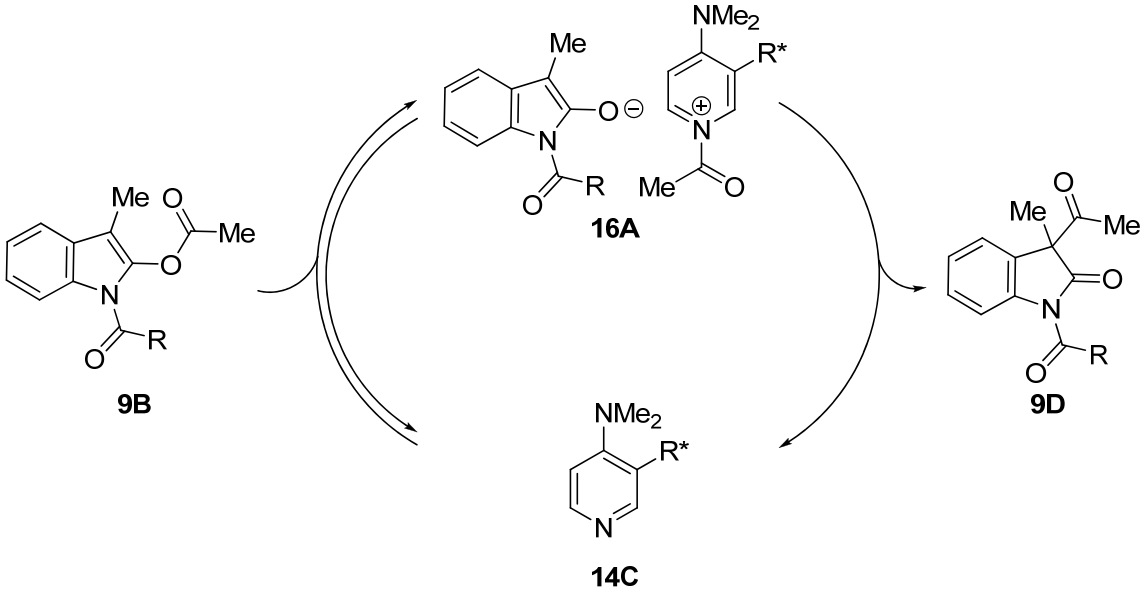
Entry	PG	Time	Yield (%)	ee (%)
1	Ac (**a**)	3.5 h	94	61
2	Ts (**e**)	20 h	nd[a]	46
3	*p*-Ns (**f**)	2 h	81	57
4	*o*-Ns (**g**)	2 h	83	58
5	*i*-PrCO (**j**)	2 h	92	77
6	Piv (**k**)	24 h	67	77
7	$PhCH_2CO$ (**h**)	2.5 h	96	75
8	Ph_2CHCO (**i**)	2.5 h	89	86

[a] not determined

The effect of the *N*-acyl substituent steric bulk on the rate of reaction is worth noting. When the carbamate protected oxindoles were treated with DMAP, the more hindered BOC-protected substrate **9Bd** rearranged at a much slower rate than methyl carbamate **9Bb** (Table 2-13) suggesting that increased steric hindrance around the enol acetate reduced reactivity. Although reactivity differences between N-acyl substrates were not apparent using the DMAP

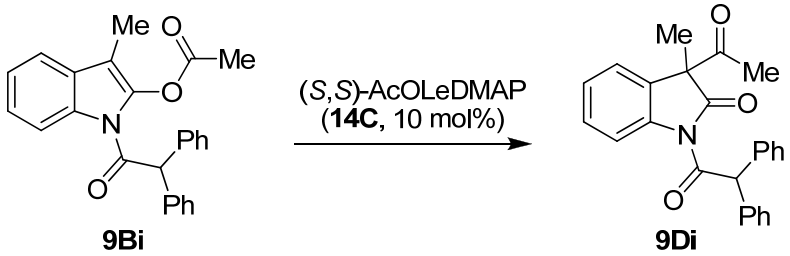
catalyst, with the more hindered, and therefore less reactive, chiral AcOLeDMAP these differences were noticeable. Based on the proposed mechanism of the nucleophile-catalyzed rearrangement an increase in steric bulk of the protecting group could increase the hindrance around the acetyl migrating group and thereby decrease the rate of formation of ion pair **16A** (Scheme 2-16). On the other hand, once the ion pair forms, the rate of the unproductive recombination via C-O bonding (oxygen attack at the *N*-acyl pyridinium ion) would decrease as the steric bulk of the protecting group increases. The intermediate ion pair would then favor recombination with carbon acting as the nucleophile to give rearranged product **9D**. With branched amide protecting groups, the latter effect appears to dominate over the steric hindrance of the enol acetate starting material **9B**, but for the very bulky pivaloyl-protected **9Bk** the initial attack of the catalyst is slowed, like with bulky carbamates.

Scheme 2-16. Mechanism of Nucleophile-Catalyzed Rearrangement.



The enantioselectivity of the rearrangement in different solvents was examined next (Table 2-17). The AcOLeDMAP-catalyzed rearrangement of **9Bi** was less enantioselective in both very polar and very nonpolar solvents, but the solvent effect was small. The optimal enantioselectivity was obtained in moderately polar aprotic solvents such as tetrahydrofuran and ethyl acetate. Although the temperature effect was also modest, lowering the temperature to 0 °C of the rearrangement in ethyl acetate gave the rearranged product **16Ai** in 92 %ee.

Scheme 2-17. Solvent Effect on Enantioselectivity of AcOLeDMAP-Catalyzed Rearrangement.



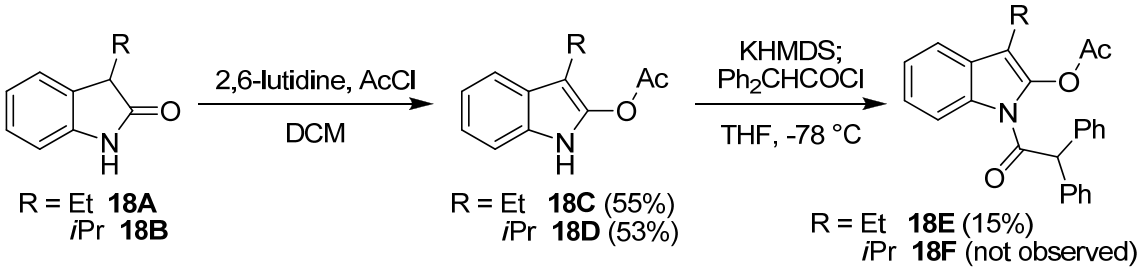
9Bi **9Di**

Table 2-17. Solvent Effect on Enantioselectivity of AcOLeDMAP-Catalyzed Rearrangement.

Entry	Solvent	Temp	ee (%)
1	*t*-amyl alcohol	rt	62
2	toluene	rt	61
3	DMF	rt	77
4	DCM	rt	79
5	MeCN	rt	80
6	Et_2O	rt	81
7	Acetone	rt	86
8	THF	rt	89
9	EtOAc	rt	88
10	EtOAc	0 °C	92

Since a highly enantioselective rearrangement of enol acetate **9Bi** was at hand, additional 3-substituted oxindole substrates were needed to explore the scope of the rearrangement. The formation of enol acetates **18C** and **18D**, from oxindoles **18A** and **18B**,[31] proceeded as expected, but the protection of these enol acetates was difficult. The deprotonated indole can either add to the acid chloride or deprotonate the acidic proton of the hindered $Ph_2CHCOCl$ generating the relatively stable diphenylketene. The latter possibility is implied as little, if any, of the desired product was formed using the conditions optimized for acetyl protection. Alternate diphenylacetyl protections of the enol acetate indole **9A** by heating with diphenylacetyl chloride and either triethylamine, or camphorsulfonic acid, gave none of the desired product, so a new route was needed. In addition, while the unprotected enol acetates **9A**, **18C**, and **18D** could be isolated, they were unstable and decomposed in the -20 °C freezer within two weeks.

Scheme 2-18. Attempted Synthesis of Different 3-Alkyl Substituted Oxindole Substrates.



R = Et **18A**
*i*Pr **18B**

R = Et **18C** (55%)
*i*Pr **18D** (53%)

R = Et **18E** (15%)
*i*Pr **18F** (not observed)

The desired enol acetates could be synthesized by switching the order of functionalization of the oxindoles. The nitrogen of oxindoles can protected by heating in an acid chloride or anhydride in the absence of base.[32] Thus oxindole **5C** was cleanly *N*-protected by heating a neat mixture of **5C** and $Ph_2CHCOCl$ for several hours (Scheme 2-19). The selective acetylation of oxygen was then attempted. Deprotonation of oxindole **19A** followed by quenching with acetic anhydride afforded *C*-acetylated **9Di** as the predominant product (Table 2-19, entry 1). However switching to the more reactive acetyl chloride reversed the selectivity, giving *O*-acetylated **9Bi** as the predominant product (entry 2). This selectivity was again reversed when the solvent was changed from DMF to the less polar THF indicating that the dissociated anion favored selective *O*-acetylation (entry 3). In a separate attempt to synthesize the *O*-acetylated oxindoles, mildly basic conditions were screened and a similar trend with the acetyl donor was observed (Table 2-19, entries 4-6). Hence, with acetic anhydride the mixtures of *O*-acetylated **9Bi** and *C*-acetylated **9Di** favored the latter (entry 4). On the other hand, when the reaction was conducted with the more electrophilic acetyl chloride, *O*-acetylated oxindole **9Bi** was the major product and could be isolated in 80% yield (Table 2-19, entry 5). In contrast to the strongly basic conditions, changing the solvent to the more polar THF from Et_2O, when using triethylamine as the base, greatly diminished this selectivity.

Scheme 2-19. Optimization of the Synthesis of *N*-Diphenylacetyl Oxindole Enol Acetates.

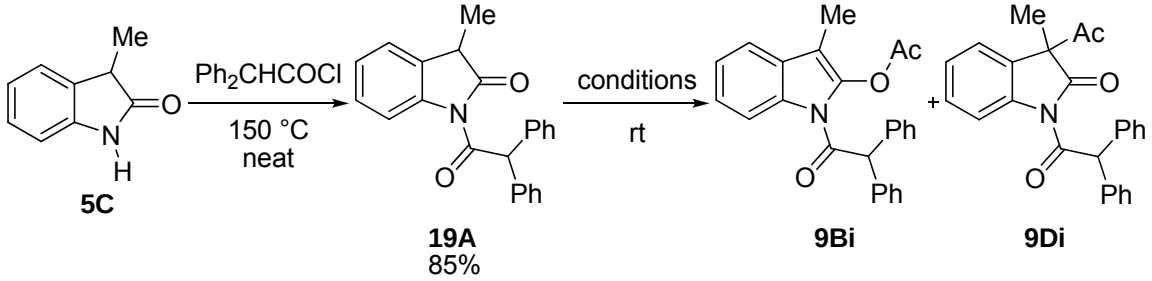


Table 2-19. Optimization of the Synthesis of *N*-Diphenylacetyl Oxindole Enol Acetates.

		Product Ratios[a]		
Entry	Conditions	**19A**	**9Bi**	**9Di**
1	NaH; Ac_2O, DMF	4	1	15
2	NaH; AcCl, DMF	1	8	1
3	NaH; AcCl, THF	1	1	8
4	Ac_2O, Et_3N, Et_2O	4	1	2
5	AcCl, Et_3N, Et_2O	--	19[b]	1
6	AcCl, Et_3N, THF	1	3	1

[a] by ^1H NMR spectroscopy [b] 80% isolated yield

Due to the higher selectivity and ease of conducting the reaction using the mildly basic triethylamine, these conditions were extended to a variety of 3-substituted oxindole substrates.[31] The desired enol acetates were readily synthesized (Scheme 2-20). In order to prevent desilylation of the protected alcohol in oxindole **20Bd** by the stoichiometric HCl generated during the reaction, the protection of the nitrogen was carried out with diphenylacetic anhydride[33] which gave a less reactive byproduct diphenylacetic acid. However the byproduct was sometimes difficult to remove so the acid chloride was used for the other substrates. An added benefit of the diphenylacetyl protecting group is the crystallinity of the oxindole products, which facilitated purification.

Scheme 2-20. Optimized Synthesis of *N*-Diphenylacetyl Protected Oxindole Enol Acetates.

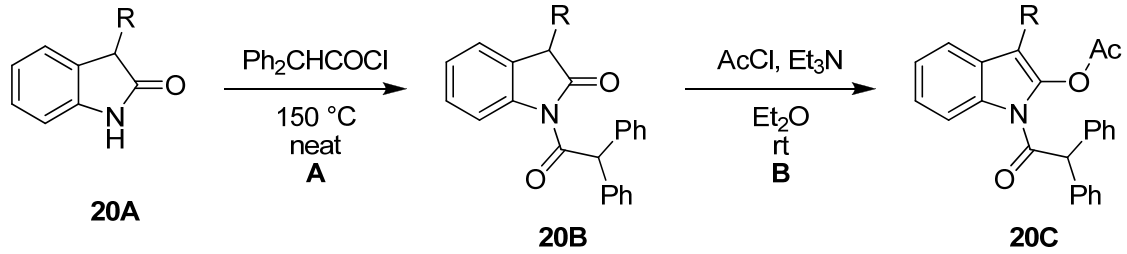


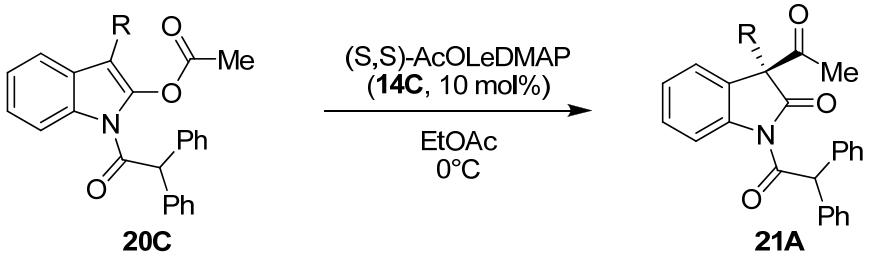
Table 2-20. Optimized Synthesis of *N*-Diphenylacetyl Protected Oxindole Enol Acetates.

Entry	R	**A**	**B**
1	Me (**a**)	85%	80%
2	Et (**b**)	84%	75%
3	Bn (**c**)	83%	70%
4	$(CH_2)_2$OTBDPS (**d**)	72%[a]	68%
5	Allyl (**e**)	74%	67%
6	*i*Pr (**f**)	83%	43%
7	Ph (**g**)	58%	86%

[a] from $(Ph_2CHCO)_2O$

The new substrates were then subjected to AcOLeDMAP catalysis. The rearrangement occurred readily in substrates with unbranched alkyl chains giving products with 86-94% ee within 3 hours at 0 °C (Scheme 2-21). Isopropyl substituted oxindole **20Cf** was significantly less reactive than the unbranched substrates, but the product was obtained in good yield and excellent enantioselectivity, albeit after 2 days at 0 °C. Notably, this is the first reported instance of the enantioselective rearrangement of any substrate containing a branched alkyl group at *C*(3). The phenyl substituted oxindole **20Cg** also rearranged readily, although the product was obtained in moderate enantioselectivity. After the 3-phenyl substituted rearranged oxindole **21Ag** was resubjected to the reaction conditions, the product was reisolated with 66% ee, indicating that the modest enantiomeric excess is not due to a reversible acetyl rearrangement. Although purification of these C-acetylated products was hampered by a retro-Claisen deacylation on silica gel, the use of recrystallized substrates and anhydrous conditions provided *C*-acetylated oxindoles **21A** cleanly, allowing purification by quick filtration over a silica plug.

Scheme 2-21. Optimized AcOLeDMAP-Catalyzed Rearrangement of Enol Acetates.



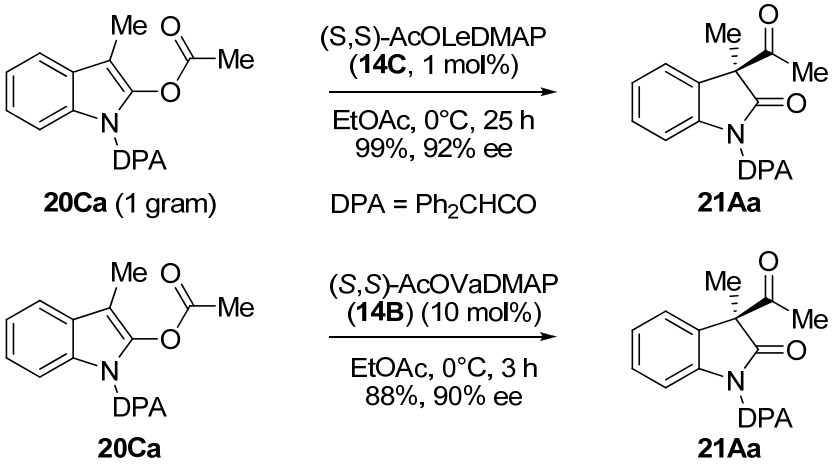
20C **21A**

Table 2-21. Optimized AcOLeDMAP-Catalyzed Rearrangement of Enol Acetates.

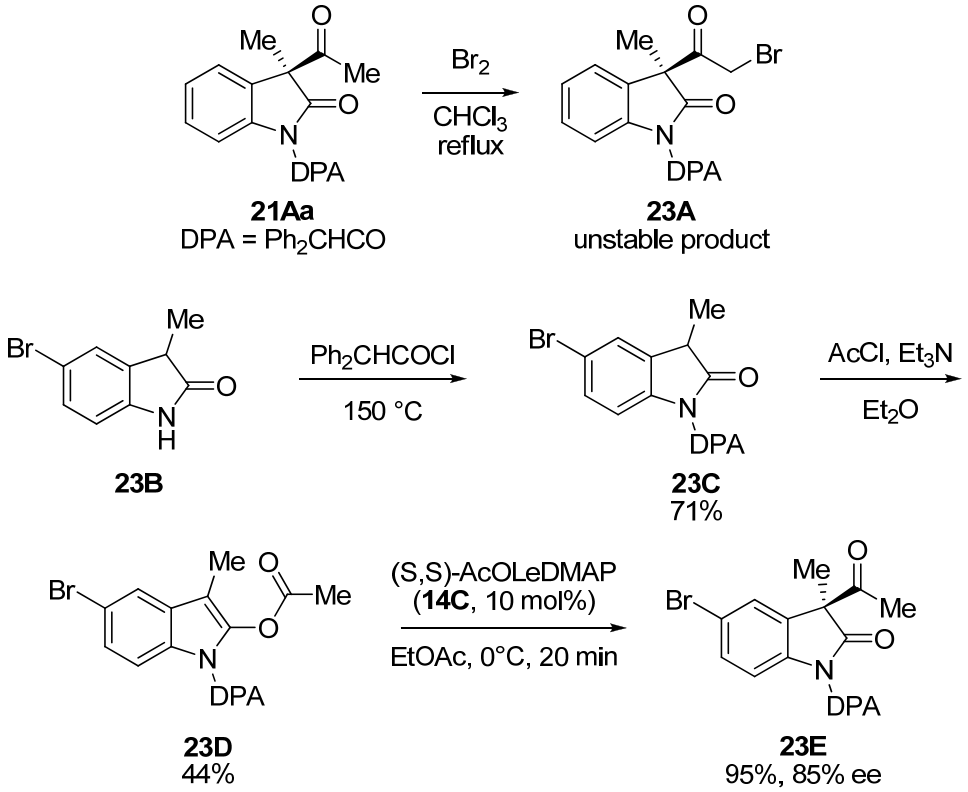
Entry	R^4	time	yield	ee
1	Me (**a**)	2 h	94%	92%
2	Et (**b**)	2.5 h	98%	91%
3	Bn (**c**)	3 h	96%	94%
4	$(CH_2)_2$OTBDPS (**d**)	3 h	94%	91%
5	Allyl (**e**)	2.5 h	98%	86%
6	*i*-Pr (**f**)	41.5 h	82%	94%
7	Ph (**g**)	2 h	98%	66%

For preparative application of the rearrangements, lower catalyst loading was evaluated. Thus, 1 mol % of catalyst **14C** effected the rearrangement of **20Ca** on gram-scale within 24 h without loss of enantioselectivity. Additionally, the oxindole product **21Aa** was upgraded to 99% ee by recrystallization after collecting a first crop enriched in the less soluble racemic contaminant. At this point the valine-derived catalyst **14B** (AcOVaDMAP) also was tested for the rearrangement of **21Ca** and proved to be highly enantioselective (88% yield, 90% ee). Because the enantioselectivity is nearly as high as with catalyst **14C**, AcOVaDMAP may be more practical than AcOLeDMAP for large scale applications because the cost of the valinol starting material in the catalyst synthesis is significantly less than *tert*-leucinol (*S*-valinol: 1 g/ $35, 5 g/ $122; *S*-*tert*-leucinol: 1 g/ $74, 5 g/ $199). This cost differential is especially important for the "unnatural" enantiomers of the amino alcohols required to make the enantiomeric catalysts (*R*-valinol: 1 mL/ $40, 5 mL/ $139; *R*-*tert*-leucinol 100 mg/ $107, Aldrich pricing 4/20/08).

Scheme 2-22. Conditions for Large-Scale Applications.



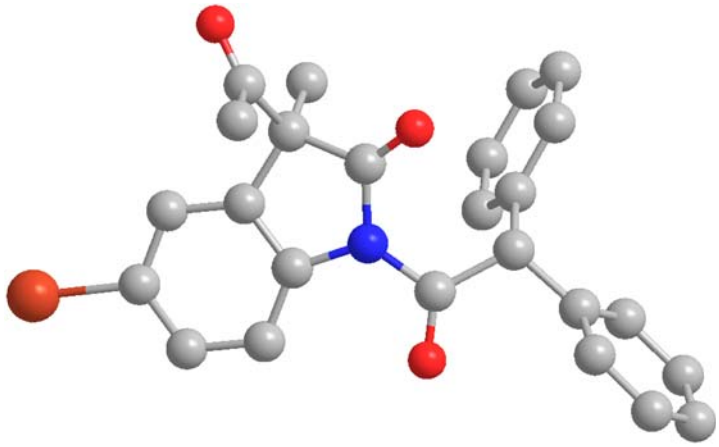
Scheme 2-23. Synthesis of a Brominated 3,3-Disubstituted Oxindole.



A halogen was introduced to allow determination of absolute configuration by X-ray crystallographic techniques. Bromination of oxindole **21Aa** gave bromoacetyl **23A**, but this product did not crystallize and was unstable. Therefore 5-bromo-3-methyloxindole (**23B**)[34] was carried through the standard protection and acetylation steps to obtain enol acetate **23D**. This

enol acetate was then treated with AcOLeDMAP and rearrangement occurred within 20 minutes to yield bromine-containing oxindole **23E** in good enantioselectivity. Since oxindole **23E** crystallized as a scalemic mixture, the enantiomers were separated by HPLC on chiral support, and crystals were grown of the major enantiomer of oxindole **23E**. X-Ray crystallographic analysis of **23E** revealed the stereocenter to be of (*S*) configuration by anomalous dispersion (Figure 2-3). Assuming that all the oxindole products have the same sense of optical rotation, the other oxindoles (**21A**) were assigned the (*S*)-configuration by analogy based on the similar sign (-) of rotation observed for the major enantiomers in HPLC studies using the polarimeter detector.

Figure 2-3. X-Ray Crystal Structure of 3-Acetyl-5-Bromo-1-Diphenylacetyl-3-Methyloxindole **23E**.

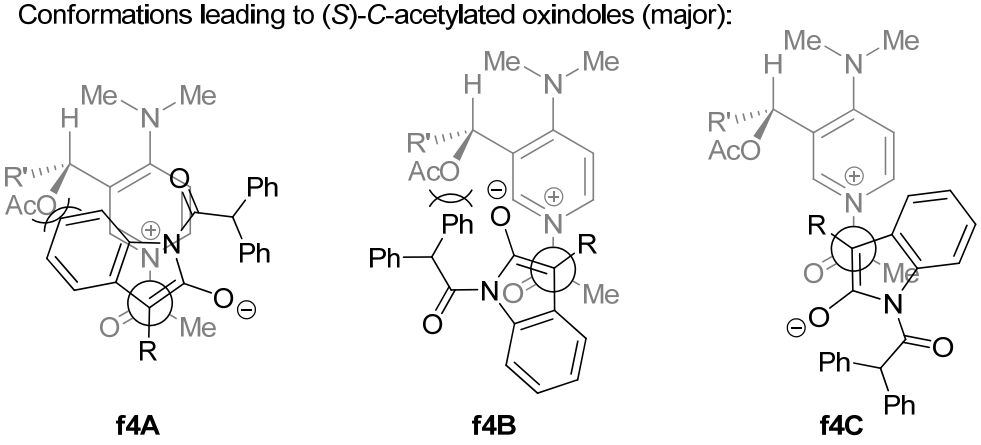


Using the known configurations of (*S*,*S*)-AcOLeDMAP (**14C**) and the 3-acetylated oxindole products **21A** and **23E**, a model for the stereoinduction was developed. The approach of the enolate of the ion pair intermediate to the *N*-acetyl pyridinium will occur from the less hindered face of the pyridinium, and the possible conformations of this approach are shown in Figure 2-4. Conformations shown in **f4A**, **f4B**, **f4D**, and **f4E** all encounter steric repulsion between the substrate and the benzylic acetate of the catalyst so these will be disfavored. Both **f4C** and **f4F** minimize this steric replusion and therefore are the likely conformations leading to the products. The approach shown in **f4C** should be favored over **f4F** as it minimizes the interaction between the bulky diphenylacetyl protecting group and the catalyst. The higher enantioselectivies observed with larger, extended nitrogen protecting groups results from an

increased steric repulsion between the catalyst and the protecting group, and this trend lends support for this model.

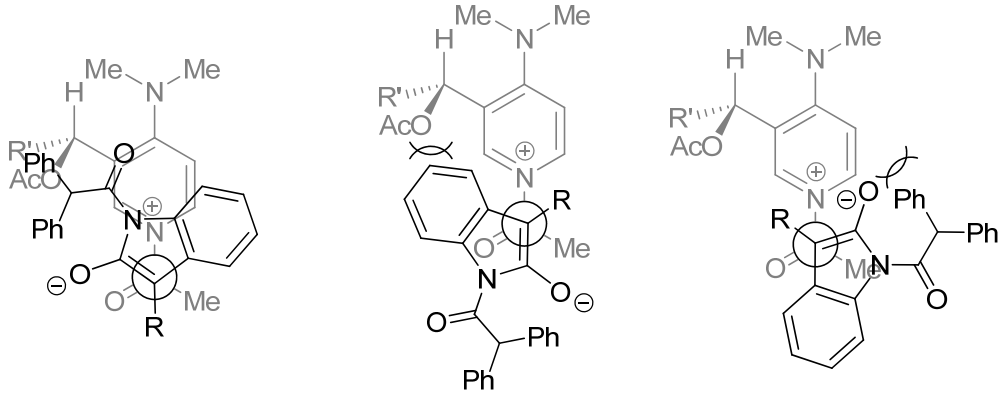
Figure 2-4. Proposed Model of Stereoinduction for Acetyl Migration.

Conformations leading to (*S*)-*C*-acetylated oxindoles (major):



f4A **f4B** **f4C**

Conformations leading to (*R*)-*C*-acetylated oxindoles (minor):

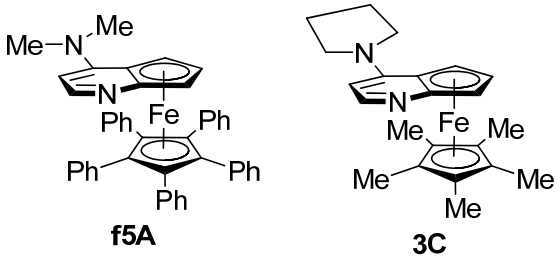


f4D **f4E** **f4F**

The commerically-available planar-chiral catalysts **f3A** and **3C**[16] were also evaluated for the rearrangement of the enol acetates (Figure 2-5). Dimethylaminopyridine derivative **f5A** was completely unreactive in the case of enol acetate **20Ca** in EtOAc at rt with only starting material apparent by TLC after 24 hours. Apparently, the reactivity of this catalyst for the rearrangement of oxindole-derived substrates is significantly less compared to the 3-substituted DMAP catalysts developed in our laboratories. This decrease in reactivity may be due to the substitution at the 2-position of the pyridine ring which has been shown to decrease the nucleophilicity of pyridine derivative or to excessive steric hindrance from the pentaphenylferrocenyl moiety. On the other

hand, pyrrolidinopyridine derivative **3C** allowed complete rearrangement within 45 minutes (EtOAc, rt), but the product **21Aa** was obtained in only 16% ee. This low enantioselectivity is not entirely surprising since each chiral catalyst has its own mode of stereoinduction and the optimized substrate and reaction conditions for one catalyst are not necessarily optimal for other catalysts. No attempt was made to optimize the migrating group or the conditions using **3C**. Unfortunately, we did not have access to the catalyst used by Fu in the previous studies on oxindole enol carbonates (**4D**) to conduct a direct comparison.

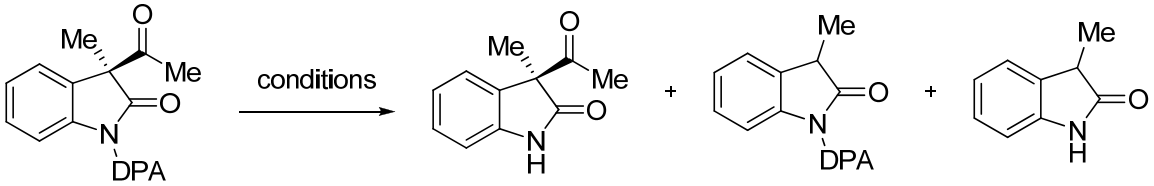
Figure 2-5. Commercially Available Planar-Chiral Catalysts.



f5A **3C**

Along with the greatly enhanced rate of reaction, the amide protected oxindole provided the opportunity for a more easily deprotected product than the *N*-methyl oxindoles examined by Fu. The substrate **21Aa** proved unreactive to acidic[35] and photochemical conditions,[36] so basic conditions were tested. Treatment of oxindole **21Aa** with methoxide resulted in extensive decomposition after one hour.[37] Even when the reaction was stopped after 1 minute, the major product was the deprotected and deacetylated oxindole **5C**. Neutral isopropanol was not nucleophilic enough to add into the amide carbonyl under mildly acidic or basic conditions. In contrast, isopropylamine was too nucleophilic and reacted unselectively with both the *C*-acetyl and *N*-diphenylacetyl groups at room temperature. The secondary diisopropyl amine was too hindered and gave slow conversion to the deprotected product, but diethylamine selectively cleaved the diphenylacetyl group to give oxindole **10A** in 75% yield under optimized conditions. Similarly, oxindole **21Ac** could be deprotected to yield **e7A** in 65% yield (equation 7).

Scheme 2-24. Deprotection of Rearranged Oxindole Product.

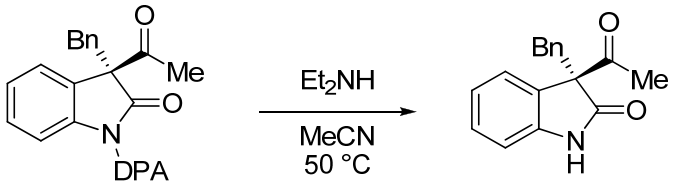


21Aa **10A** **20Ba** **5C**

Table 2-24. Deprotection of Rearranged Oxindole Product.

					Product Ratio[a]			
Entry	Nucleophile	Solvent	Temp	Time	**21Aa**	**10A**	**20Ba**	**5C**
1	NaOH/MeOH	THF	rt	1 h		decomposition		
2	NaOH/MeOH	THF	rt	1 min	--	--	1	9
3	*i*-PrOH, TsOH	toluene	reflux	20 h	9	--	1	--
4	*i*-PrOH, Et_3N	toluene	reflux	20 h	16	3	1	--
5	*i*-$PrNH_2$, Et_3N	toluene	rt	2 h	--	5	5	1
6	*i*-Pr_2NH, Et_3N	toluene	reflux	20 h	9	1	--	--
7	Et_2NH, Et_3N	toluene	reflux	20 h	--	16	1	3
8	Et_2NH	MeCN	60 °C	8 h		(75%)[b]		

[a] by NMR spectroscopy [b] isolated yield

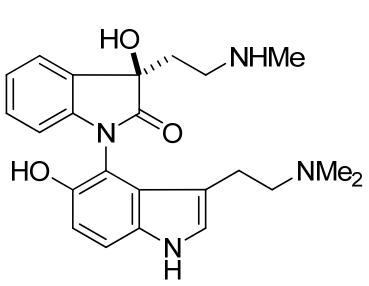


21Ac **e7A** (65%) (7)

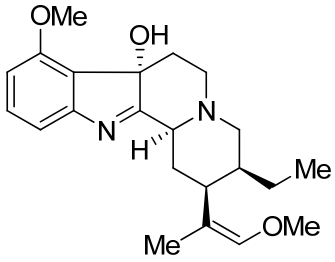
In addition to providing access to all-carbon quaternary oxindoles, the 3-acetyloxindoles potentially provide a route to 3-hydroxy-3-alkyl oxindole natural products such as the recently isolated arundaphine (**f6A**),[38] 7-hydroxymitragynine (**f6B**),[39] and paratunamide D (**f6C**).[40] Baeyer-Villiger oxidation[41] of *C*-acetyl oxindole **21Aa** to *C*-acetoxyl oxindole **e8A** provides a route to enantiomerically enriched 3-hydroxy-3-alkyloxindoles. The *m*-CPBA oxidation of the hindered ketone **21Aa** proceeded selectively to form ester **e8A**, but the reaction was slow. Addition of triflic acid[42] slowed the rate of oxidation, but under buffered conditions (bicarbonate added)[43] the rate of oxidation was accelerated and upon refluxing the reaction, good conversion to ester **e8A** occurred in 8 h (equation 8). The product of this oxidation showed no loss in enantiomeric excess as expected from the stereospecific oxidation. Because the Bayer-Villiger oxidation is not

possible with a *C*-carboxylated oxindole, the *C*-acetylated oxindole expands the scope of enantiocontrolled quaternary carbon synthesis.

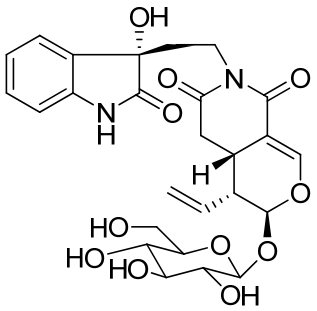
Figure 2-6. 3-Hydroxy-3-Alkyl Oxindole Derived Natural Products.



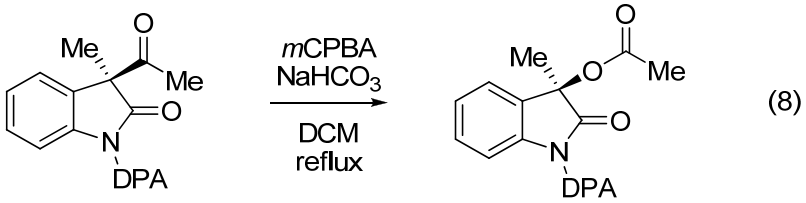
Arundaphine
f6A



7-Hydroxymitragynine
f6B



Paratunamide D
f6C



(8)

21Aa
(88% ee)

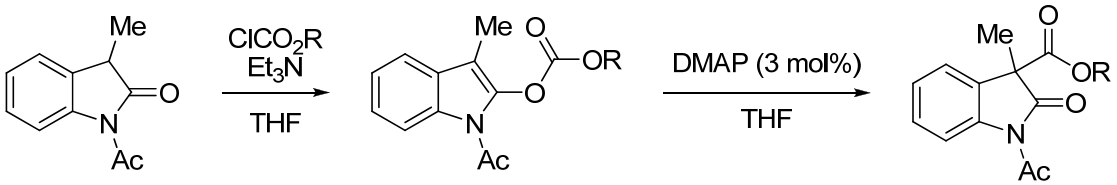
e8A
74% (87% ee)

Chiral-nucleophile catalyzed rearrangements of oxindole-derived enol carbonates.

In the previous work with chiral catalysts by Fu[18] and Scott Shaw[23] the migrating group has been alkoxycarbonyl, so it remained to be seen whether the enhancement of reactivity of the oxindole-derived enol acetates was due only to the amide protecting group or to a combination of the protecting group and the acetyl migrating group. Therefore several acetyl protected enol carbonates were synthesized from *N*-acetyl-3-methyloxindole (**9C**).[21] Interestingly, the formation of enol carbonates is much more selective for the desired *O*-functionalization than is the formation of the analogous enol acetates with only *O*-carboxylation occurring in THF (compared to 3:1 ratio of *O*- to *C*-acetylated oxindoles, Table 2-19, entry 6). Solvoylsis of acetyl chloride in alcoholic solvents has been shown to occur via ionization to an acylium ion whereas chloroformates undergo solvolysis via an addition-elimination mechanism.[44] The lower selectivity in the acetylation of oxindoles compared to the carboxylation may be due to the ionization of

acetyl chloride resulting in more *C*-acetylation. Once the enol carbonates were obtained, the DMAP-catalyzed rearrangements were tested. Under the same reaction conditions used for the acetyl rearrangements with DMAP, the alkoxycarbonyl rearrangements occurred readily to give rearranged products with a variety of substituted carboxylates (Table 2-25). The reaction slowed when the alkoxycarbonyl group was α-branched (**25Ae**), but significant reactivity was still observed. In light of the slow rearrangement of carbamate-protected **9Bb-d** (Table 2-13), it is apparent that the enhanced reactivity of the amide-protected indolyl enol carbonates **9Ba**,**h-l** and **25A** as compared to *N*,*O*-di-alkoxycarbonyl oxindoles studied by Shaw[23] is primarily due to the amide protecting group and not the migrating group.

Scheme 2-25. Synthesis and Rearrangement of *N*-Acetyl Oxindole-Derived Enol Carbonates.



9C **25A** **25B**

a: R = Ph (81%)
b: R = Me (30%)
c: R = Et (73%)
d: R = Bn (59%)
e: R = *i*-Pr (53%)

Table 2-25. Synthesis and Rearrangement of *N*-Acetyl Oxindole-Derived Enol Carbonates.

Entry	R	Time	Result[a]
1	Ph (**a**)	10 min	>95%
2	Me (**b**)	20 min	>95%
3	Et (**c**)	20 min	>95%
4	Bn (**d**)	30 min	>95%
5	*i*-Pr (**e**)	20 min	69%

[a] Percent conversion ^{1}H NMR spectroscopy

The enantioselective rearrangement occurred readily when enol carbonate **25Aa** was exposed to AcOLeDMAP. Thus, substrate **25Aa** gave product *C*-carboxyl oxindole **25Ba** in low enantiomeric excess contaminated with decarboxylated oxindole **9C** (equation 9). Surprisingly, analysis of catalyst recovered from the reaction using ^{1}H NMR revealed small signals for AcOLeDMAP, but the major signals in the spectrum belonged to a new DMAP derivative missing the signals for the acetate and the amide protons while the benzylic proton had shifted upfield ~1

ppm. In addition, the molecular ion in the mass spectrum corresponded to the loss of HOAc from AcOLeDMAP. Later isolation of this decomposition product allowed characterization and structural assignment as the oxazoline **f7A** based on comparison of chemical shifts with similar oxazoline structures in the literature (Figure 2-7).[45] A significant NOE between the benzylic hydrogen and the *tert*-butyl group and the absence of a strong NOE between H_a and H_b support the formation of the *trans*-oxazoline as drawn. Oxazoline formation had not been observed in any of the acetyl rearrangements, so this process is associated with the change from an acyl to a carboxyl migrating group.

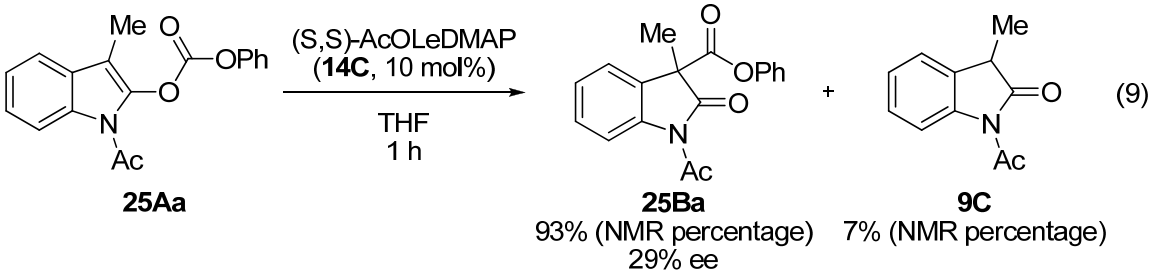
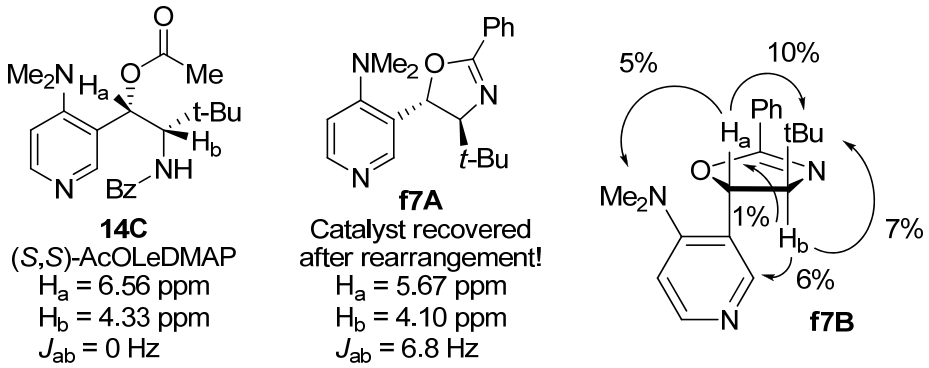


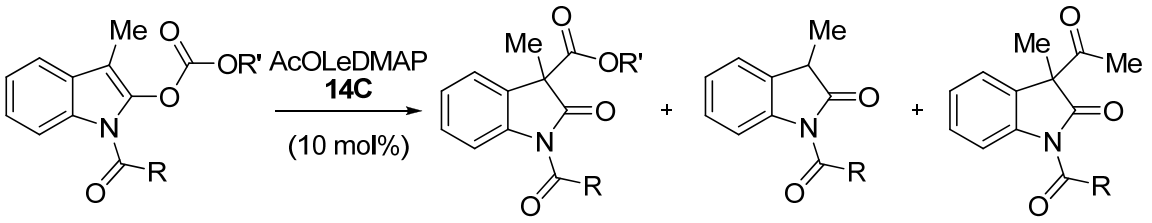
Figure 2-7. Recovered Catalyst's Structure and NOE Data.



In attempts to prevent the catalyst decomposition, several *O*-carboxylated substrates were tested under various reaction conditions. The less reactive enol carbonates derived from aliphatic chloroformates (**25Ab**-**e**) all gave complete catalyst decomposition within the time scale of the rearrangement (Table 2-26, entries 1-4). Interestingly, a small amount of *N*,*C*-diacetylated oxindole **9Da** was also formed during these rearrangements apparently derived from incorporation of the acetyl group of the catalyst (~90% based on catalyst loading). With the more reactive phenyl enol carbonate **25Aa**, the rearrangement was significantly faster and the catalyst

recovered was not completely decomposed (entry 5). The temperature of the rearrangement was lowered to determine whether the catalyst decomposition could be suppressed without hindering the rearrangement. The decomposition did slow at -10 °C, but so did the rate of rearrangement (entries 6 and 7). At -40 °C the percentage of decomposition was much lower relative to the percentage of rearranged product, but at all temperatures tested the catalyst decomposition could not be entirely suppressed (entries 8 and 9). Since the diphenylacetyl protecting group accelerated the rate of rearrangement in the acetyl series, the benzyl enol carbonate of the diphenylacetyl protected oxindole **26A** was synthesized (equation 10) and tested. Although the rate of rearrangement was slightly increased, the catalyst decomposition was still competitive (entry 10).

Scheme 2-26. Catalyst Decomposition as a Function of Oxindole Structure.



25A (R = Me)
26A (R = $CHPh_2$)

25B (R = Me)
26B (R = $CHPh_2$)

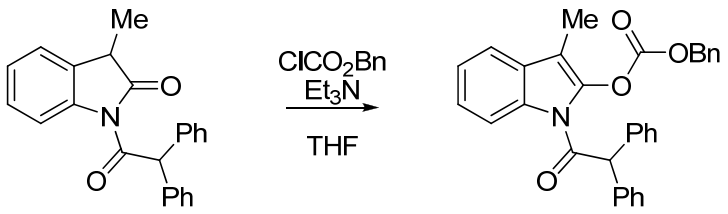
9C (R = Me)
20Ba (R = $CHPh_2$)

9Da (R = Me)
9Di (R = $CHPh_2$)

Table 2-26. Catalyst Decomposition as a Function of Oxindole Structure.

Entry	R	R'	Solvent, Temp	Time	Result[a]				
					25A 26A	**25B 26B**	**9C 20Ba**	**9D**	% catalyst decomposition
1	Me	Me	*t*-amyl alcohol, rt	5 h	--	89	3	8	quant.
2	Me	Et	*t*-amyl alcohol, rt	5 h	--	88	4	8	quant.
3	Me	Bn	*t*-amyl alcohol, rt	5 h	--	84	6	10	quant.
4	Me	*i*-Pr	*t*-amyl alcohol, rt	5 h	--	86	5	9	quant.
5	Me	Ph	THF, rt	1 h	--	93	7	--	84%
6	Me	Ph	THF, -10 °C	5 min	91	9	--	--	5%
7	Me	Ph	THF, -10 °C	25 min	71	29	--	--	8%
8	Me	Ph	THF, -40 °C	2 h	88	12	trace	--	6%
9	Me	Ph	THF, -40 °C	25 h	6	94	trace	--	20%
10	Ph_2CH	Bn	$CDCl_3$, rt	2 h	33	62	5	--	80%

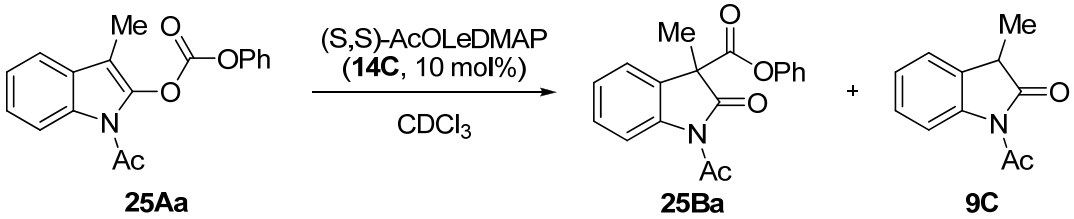
[a] Percent conversion by ^1H NMR spectroscopy



20A **26A** (74%) (10)

When the reaction was monitored by ^{1}H NMR spectroscopy, it was observed that the rearrangement and catalyst decomposition occurred at similar rates in the phenoxycarbonyl migration. After only 10 minutes, 50% of the rearranged oxindole **25Ba** was observed. Simultaneously, ~35% of the catalyst had decomposed and the decarboxylated oxindole **9C** was also observed (~100% based on catalyst loading).

Scheme 2-27. Monitoring Catalyst Decomposition over Time.



25Aa **25Ba** **9C**

Table 2-27. Catalyst Decomposition over Time with Phenoxycarbonyl Migrating Group.

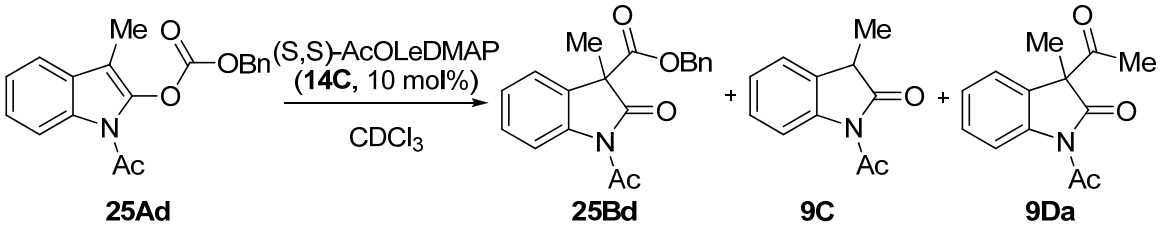
		Result[a]			
Entry	Time (min)	**25Aa**	**25Ba**	**9C**	catalyst decomposition
1	10	45	51	4	35%
2	30	14	80	6	58%
3	60	4	89	7	68%

[a] % by ^{1}H NMR spectroscopy

A similar analysis of the rearrangement of enol carbonate **25Ad** was conducted. The rearrangement of the benzyloxycarbonyl migrating group is much slower than the phenoxycarbonyl migrating group, but the decomposition of the catalyst **14C** occurred at a similar rate in both cases (Table 2-27, entry 2 and Table 2-28, entry 1). As seen with enol carbonate **25Aa**, the decarboxylated product **9C** formed at a similar rate compared to the decomposition of the catalyst. The additional *C*-acetylated product **9Da** was not detected until after the catalyst had completely decomposed. Therefore, the *C*-acetylated oxindole **9Da** does not form from direct attack of the enolate **29B** of the ion pair (**29A**+**B**) at the acetate carbonyl group of the

catalyst **29A** (Scheme 2-29). The formation of **9Da** could occur by the addition of acetate anion to the acyl pyridinium cation of **29C** to produce mixed anhydride **29D**. Nucleophilic attack by the catalyst at the acetyl carbonyl of this mixed anhydride would then form an acetylated pyridinium (**29E**) that could react with an oxindole to form **9Da**.

Scheme 2-28. Catalyst Decomposition over Time with Benzyloxycarbonyl Migrating Group.



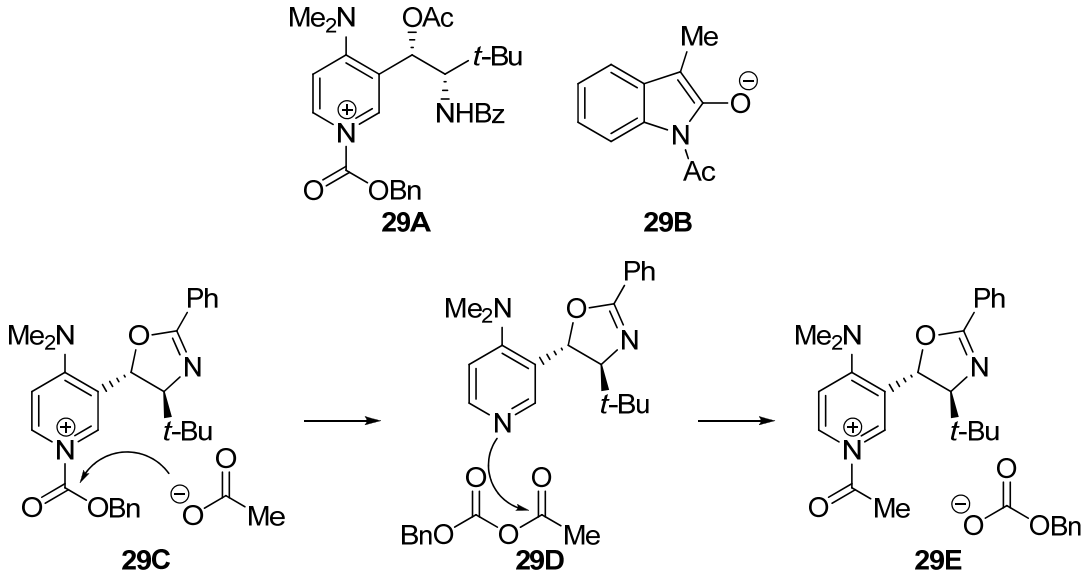
25Ad **25Bd** **9C** **9Da**

Table 2-28. Catalyst Decomposition over Time with Benzyloxycarbonyl Migrating Group.

		Result[a]				
Entry	Time	**25Ad**	**25Bd**	**9C**	**9Da**	catalyst decomposition
1	35 min	78	16	6	--	74%
2	1 h 30 min	67	27	6	--	94%
3	3 h 40 min	50	41	7	3	>95%

[a] % by ^{1}H NMR spectroscopy

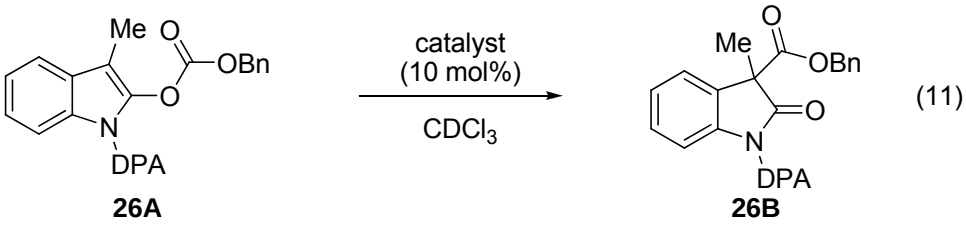
Scheme 2-29. Interchange of Acetyl and Carboxyl Pyridinium Salts.



29A **29B** **29C** **29D** **29E**

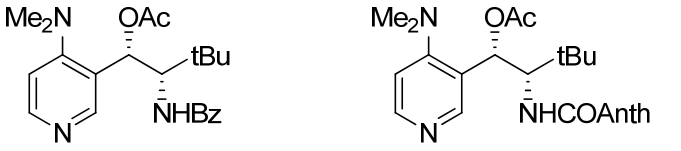
Since modifications on the oxindole substrate could not prevent catalyst decomposition, the catalyst itself was modified. As shown earlier, when AcOLeDMAP (**14C**) was used to catalyze the rearrangement of benzyloxy enol carbonate **26A,** 32% conversion to the *C*-

carboxylated product **26B** was observed and 46% of the catalyst had decomposed within 30 minutes. Protonated oxindole, **20Ba**, was also observed by NMR, suggesting that the enolate of the ion pair may be deprotonating the acidic amide proton of the catalyst **14C**. It was hypothesized that a more hindered amide on the catalyst could minimize access to the acidic amide proton, so the anthracenyl catalyst **f8A** (previously synthesized by Scott Shaw)[30] was tested. Unfortunately the increased steric hindrance around the amide did not prevent decomposition of the catalyst to an oxazoline, and it severely slowed the rate of rearrangement with only 24% conversion after 2.5 h.



26A **26B** (11)

Figure 2-8. Comparison of Decomposition of Amide Protected Catalysts.



14C
30 min
32% conversion
46% catalyst decomposition

f8A
2 h 35 min
24% conversion
24% catalyst decomposition

Several new catalysts with different side-chain amino functionalities were synthesized in attempts to prevent the oxazoline formation. Sulfonamide-derived catalyst **e12B** was synthesized by the addition of 3-lithio-DMAP to the tosyl protected amino aldehyde[46] **e12A** followed by acetylation (equation 12). When this new catalyst (**e12B**) was tested in the rearrangement, it catalyzed the rearrangement of **26A** at a slower rate (only 9% conversion after 20 min) than AcOLeDMAP (**14C**), and **e12B** readily decomposed during the rearrangement. In this case, the nitrogen atom of the sulfonamide directly displaced the acetoxy group to form *cis*-aziridine **f9A**. This structural assignment was supported by the loss of acetate and sulfonamide proton signals and the ~2.2 ppm upfield shift of the benzylic proton in the ^{1}H NMR spectrum of the reisolated

catalyst. A significant NOE between H_a and H_b and the small J_{ab} coupling constant led to the assignment of the *cis* configuration of the aziridine (Figure 2-9).

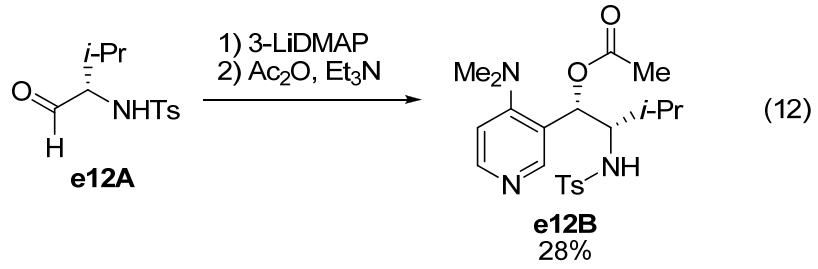
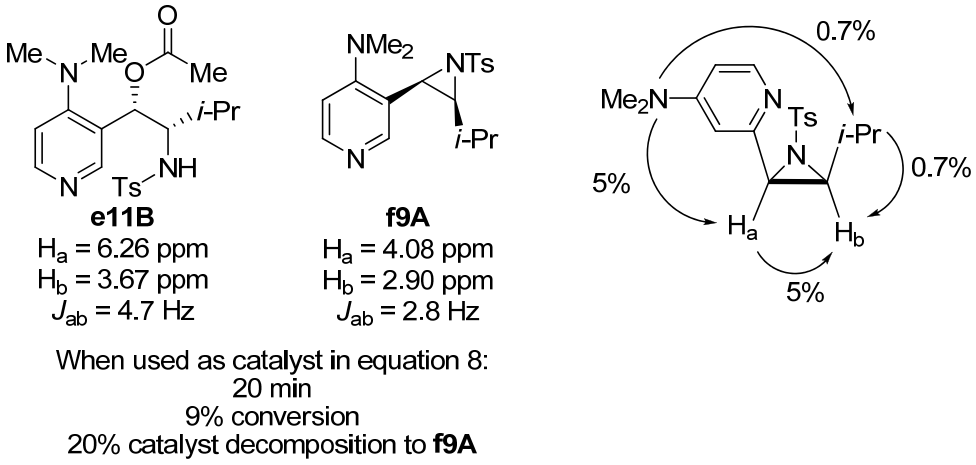


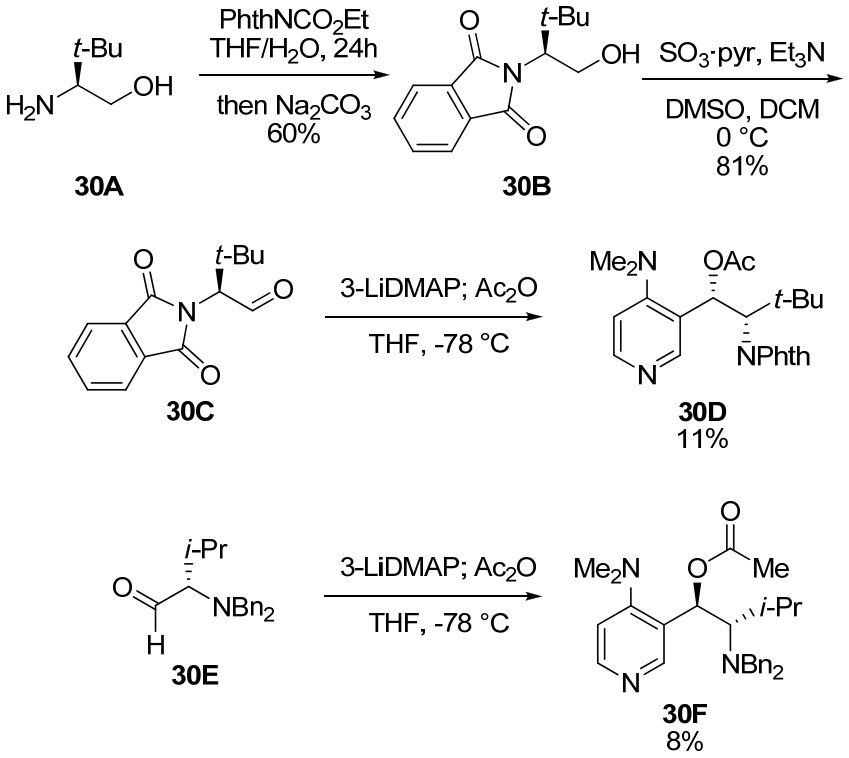
Figure 2-9. Tosyl-Protected Catalyst Decomposition.



Catalysts containing fully substituted amine side chains were targeted in order to prevent these unwanted cyclizations (Scheme 2-30). The synthesis of a phthalimide-protected catalyst commenced with the protection of amino alcohol **30A** followed by oxidation to give aldehyde **30C**. Addition of 3-lithio-DMAP into the aldehyde followed by quenching the alkoxide with acetic anhydride afforded phthalimide-protected catalyst **30D**, which lacked an acidic amide proton. However when **30D** was used to catalyze the rearrangement of the enol carbonate **26A**, the catalyst signals partially disappeared from the NMR spectrum and the mass spectrum showed a molecular ion of significantly higher molecular weight. No attempt was made to identify this undesired decomposition pathway. In an alternative approach, non-chelation controlled addition of 3-lithio-DMAP to dibenzyl-protected amino aldehyde **30E** yielded catalyst **30F**, tentatively assigned the *anti*-configuration.[47] This catalyst did not decompose during the rearrangement of **26A**, but the rearrangement was slower and product **26B** was obtained in low enantiomeric

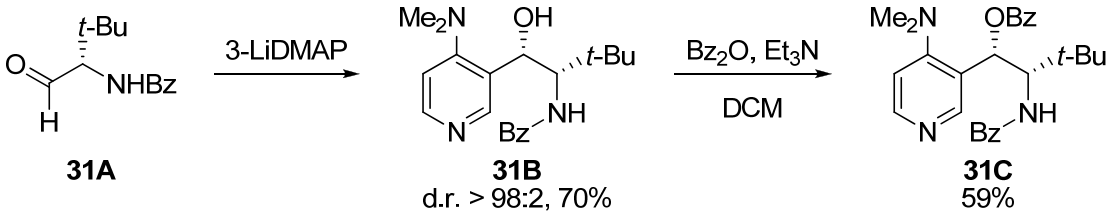
excess. Other catalysts with tertiary amide side chains could not be readily prepared by amide alkylation of AcOLeDMAP (**14C**), so attention was turned to the protecting group at the benzylic alcohol oxygen.

Scheme 2-30. Synthesis of Chiral Catalysts Without a Free N-H.



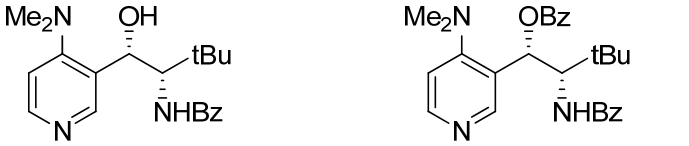
Following the original synthesis of AcOLeDMAP, the free alcohol **31B** was isolated as a single diastereomer in 70% yield (Scheme 2-31). While catalyzing the rearrangement of **26A**, the free alcohol **31B** not only decomposed during the reaction but an additional new DMAP-containing byproduct was formed, likely from carboxylation of the free alcohol, but it was not isolated. If the decomposition of the original catalyst **14C** occurred by addition of a nucleophile to the acetate carbonyl of the catalyst, then a more hindered ester might minimize this pathway. So, alcohol **31B** was then protected as a benzoate ester under standard benzoylation conditions to give catalyst **31C** (Scheme 2-31). Unfortunately, the benzoate ester reduced the reactivity of the catalyst without preventing decomposition to the oxazoline **f7A** during the rearrangement of **26A**.

Scheme 2-31. Chiral Catalysts with a Free Alcohol or Benzoate Ester.



31A | **31B** d.r. > 98:2, 70% | **31C** 59%

When used to catalyze the rearrangement of enol carbonate **26A**:

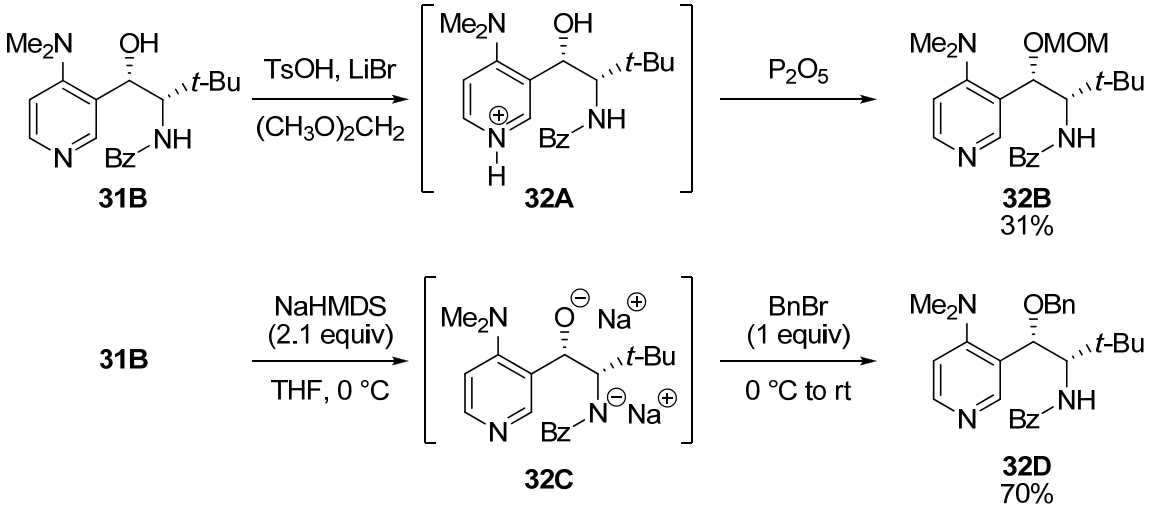


31B
30 min
35% conversion
17% catalyst decomposition
+ 33% of a new DMAP-containing molecule

31C
30 min
17% conversion
31% catalyst decomposition

A potentially less labile ether-protected catalyst was then synthesized and tested. Special care was needed for selective *O*-alkylation of the alcohol **31B** since the nucleophilic pyridine subunit can also be alkylated. Therefore, the pyridine subunit was temporarily protected by *in situ* protonation (**32A**) with tosic acid in dimethoxymethane (Scheme 2-32). The hindered alcohol was not alkylated under these MOM ether-forming conditions,[48] but MOM ether-protected catalyst **32B** formed upon addition of phosphorous pentaoxide albeit in low yield.[49] No decomposition of the MOM-protected catalyst (**32B**) was observed during the rearrangement of enol carbonate **26A**, and the rearranged product **26B** was obtained cleanly in 66% ee in 2 h at rt.

Scheme 2-32. Synthesis of Ether-Protected Amino Alcohol Derived Catalysts.

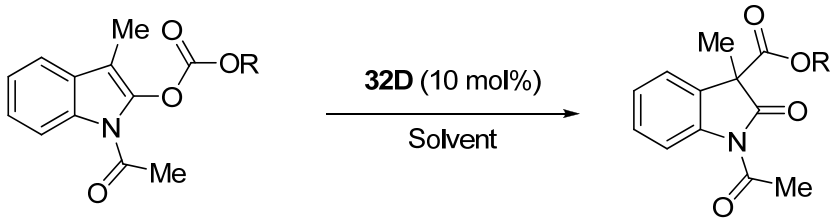


In light of the low yield of ether-protected catalyst **32B**, an alternative ether-protected catalyst was explored. Deprotonation of both the amide and the alcohol of **31B** might be expected to increase their relative nucleophilicity over that of the pyridine nitrogen. Indeed, the dianion **32C** was generated upon treatment with 2.1 equivalents of NaHMDS (Scheme 2-32). Selective trapping with 1 equivalent of benzyl bromide produced the benzyl protected catalyst **32D** is 70% yield. The benzyl-protected catalyst **32D** catalyzed the rearrangement of enol carbonate **26A** without decomposing, as also seen with the MOM-protected catalyst **32B**, and the product enol carbonate **26B** was obtained cleanly in 61% ee in 3 h at rt. The nature of the ether-protecting group in this limited sampling (**32B** versus **32D**) had little effect on either the rate of the enol carbonate rearrangement or the enantioselectivity, so the more readily available benzyl-protected catalyst **32D** was used for further optimization of this rearrangement. The rearrangement of enol acetate **20Ca** with catalyst **32D** produced the rearranged **21Aa** in 77% ee (EtOAc, 0 °C, 3h) as shown by Eoghan McGreevy. Although this new catalyst is less enantioselective than is AcOLeDMAP (**14C**) in the corresponding rearrangement, the change has not dramatically affected the chirotopic environment of the catalyst as both give the same major enantiomer of the product.

Several of the *N*-acetyl-protected oxindole-derived enol carbonates were screened for enantioselectivity with the new benzyl ether catalyst (**32D**). Oxindole-derived phenyl enol

carbonate **25Aa** rearranged with minimal enantioselectivity (Table 2-33, entry 1). Slightly higher enantiomeric excesses were obtained with the alkoxycarbonyl migrating groups of **25Ab** and **25Ad**, but little difference was seen in the % ee between the two different migrating groups tested (33 and 40% ee, Table 2-33, entries 2 and 3). Unfortunately the modest enantiomeric excess obtained with substrate **25Ad** was not significantly improved in any other solvent tested.

Scheme 2-33. Rearrangement of *N*-Acetyl Oxindole Enol Carbonates with Catalyst **32D**.



25A **25B**

Table 2-33. Rearrangement of *N*-Acetyl Oxindole Enol Carbonates with Catalyst **32D**.

Entry	Solvent	Substrate	R	%ee
1	EtOAc	**25Aa**	Ph	5
2	EtOAc	**25Ab**	Me	33
3	EtOAc	**25Ad**	Bn	40
4	Toluene	**25Ad**	Bn	40
5	Et_2O	**25Ad**	Bn	48
6	THF	**25Ad**	Bn	42
7	DCM	**25Ad**	Bn	35

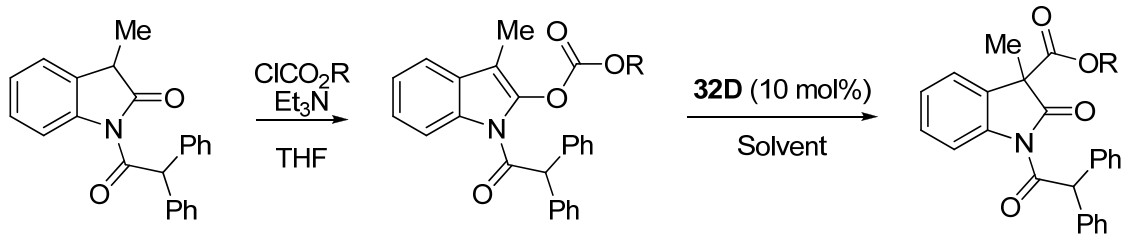
Since all the rearrangements of acetyl-protected enol carbonates were less enantioselective than the rearrangement of diphenylacetyl-protected enol carbonate **26A**, further studies focused on the diphenylacetyl-protected enol carbonates. In this system, the enantioselectivity of the rearrangement had a much greater dependence on the solvent. The rearrangement occurred with poor enantioselectivity in either nonpolar solvents, such as toluene and ether, or in polar aprotic oxygenated solvents (Table 2-34, entries 1-4). In halogenated solvents, the rearrangement was more selective with chloroform giving the superior selectivity. This selectivity could be increased by lowering the temperature, but the rate of the reaction decreased. The hindered *tert*-amyl alcohol also gave rearrangement with moderate selectivity. However, the highly crystalline enol carbonate **26A** was poorly soluble in the alcohol, reducing the rate of rearrangement.

Table 2-34. Solvent Effect on the Rearrangement of Enol Carbonate **26A** with Catalyst **32D**.

Entry	Solvent	Time	% ee
1	toluene	6 h	5
2	Et_2O	3 h	8
3	THF	3 h	14
4	EtOAc	3 h	25
5	DCM	3 h	35
6	*t*-amyl alcohol	6 h	60
7	$CHCl_3$	3 h	61
8	$CHCl_3$ (-20 °C)	24 h	74

While changing the solvent and temperature of the reaction did increase the enantioselectivity to 74% ee, this was the best result observed with the benzyloxycarbonyl migrating group. Therefore the effect of the migrating group was examined. Methyl enol carbonate **35Aa** rearranged with poor enantioselectivity (Table 2-35, entry 1) which was surprising since the very similar acetyl substrate **20Ca** was much more enantioselective (77% ee). The rearrangement of the bulky trichloro-*tert*-butyl enol carbonate **35Ab** and the phenyl enol carbonate **35Ac** were similarly unselective (entries 2-3). On the other hand, extending the steric bulk of the migrating group further away from the carbonate increased the stereoselectivity of the rearrangement (**35Ad-f**, entries 4-7). The rearrangement of the benzyl enol carbonate **26A** was still the most enantioselective, so substituted benzyloxycarbonyl migrating groups were examined. The electron-deficient *para*-nitrobenzyloxycarbonyl migrating group (**35Ah**) rearranged in a shorter time-frame but with slightly lower enantiomeric excess. This more reactive enol carbonate allowed the rearrangement to occur within 16h at -40 °C but the enantiomeric excess did not increase significantly. Fortunately, the rearrangement of the larger (1-naphthyl)methyl enol carbonate (**35Ai**) was more enantioselective (71% ee, entry 12). This enantioselectivity could be further increased to 90% ee by lowering the temperature to -20 °C.

Scheme 2-35. Rearrangement of *N*-Diphenylacetyl Oxindole Enol Carbonates with Catalyst **32D**.



20Ba **35A** **35B**

Yields for formation of **35A**

a: R = Me (75%)
b: R = $Cl_3C(Me)_2C$ (32%)
c: R = Ph (88%)
d: R = *i*-Bu (82%)
e: R = Cl_3CCH_2 (58%)
f: R = Et (73%)
g: R = Allyl (78%)
h: R = *p*-NO_2Bn (65%)
i: R = (1-Naphthyl)CH_2 (68%)

Table 2-35. Rearrangement of *N*-Diphenylacetyl Oxindole Enol Carbonates with Catalyst **32D**.

Entry	R	Solvent	Time	% ee
1	Me	$CHCl_3$	4 h	12
2	$Cl_3C(Me)_2C$	$CHCl_3$	6 h	18
3	Ph	$CHCl_3$	2 h	32
4	*i*-Bu	$CHCl_3$	4 h	41
5	Cl_3CCH_2	$CHCl_3$	2 h	45
6	Et	$CHCl_3$	4 h	48
7	Allyl	$CHCl_3$	4 h	52
8	Bn	$CHCl_3$	3 h	61
9	Bn	$CHCl_3$ (-20 °C)	24 h	74
10	*p*-NO_2Bn	$CHCl_3$	2 h	55
11	*p*-NO_2Bn	$CHCl_3$ (-40 °C)	16 h	67
12	(1-Naphthyl)CH_2	$CHCl_3$	4 h	71
13	(1-Naphthyl)CH_2	$CHCl_3$ (-20 °C)	24 h	90

After optimizing solvent and temperature for the enol carbonate rearrangement reactions, several different 3-substituted oxindole-derived enol carbonates **36A**-**36D** were prepared and tested (Scheme 2-36). As seen before in the acetyl rearrangements, the carboxyl rearrangements were readily extended to other *C*-3 alkyl substrates **36A** and **36B** to afford 3,3-disubstituted oxindoles **36E** and **36F** with high enantiomeric excess. The *C*-3 phenyl substrate **36C**, which in the acetyl rearrangements gave product in only 66% ee, rearranged with 90% ee within 2 h. The increased reactivity of this oxindole was attributed to the additional stabilization of the enolate intermediate by the phenyl substituent. A similar rate enhancement was seen in the ring-brominated substrate **36D** which rearranged in 4 h to oxindole **36H** with 90% ee. In this

case, the enhanced reactivity is probably due to the electron-withdrawing effect of bromine on enolate stability.

Scheme 2-36. Synthesis and Rearrangement of Optimized Enol Carbonates with Catalyst **32D**.

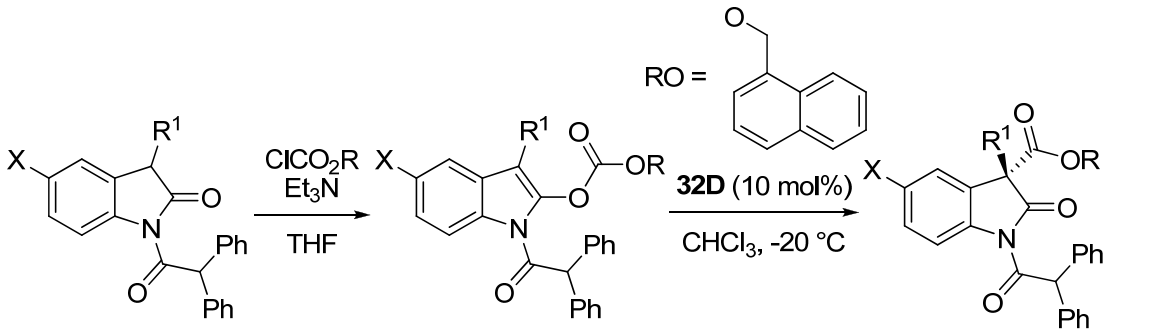
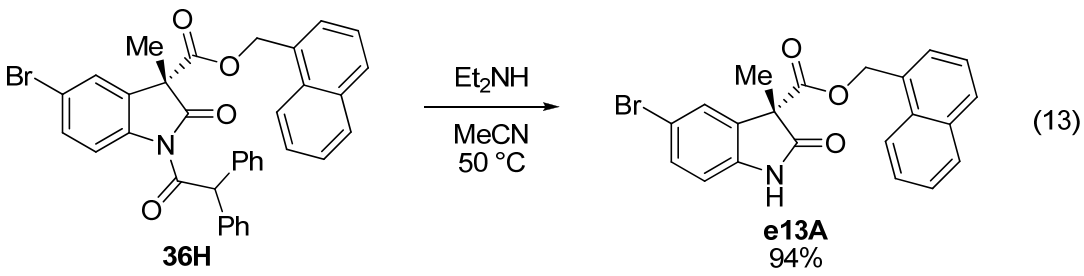


Table 2-36. Synthesis and Rearrangement of Optimized Enol Carbonates with Catalyst **32D**.

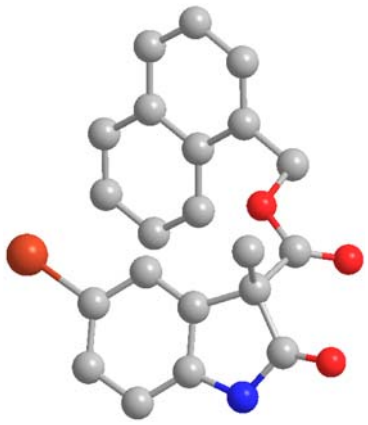
Entry	Substrate	R^1	X	Time	Yield (%)	%ee
1	**35Ai**	Me	H	22.5 h	91	90
2	**36A**	Bn	H	22.5 h	98	92
3	**36B**	$CH_2CH_2OTBDPS$	H	22.5 h	99	94
4	**36C**	Ph	H	2 h	98	91
5	**36D**	Me	Br	5 h	92	90

The brominated oxindole **36H** was used to determine the absolute stereochemistry of the carboxyl rearranged products. X-Ray quality crystals of oxindole **36H** could not be grown, so the nitrogen was deprotected using the optimized deprotection conditions from the *C*-acetylated oxindoles. Thus, treating oxindole **36H** with a warm solution of diethylamine in acetonitrile afforded the deprotected oxindole **e13A** in 94% yield (equation 13). A single recrystallization of oxindole **e13A** upgraded the enantiomeric excess form 90% ee to 99% ee, and crystals were grown from the upgraded material. X-Ray crystallographic analysis revealed the absolute configuration of oxindole **e13A** to be (*S*) by anamolous dispersion (Figure 2-11). Given the same sign of optical rotation (+) for all of the *C*-carboxylated oxindoles, the absolute configuration of the other carboxyl migration products was assigned to be (*S*) by analogy.



(13)

Figure 2-10. X-Ray Crystal Structure of oxindole **e13A**.

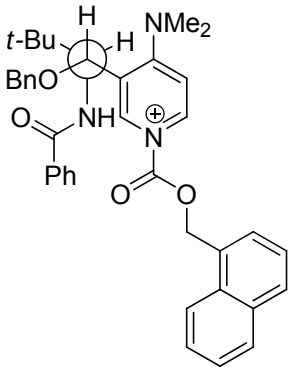


Given the opposite signs of optical rotation and the crystal structures of *C*-acetylated oxindole **23E** (Figure 2-3, pg 60) and *C*-carboxylated oxindole **e13A** (Figure 2-10), the carbonyl groups have been delivered to opposite faces of the oxindole enolate. Using the chiral catalysts **14C** and **32D**, the acetyl group is delivered to the *re* face of the oxindole enolate to form the (*S*)-*C*-acetylated product **21A**. In contrast, chiral catalyst **32D** delivers the carboxyl group to the *si* face of the enolate to form the (*S*)-*C*-carboxylated oxindoles **36E-H**. The absolute configuration of both products is (*S*) due to a change in priority of the substituents in the carboxyl migration products.

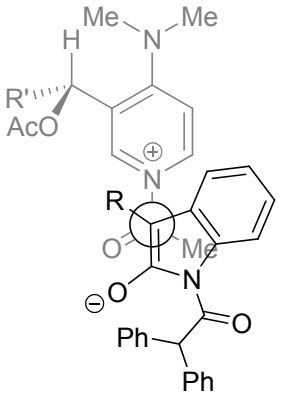
Analysis of the possible conformations leading to the carboxyl migration product required consideration of the rotamers around the pyridinium-carbonate bond (Figure 2-11). The rotamer with the (1-naphthyl)methoxycarbonyl group directed towards the catalyst sidechain (**f11B**) is disfavored compared to the rotamer with the bulky alkoxy group directed away from the catalyst sidechain (**f11A**) due to a steric repulsion between the napthyl and the benzamide subunits of the pyridinium ion, so rotamer **f11A** was used for further evaluations. The two enolate approach conformations, **f4C** and **f4F** (pg. 61, also in Figure 2-11), which minimize catalyst/enolate steric

repulsions in the acetyl migration series were also considered for the carboxyl migrations. Although **f4C** is the favored approach for the oxindole in the acetyl migrations, the similar approach, **f11C**, for the carboxyl migration series results in a destabilizing steric repulsion between the diphenylacetyl group on the oxindole nitrogen and the naphthyl subunit of the carboxyl migrating group. In contrast, the approach depicted in **f11D** minimizes the steric repulsion between the diphenylacetyl and the napthyl groups and therefore becomes the favored approach.

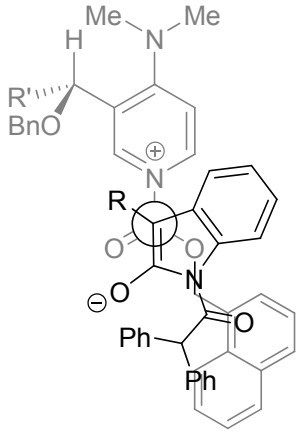
Figure 2-11. Proposed Model of Stereoinduction for Carboxyl Migration.



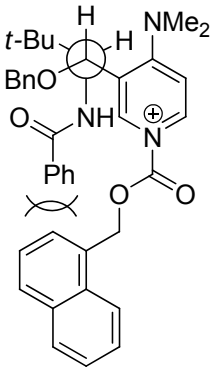
f11A



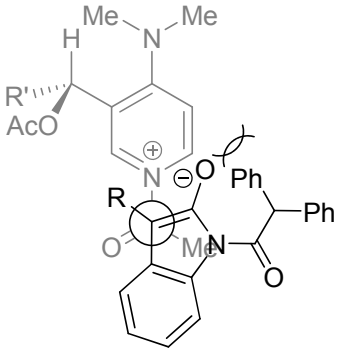
f4C



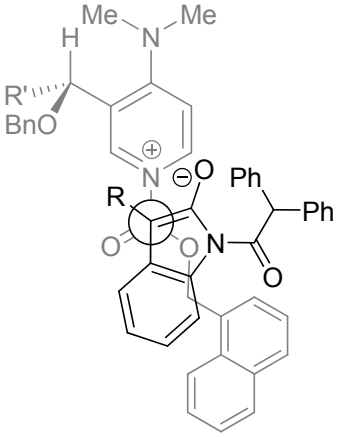
f11C
Conformation leading to (*R*)-*C*-carboxylated oxindoles (minor)



f11B

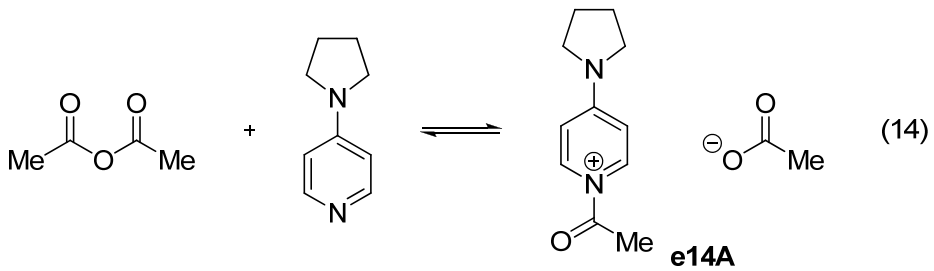


f4F



f11D
Conformation leading to (*S*)-*C*-carboxylated oxindoles (major)

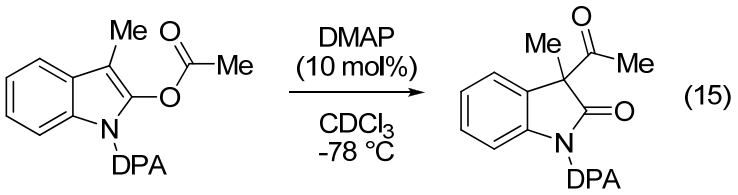
In an attempt to determine why AcOLeDMAP **14C** decomposes during the rearrangement of enol carbonates but not enol acetates, low temperature NMR spectra of enol acetate **20Ca** and enol carbonate **26Aa** on exposure to DMAP were recorded (equations 14 and 15). Although DMAP and 4-pyrrolidinopyridine do not form appreciable amounts of pyridinium salts with acetic anhydride at room temperature, Steglich and Holfe reported that acylated pyridinium salt **e14A** could be observed by NMR at low temperatures (equation 14).[50] As the temperature decreased, the equilibrium began to shift toward the enthalpically favored pyridinium salt **e14A** (estimated to be 25 kJ/mol more stable than the starting materials). No evidence of ion pair formation was observed by ^{1}H NMR spectroscopy for either **20Ca** or **35Aa** + DMAP at -50 °C even though significant conversion to the *C*-functionallized products had occurred. However, upon freezing the chloroform solutions at -78 °C, in an attempt to halt the course of the rearrangement, a deep purple color developed from the enol carbonate **35Aa** + DMAP frozen solution (Figure 2-12b) while the enol acetate **20Ca** + DMAP frozen solution (Figure 2-12a) was white. Upon thawing the solution, the color disappeared and the NMR spectra revealed only rearranged products and DMAP. In the related DMAP catalyzed rearrangements of benzofuranone-derived enol carbonates a purple color was associated with the formation of the ion pair intermediate. Although the formation of the purple color in the frozen enol carbonate rearrangement is not concrete evidence for the existence of the ion pair, these experiments may provide clues to the difference between the enol carbonate and enol acetate systems. If the color does in fact represent the ion pair **f13A**, the formation of this color in the presence of enol carbonate but not enol acetate suggests that this ion pair is more stable than the corresponding enol acetate ion pair. This may lead to a longer lifetime of the intermediate **f13A** (although the concentration may be too dilute to be observed by NMR) allowing for catalyst decomposition pathways to occur.



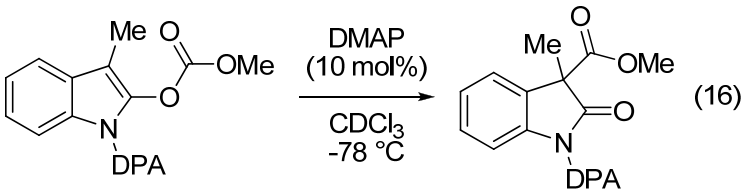
e14A (14)

Table 2-37. Temperature Effect on the Formation of Pyridinium Salt **e13A**.

Entry	Temperature	% **e13A** by NMR
1	rt	5-10% (extrapolated)
2	-70 °C	50
3	-100 °C	80

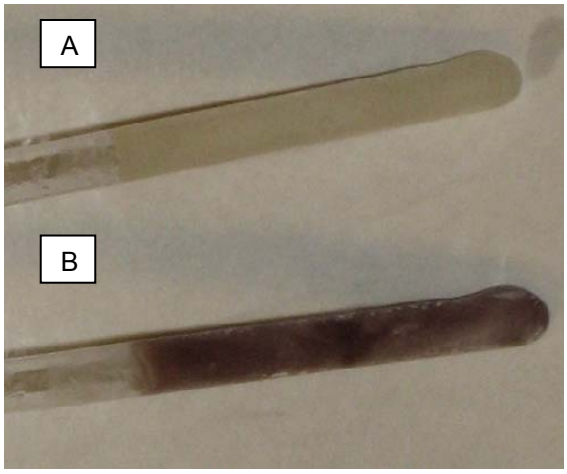


20Ca **21Aa** (15)



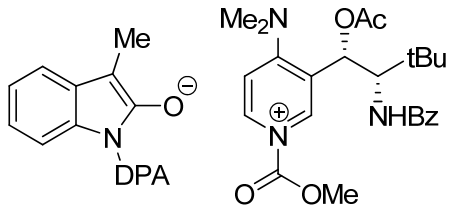
35Aa **35Ba** (16)

Figure 2-12. Frozen Solutions of DMAP plus Enol Acetate **20Ca** and Enol Carbonate **35Aa.**



10A. **20Ca** + DMAP, 10B. **35Aa** + DMAP

Figure 2-13. Possible Ion Pair Intermediate.



f13A

In conclusion, the nucleophile-catalyzed rearrangements of enol acetates and enol carbonates derived from oxindoles have been successfully developed. A strong dependence of the reaction rate on the oxindole protecting group was demonstrated. Amide and sulfonamide protecting groups at the nitrogen of the oxindole greatly enhance the rate of rearrangement relative to the alkyl and carbamate protecting groups. Taking advantage of this enhanced reactivity allowed for a highly enantioselective rearrangement of enol acetates within a few hours with the readily available AcOLeDMAP catalyst. Enol carbonates of amide protected oxindoles were also very reactive, but the chiral catalyst AcOLeDMAP decomposed over the course of the reaction. Replacement of the acetyl protecting group at oxygen on the catalyst by benzyl circumvented this problem, thereby allowing the development of highly enantioselective rearrangements of enol carbonates as well.

III. Experimental.

General Experimental

Et_2O, THF and CH_2Cl_2 were dried by passing through a column of activated alumina. Ethyl acetate and Et_3N were distilled over CaH_2 prior to use. Et_2NH was distilled over KOH prior to use. *t*-Amyl alcohol was carefully distilled over molten sodium. Organolithium reagents were titrated with diphenylacetic acid in THF prior to use. All other reagents were used as received from the manufacturer. Analytical thin layer chromatography (tlc) was accomplished using Whatman 0.25 mm K6F Silica Gel 60 Å plates, and visualized with the aid of UV light or iodine vapor. Flash chromatography was accomplished according to the Still procedure[10] using Whatman Silica Gel: Puracil 60 Å (230-400 mesh). All reactions were performed under an atmosphere of nitrogen in oven-dried glassware.

Synthesis of 2-acetoxy-3-methylindole (9A). To a solution of 3-methyloxindole (1.48 g, 10.0 mmol) in DCM (20 mL) was added 2,6-lutidine (2.3 mL, 19.7 mmol, 2.0 equiv) and the solution was cooled in an ice bath. AcCl (1.4 mL, 19.7 mmol, 2.0 equiv) was added dropwise and the solution was stirred overnight. The reaction was poured over ice and brine (20 mL) after 16 h and the layers were separated. The aqueous layer was extracted with DCM (3x, 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was purified by filtration through a plug of silica (3:1 Hex:Et_2O) to yield **9A** (1.55 g, 81%) as a white powder. The product decomposed at rt, so it was kept under nitrogen in a -20 °C freezer and was stable for up to 2 weeks. Molecular ion calcd for $C_{11}H_{11}NO_2$: 189.0790; [M+], EIMS found *m/z*= 189.0789; IR (neat, cm^{-1}) 3386 (br), 1762; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.46 (1H, br s) 7.49 (1H, d, *J*= 7.4 Hz) 7.25 (1H, d, *J*= 7.4 Hz) 7.16 (1H, dd, *J*= 7.4, 7.0 Hz) 7.12 (1H, dd, *J*= 7.4, 7.0) 2.35 (3H, s) 2.17 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.6, 139.6, 131.3, 127.2, 121.7, 119.8, 118.5, 110.7, 95.7, 20.9, 7.0.

Rearrangement of 2-acetoxy-3-methylindole (9A). Enol ester **9A** (19 mg, 0.10 mmol) was treated with DMAP (1.0, 0.02M in DCM) and stirred at rt for the times indicated in Table 2-10.

After the allotted time, the solution was filter through a silica plug (0.5 cm X 3 cm) with Et_2O and the solvent evaporated. The residue was assayed by NMR for product ratios.

General Procedure for the synthesis of *N*-protected enol acetates: 2-Acetoxy-1-methoxycarbonyl-3-methylindole (9Bb). To a solution of KHMDS (446 mg, 2.2 mmol, 1.1 equiv) in THF (10 mL) at -78 °C was added dropwise a solution of 2-acetoxy-3-methylindole (**9A**, 378 mg, 2.0 mmol) in THF (10 mL) at -78 °C. The resulting solution was stirred for 5 min and then added dropwise to a solution of MeO_2CCl (1.5 mL, 19.4 mmol, 10 equiv) in THF (10 mL) at -78 °C. The resulting solution was stirred for 1 h at -78 °C and then allowed to warm to rt and poured over ice and brine (25 mL). The layers were separated and the aqueous layer was extracted with DCM (3x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. Purification by flash chromatography (8:1:1 Hex:Et_2O:DCM) yielded **9Bb** as a white solid (188 mg, 38%) Molecular ion calcd for $C_{13}H_{13}NO_4$: 270.0742; [M+Na], ESMS found *m/z*= 270.0752; IR (neat, cm^{-1}) 1783, 1737; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.00 (1H, d, *J*= 7.4 Hz) 7.44 (1H, d, *J*= 7.0 Hz) 7.32-7.23 (2H, m) 3.99 (3H, s) 2.38 (3H, s) 2.11 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.9, 150.8, 137.5, 132.1, 128.2, 124.3, 123.1, 118.6, 115.3, 105.2, 53.6, 20.4, 6.9.

2-Acetoxy-1-acetyl-3-methylindole (9Ba). Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (188 mg, 1.0 mmol), KHMDS (218 mg, 1.1 mmol, 1.1 equiv), and acetyl chloride (0.7 mL, 9.8 mmol, 10 equiv), acetyl protected indole **9Ba** was isolated as a white solid (70 mg, 31%). Molecular ion calcd for $C_{13}H_{13}NO_3$: 254.0793; [M+Na], ESMS found *m/z*= 254.0801; IR (neat, cm^{-1}) 1781, 1698; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.27 (1H, d, *J*= 7.4 Hz) 7.45 (1H, dd, *J*= 7.4, 1.6 Hz) 7.32 (1H, ddd, *J*= 7.4, 7.4, 1.6 Hz) 7.28 (1H, ddd, *J*= 7.4, 7.4, 1.2 Hz) 2.57 (3H, s) 2.41 (3H, s) 2.07 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.9, 167.7, 137.0, 132.6, 128.3, 124.9, 123.6, 118.4, 116.2, 105.5, 25.9, 20.7, 7.4.

2-Acetoxy-1-benzyloxycarbonyl-3-methylindole (9Bc). Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (188 mg, 1.0

mmol), KHMDS (5 mL, 0.24M in THF, 1.2 mmol, 1.2 equiv), and benzylchloroformate (1.10 g, 1.4 mmol, 1.4 equiv), benzyloxycarbonyl indole **9Bc** was isolated as a clear oil (117 mg, 36%). IR (neat, cm^{-1}) 1783, 1733, 1646; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.09 (1H, dd, *J*= 8.2, 1.5 Hz) 7.49-7.39 (6H, m) 7.31-7.25 (2H, m) 5.39 (2H, s) 2.10 (3H, s) 2.03 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.8, 150.1, 137.3, 134.7, 132.4, 128.9, 128.9, 128.8, 128.3, 124.4, 123.2, 118.6, 116.4, 105.2, 68.9, 20.0, 6.9.

2-Acetoxy-1-*tert*-butoxycarbonyl-3-methylindole (9Bd). Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (190 mg, 1.0 mmol), KHMDS (5 mL, 0.24M in THF, 1.2 mmol, 1.2 equiv), and di-*tert*-butyl dicarbonate (329 g, 1.5 mmol, 1.5 equiv), *tert*-butoxycarbonyl protected indole **9Bd** was isolated as a clear oil (179 mg, 62%). Molecular ion calcd for $C_{16}H_{19}NO_4$: 312.12.12; [M+Na], ESMS found *m/z*= 312.1208; IR (neat, cm^{-1}) 1785, 1731, 1640; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.00 (1H, dd, *J*= 8.2, 1.2 Hz) 7.44 (1H, dd, *J*= 7.0, 1.2 Hz) 7.31-7.20 (2H, m) 2.38 (3H, s) 2.10 (3H, s) 1.64 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.7, 148.9, 137.8, 132.3, 128.0, 122.7, 118.5, 115.3, 104.3, 83.9. 28.2, 20.6, 6.9.

2-Acetoxy-3-methyl-1-toluenesulfonylindole (9Be): Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (151 mg, 0.80 mmol), KHMDS (183 mg, 0.97 mmol, 1.2 equiv), and *p*-toluenesulfonyl chloride (307.1 g, 1.9 mmol, 2.4 equiv), *p*-toluenesulfonyl protected indole **9Be** was isolated as a clear oil (115 mg, 42%) after flash chromatography (8:1:1 Hex:Et_2O:DCM). Molecular ion calcd for $C_{18}H_{17}NO_4$: 366.0776; [M+Na], ESMS found *m/z*= 366.0764; IR (neat, cm^{-1}) 1791, 1646, 1451, 1366, 1177; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.02 (1H, d, *J*= 8.3 Hz) 7.73 (2H, d, *J*= 8.3 Hz) 7.37 (1H, dd, *J*= 7.8, 1.5 Hz) 7.29 (1H, ddd, *J*= 8.3. 7.3, 1.5 Hz) 7.23 (1H, ddd, *J*= 7.8, 7.3, 1.5 Hz) 7.20 (2H, d, *J*= 8.3 Hz) 2.45 (3H, s) 2.33 (3H, s) 2.03 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.1, 144.9, 137.4, 135.5, 132.6, 129.7, 128.9, 126.8, 124.5, 123.6, 118.9, 114.4, 106.5, 21.6, 20.5, 7.2.

2-Acetoxy-3-methyl-1-*p*-nitrophenylsulfonylindole (9Bf). Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (474 mg, 2.5 mmol), KHMDS (545 mg, 2.7 mmol, 1.1 equiv), and *p*-nosyl chloride (1.10 g, 5.0 mmol, 2 equiv),

p-nosyl protected indole **9Bf** was isolated as a bright yellow solid (295 mg, 32%). Molecular ion calcd for $C_{17}H_{14}N_2O_6S$: 397.0470; [M+Na], ESMS found *m/z*= 397.0455; IR (neat, cm^{-1}) 1791; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25 (1H, d, *J*= 9.0 Hz) 8.02 (1H, d, *J*= 9.0 Hz) 7.39 (1H, d, *J*= 7.4 Hz) 7.35-7.25 (3H, m) 2.47 (3H, s) 2.04 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.0, 150.6, 143.3, 137.1, 132.4, 129.2, 128.1, 125.2, 124.5, 124.4, 119.3, 114.3, 108.1, 20.5, 7.3.

2-Acetoxy-3-methyl-1-*o*-nitrophenylsulfonylindole (9Bg): Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (434 mg, 2.3 mmol), KHMDS (540 mg, 2.7 mmol, 1.2 equiv), and *o*-nitrobenzenesulfonyl chloride (1.03 g, 4.6 mmol, 2 equiv), *o*-nitrobenzenesulfonyl protected indole **9Bg** was isolated as a light brown solid after recrystallization from ethanol/water (239 mg, 28%). Molecular ion calcd for $C_{17}H_{14}N_2O_6S$: 397.0470; [M+Na], ESMS found *m/z*= 397.0468; IR (neat, cm^{-1}) 1791, 1648, 1544, 1368, 1150; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.88-7.84 (1H, m) 7.44 (1H, dd, *J*= 8.2. 1.2 Hz) 7.67 (1H, ddd, *J*= 7.8, 7.4, 1.2 Hz) 7.52 (1H, ddd, *J*= 7.8, 7.4, 1.2 Hz) 7.50-7.46 (1H, m) 7.39 (1H, dd, *J*= 8.2. 1.2 Hz) 7.34-7.28 (2H, m) 2.34 (3H, m) 2.10 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.0, 147.9, 137.6, 134.4, 133.0, 132.8, 132.3, 128.7, 128.3, 125.1, 124.7, 127.2, 119.2, 114.3, 106.9, 20.3, 7.3.

2-Acetoxy-3-methyl-1-phenylacetylindole (9Bh): Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (433 mg, 2.29 mmol), KHMDS (546 mg, 2.74 mmol, 1.2 equiv), and phenylacetyl chloride (1.5 mL, 11.3 mmol, 5.0 equiv), phenylacetyl protected indole **9Bh** was isolated as white crystals after recrystallization from ethanol/water (187 mg, 27%). Molecular ion calcd for $C_{19}H_{17}NO_3$: 330.1106; [M+Na], ESMS found *m/z*= 330.1102; IR (neat, cm^{-1}) 1785, 1704, 1638, 1164; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.32-8.29 (1H, m) 7.47-7.43 (1H, m) 7.38-7.23 (7H, m) 4.21 (2H, s) 2.27 (3H, s) 2.06 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 169.0, 167.5, 136.8, 133.6, 132.8, 129.3, 128.7, 128.4, 127.3, 125.0, 123.7, 118.4, 116.3, 105.8, 44.1, 20.5, 7.5.

2-Acetoxy-1-diphenylacetyl-3-methylindole (9Bi). Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (446 mg, 2.4 mmol), KHMDS (546 mg, 2.7 mmol, 1.2 equiv), and diphenylacetyl chloride (1.21 g, 90%, 4.7 mmol, 2 equiv),

diphenylacetyl protected indole **9Bi** was isolated as a white solid after recrystallization from ethanol/hexanes (356 mg, 39%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.4. Molecular ion calcd for $C_{25}H_{21}NO_3$: 406.1419; [M+Na], ESMS found *m/z*= 406.1420; IR (neat, cm^{-1}) 1785, 1694; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.34-8.29 (1H, m) 7.46-7.42 (1H, m) 7.34-7.22 (12H, m) 5.92 (1H, s) 2.01 (3H, s) 1.95 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.5, 167.0, 139.3, 136.7, 133.1, 129.2, 128.7, 128.4, 127.4, 125.0, 123.8, 118.4, 116.3, 106.2, 58.5, 20.1, 7.7.

2-Acetoxy-1-*iso*butyryl-3-methylindole (9Bj). Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (460 mg, 2.4 mmol), KHMDS (540 mg, 2.7 mmol, 1.1 equiv), and *iso*butyryl chloride (1.3 mL, 12.4 mmol, 5 equiv), *iso*butyryl protected indole **9Bj** was isolated as a colorless oil (295 mg, 47%). Molecular ion calcd for $C_{15}H_{17}NO_3$: 282.1106; [M+Na], ESMS found *m/z*= 282.1098; IR (neat, cm^{-1}) 1785, 1704; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.20 (1H, d, *J*= 7.4 Hz) 7.46 (1H, d, *J*= 7.4 Hz) 7.31 (1H, ddd, *J*= 7.4, 7.4, 1.6 Hz) 7.27 (1H, ddd, *J*= 7.4, 7.4, 1.2 Hz) 3.35 (1H, septet, *J*= 6.6 Hz) 2.41 (3H, s) 2.07 (3H, s) 1.30 (6H, d, *J*= 6.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 176.0, 167.5, 137.0, 132.7, 128.4, 124.7, 123.4, 118.4, 116.0, 105.4, 35.3, 20.6, 19.5, 7.5.

2-Acetoxy-3-methyl-1-pivaloylindole (9Bk). Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (444 mg, 2.4 mmol), KHMDS (544 mg, 2.7 mmol, 1.2 equiv), and pivaloyl chloride (1.5 mL, 12.2 mmol, 5 equiv), pivaloyl protected indole **9Bk** was isolated as a white solid (140.8 mg, 22%). Molecular ion calcd for $C_{16}H_{19}NO_3$: 296.1263; [M+Na], ESMS found *m/z*= 296.1257; IR (neat, cm^{-1}) 1789, 1702; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.58 (1H, d, *J*= 7.4 Hz) 7.47 (1H, d, *J*= 7.0 Hz) 7.25 (1H, ddd, *J*= 7.4, 7.0, 1.6 Hz) 7.20 (1H, ddd, *J*= 7.4, 7.4, 1.2 Hz) 2.36 (3H, s) 2.09 (3H, s) 1.41 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 181.2, 167.2, 137.0, 132.5, 127.8, 123.6, 121.9, 118.6, 113.3, 102.8, 43.3, 27.8, 20.7, 7.7.

2-Acetoxy-1-benzoyl-3-methylindole (9Bl): Following the general procedure for the synthesis of *N*-protected enol acetates starting from indole **9A** (433 mg, 2.29 mmol), KHMDS (546 mg, 2.74 mmol, 1.2 equiv), and benzoyl chloride (1.5 mL, 11.3 mmol, 5.0 equiv), benzoyl protected indole **9Bl** was isolated as an impure oil (162 mg, 55%) after flash chromatography

(10% Et_2O in hexanes). IR (neat, cm^{-1}) 1781, 1684, 1640; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.72-7.45 (7H, m) 7.30-7.20 (2H, m) 2.10 (3H, s) 1.73 (3H, s).

Synthesis of 2-acetoxy-1-benzyl-3-methylindole (9Bm). A solution of 1-benzyl-3-methyloxindole[51] (216 mg, 0.91 mmol) in DCM (3.6 mL) was treated with 2,6-lutidine (1.1 mL, 9.4 mmol, 10 equiv) and AcCl (0.66 mL, 9.3 mmol, 10 equiv) and stirred for 3 days. The solution was poured over a cold brine solution (10 mL) and extracted with DCM (3x 10 mL). Combined organic layers were dried over $MgSO_4$, filtered and evaporated. Crude NMR revealed 45% conversion to product. Product was purified by flash chromatography (5% acetone in hexanes) to yield a white solid (107 mg, 42%). Molecular ion calcd for $C_{18}H_{17}NO_2$: 302.1157; [M+Na], ESMS found *m/z*= 302.1144; IR (neat, cm^{-1}) 1775; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.54 (1H, m) 7.29-7.19 (3H, m) 7.16-7.08 (5H, m) 5.17 (2H, s) 2.24 (3H, s) 2.16 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.8, 138.9, 137.3, 132.4, 128.7, 127.5, 126.8, 126.5, 121.5, 119.6, 118.7, 109.3, 97.2, 45.9, 20.2, 7.6.

Synthesis of 2-acetoxy-1-allyl-3-methylindole (9Bn). A solution of 1-allyl-3-methyloxindole[52] (378 mg, 2.0 mmol) in DCM (8 mL) was treated with 2,6-lutidine (0.46 mL, 4.0 mmol, 2 equiv) and AcCl (0.28 mL, 3.9 mmol, 2 equiv) and stirred for 3 days. The solution was poured over a cold brine solution (10 mL) and extracted with DCM (3x 10 mL). Combined organic layers were dried over $MgSO_4$, filtered and evaporated. Crude NMR revealed 34% conversion to product. Product was purified by flash chromatography (5% acetone in hexanes) to yield a white solid (93 mg, 20%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.52 (1H, m) 7.23-7.09 (3H, m) 5.93-5.82 (1H, m) 5.15-5.01 (2H, m) 4.55 (1H, ddd, *J*= 5.1, 2.0, 1.6 Hz) 2.36 (3H, s) 2.14 (3H, s).

General Procedure of DMAP-Catalyzed Rearrangements: *rac*-3-Acetyl-1-benzyl-3-methyloxindole (9Dm). Enol acetate **9Bm** (27 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 5 h at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (27 mg). NMR analysis of the residue revealed 89% conversion to *C*-acylated oxindole **9Dm**. Molecular ion calcd for $C_{18}H_{17}NO_2$: 302.1157; [M+Na],

ESMS found *m/z*= 302.1160; IR (neat, cm^{-1}) 1723, 1704; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.35-7.27 (5H, m) 7.24 (1H, ddd, *J*= 7.8, 7.8, 1.0 Hz) 7.15 (1H, dd, *J*= 7.3, 1.0 Hz) 7.05 (1H, ddd, *J*= 7.8, 7.3, 1.0 Hz) 6.84 (1H, d, *J*= 7.8 Hz) 5.04 (1H, d, *J*= 15.1 Hz) 4.91 (1H, d, *J*= 15.1 Hz) 1.99 (3H, s) 1.63 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 200.9, 176.0, 142.8, 135.6, 129.4, 129.0, 128.9, 127.9, 127.4, 123.6, 123.2, 109.6, 61.9, 44.1, 26.1, 19.2.

***rac*-3-Acetyl-1-allyl-3-methyloxindole (9Dn).** Enol acetate **9Bn** (22 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 5 h at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (20 mg). NMR analysis of the residue revealed 73% conversion to *C*-acylated oxindole **9D**. Analytical tlc, 25% Et_2O in hexanes, Rf= 0.15. Molecular ion calcd for $C_{14}H_{15}NO_2$: 252.1000; [M+Na], ESMS found *m/z*= 252.1008; IR (neat, cm^{-1}) 1723, 1704, 1609, 1353; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32 (1H, ddd, *J*= 7.8, 7.8, 1.5 Hz) 7.16 (1H, dd, *J*= 7.8, 1.0 Hz) 7.08 (1H, ddd, *J*= 7.8, 7.8, 1.0 Hz) 6.92 (1H, d, *J*= 7.8, 1.5 Hz) 5.87 (1H, dddd, *J*= 17.1, 10.3, 5.4, 5.4 Hz) 5.30-5.25 (2H, m) 4.47 (1H, dddd, *J*= 16.1, 5.4, 1.9, 1.5 Hz) 4.36 (1H, dddd, *J*= 16.1, 5.4, 1.9, 1.5 Hz) 1.99 (3H, s) 1.59 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 200.9, 175.6, 142.9, 131.0, 129.4, 129.0, 123.6, 123.2, 118.1, 109.5, 61.9, 42.6, 25.9, 19.1.

***rac*-3-Acetyl-1-methoxycarbonyl-3-methyloxindole (9Db).** Enol acetate **9Bb** (13 mg, 0.05 mmol) was treated with a solution of DMAP in THF (6 mM, 0.25 mL, 3 mol%). After 5 h at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (12 mg). NMR analysis of the residue revealed 78% conversion to *C*-acylated oxindole **9Db** and 8% 1-methoxycarbonyl-3-methyloxindole **(A)**. Attempted purification resulted in increased conversion to **A**. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.99 (1H, d, *J*= 8.3 Hz) 7.40 (1H, ddd, *J*= 8.3, 7.8, 1.5 Hz) 7.23 (1H, ddd, *J*= 7.8, 7.3, 1.0 Hz) 7.17 (1H, dd, *J*= 7.3, 1.0 Hz) 4.06 (3H, s) 2.05 (3H, s) 1.65 (3H, s). In addition, signals were observed at 4.02 (3H, s), 3.61 (1H, q, *J*= 7.4 Hz), 1.54 (3 H, d, *J*= 7.4 Hz) tentatively attributed to **A**.

***rac*-3-Acetyl-1-benzoxycarbonyl-3-methyloxindole (9Dc).** A solution of enol acetate **9Bc** (16 mg, 0.05 mmol) in THF (0.13 mL) was treated with a solution of DMAP in THF (12 mM, 0.12 mL, 3 mol%). After 5 h at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (13 mg). NMR analysis of the residue revealed 68% conversion to *C*-acylated oxindole **9Dc**.

***rac*-3-Acetyl-1-*tert*-butoxycarbonyl-3-methyloxindole (9Dd).** A solution of enol acetate **9Bd** (29 mg, 0.1 mmol) in THF (0.13 mL) was treated with a solution of DMAP in THF (12 mM, 0.12 mL, 3 mol%). After 5 h at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (27 mg). NMR analysis of the residue revealed 30% conversion to *C*-acylated oxindole **9Dd**.

***rac*-3-Acetyl-3-methyl-1-*p*-toluenesulfonyloxindole (9De):** A solution of enol acetate **9Be** (0.15 mL, 0.33M in THF, 0.05 mmol) was treated with a solution of DMAP in THF (15 mM, 0.10 mL, 3 mol%). After 50 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (27 mg). NMR analysis of the residue revealed >95% conversion to *C*-acylated oxindole **9De**. Analytical tlc, 25% Et_2O in hexanes, Rf= 0.22. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.02-7.97 (3H, m) 7.41 (1H, ddd, *J*= 7.8, 7.4, 1.6 Hz) 7.34 (2H, d, *J*= 8.6 Hz) 7.20 (1H, ddd, *J*= 7.8, 7.4, 0.8 Hz) 7.10 (1H, dd, *J*= 7.8, 1.6 Hz) 2.43 (3H, s) 1.72 (3H, s) 1.50 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 198.8, 174.1, 146.1, 139.1, 134.7, 129.9, 129.8, 128.3, 128.0, 127.9, 125.5, 123.7, 114.2, 62.1, 25.9, 21.7, 19.5.

***rac*-3-Acetyl-3-methyl-1-*p*-nitrophenylsulfonyloxindole (9Df).** Enol acetate **9Bf** (19 mg, 0.05 mmol) was treated with a solution of DMAP in THF (6 mM, 0.25 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a white solid (18 mg). NMR analysis of the residue revealed full conversion to *C*-acylated oxindole **9Df**. Molecular ion calcd for $C_{17}H_{14}N_2O_6S$: 397.0470; [M+Na], ESMS found *m/z*= 397.0470; IR (neat, cm^{-1}) 1754,

1727; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.41 (1H, d, *J*= 9.3 Hz) 8.33 (1H, d, *J*= 9.3 Hz) 7.99 (1H, d, *J*= 8.3 Hz) 7.45 (1H, ddd, *J*= 8.3, 7.8, 1.5 Hz) 7.26 (1H, ddd, *J*= 7.8, 7.8, 1.0 Hz) 7.17 (1H, dd, *J*= 7.8, 1.5 Hz) 1.86 (3H, s) 1.52 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 198.3, 174.2, 151.2, 142.8, 138.4, 130.1, 129.5, 128.2, 126.1, 124.4, 124.1, 114.0, 62.0, 26.0, 19.7.

***rac*-3-Acetyl-3-methyl-1-*o*-nitrophenylsulfonyloxindole (9Dg):** Enol acetate **9Bg** (37 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a white solid (30 mg). NMR analysis of the residue revealed full conversion to *C*-acylated oxindole **9Dg**. Molecular ion calcd for $C_{17}H_{14}N_2O_6S$: 397.0470; [M+Na], ESMS found *m/z*= 397.0470; IR (neat, cm^{-1}) 1750, 1723, 1542, 1380, 1360, 1185; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.61-8.55 (1H, m) 7.90-7.81 (4H, s) 7.45 (1H, ddd, *J*= 8.2, 7.4, 1.6 Hz) 7.26 (1H, ddd, *J*= 7.8, 7.4, 0.8 Hz) 7.17 (1H, dd, *J*= 7.8, 1.6 Hz) 1.87 (3H, s) 1.57 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 198.5, 174.3, 148.0, 139.3, 135.7, 134.9, 132.3, 130.9, 129.9, 127.8, 125.7, 124.8, 123.5, 115.1, 62.0, 26.1, 19.4.

***rac*-1,3-Diacetyl-3-methyloxindole (9Da).** Enol acetate **9Ba** (11 mg, 0.05 mmol) was treated with a solution of DMAP in THF (6 mM, 0.25 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (10 mg). NMR analysis of the residue revealed full conversion to *C*-acylated oxindole **9Da**. Molecular ion calcd for $C_{13}H_{13}NO_3$: 254.0793; [M+Na], ESMS found *m/z*= 254.0805; IR (neat, cm^{-1}) 1748, 1719, 1704; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.28 (1H, d, *J*= 8.3 Hz) 7.40 (1H, ddd, *J*= 8.3, 8.0, 1.5 Hz) 7.25 (1H, ddd, *J*= 8.0, 7.8, 1.4 Hz) 7.17 (1H, dd, *J*= 7.8, 1.4 Hz) 2.73 (3H, s) 2.04 (3H, s) 1.66 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 199.4, 176.6, 170.7, 140.0, 129.5, 128.5, 125.8, 123.1, 117.0, 62.6, 26.7, 26.1, 20.0.

***rac*-3-Acetyl-3-methyl-1-phenylacetyloxindole (9Dh).** Enol acetate **9Bh** (30 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (25 mg). NMR

analysis of the residue revealed full conversion to *C*-acylated oxindole **9Dh**. Molecular ion calcd for $C_{19}H_{17}NO_3$: 330.1106; [M+Na], ESMS found *m/z*= 330.1100; IR (neat, cm^{-1}) 1754, 1719; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.26 (1H, d, *J*= 8.3 Hz) 7.40-7.20 (7H, m) 7.16-7.13 (1H, m) 4.55 (1H, d, *J*= 17.1 Hz) 4.38 (1H, d, *J*= 17.1 Hz) 1.82 (3H, s) 1.62 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 199.3, 176.3, 171.8, 140.2, 133.4, 129.6, 129.5, 128.6, 128.5, 127.3, 125.9, 123.1, 116.9, 62.6, 44.6, 25.8, 19.9.

***rac*-3-Acetyl-1-diphenylacetyl-3-methyloxindole (9Di).** Enol acetate **9Bi** (38 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (36 mg). NMR analysis of the residue revealed full conversion to *C*-acylated oxindole **9Di**. Analytical tlc, 25% Et_2O in hexanes, Rf= 0.5. Molecular ion calcd for $C_{25}H_{21}NO_3$: 406.1419; [M+Na], ESMS found *m/z*= 406.1420; IR (neat, cm^{-1}) 1753, 1719; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.30 (1H, d, *J*= 7.8 Hz) 7.40-7.22 (11H, m) 7.21 (1H, ddd, *J*= 7.4, 7.1, 1.2 Hz) 7.10 (1H, dd, *J*= 7.1, 1.6 Hz) 6.59 (1H, s) 1.53 (3H, s) 1.49 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 199.1, 175.9, 173.1, 140.4, 137.8, 137.6, 129.6, 129.3, 129.3, 128.8, 128.5, 128.5, 127.5, 127.4, 125.9, 123.1, 116.7, 62.5, 58.0, 25.4, 19.7.

***rac*-3-Acetyl-1-*iso*butyryl-3-methyloxindole (9Dj).** Enol acetate **9Bj** (25 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (23 mg). NMR analysis of the residue revealed full conversion to *C*-acylated oxindole **9Dj**. Molecular ion calcd for $C_{15}H_{17}NO_3$: 282.1106; [M+Na], ESMS found *m/z*= 282.1112; IR (neat, cm^{-1}) 1750, 1715; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25 (1H, d, *J*= 8.2 Hz) 7.39 (1H, ddd, *J*= 7.4, 7.4, 1.6 Hz) 7.23 (1H, ddd, *J*= 7.4, 7.0, 1.2 Hz) 7.16 (1H, dd, *J*= 7.0, 1.6 Hz) 3.90 (1H, septet, *J*= 6.6 Hz) 2.03 (3H, s) 1.65 (3H, s) 1.29 (3H, d, *J*= 6.6 Hz) 1.27 (3H, d, *J*= 6.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 199.6, 178.4, 176.2, 140.5, 129.5, 128.6, 125.7, 123.0, 117.1, 62.8, 35.3, 26.1, 20.0, 18.9, 18.8.

***rac*-3-Acetyl-3-methyl-1-pivaloyloxindole (9Dk).** Enol acetate **9Bk** (27 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (25 mg). NMR analysis of the residue revealed 84% conversion to *C*-acylated oxindole **9Dk**. Molecular ion calcd for $C_{16}H_{19}NO_3$: 296.1263; [M+Na], ESMS found *m/z*= 296.1262; IR (neat, cm^{-1}) 1746, 1713; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 7.52 (1H, d, *J*= 8.3 Hz) 7.35 (1H, ddd, *J*= 7.3, 6.8, 2.0 Hz) 7.20-7.13 (2H, m) 2.36 (3H, s) 2.09 (3H, s) 1.41 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 199.8, 182.3, 175.1, 141.0, 129.3, 129.3, 124.9, 123.4, 114.6, 62.6, 43.6, 26.7, 26.2, 19.8.

***rac*-3-Acetyl-3-methyl-1-benzoyloxindole (9Dl).** Enol acetate **9Bl** (29 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (25 mg). NMR analysis of the residue revealed 57% conversion to *C*-acylated oxindole **9Dl**.

Representative example for the chiral nucleophile catalyzed rearrangement of enol acetate 9Ba: TADMAP (7C) catalyzed rearrangement of enol acetate 9Ba to 1,3-diacetyl-3-methyloxindole (9Da). Enol acetate **9Ba** (23 mg, 0.1 mmol) and TADMAP (**7C**) (4.4 mg, 0.01 mmol, 10 mol%) were stirred in DCM (1.0 mL) at rt. After 3 h, the catalyst was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with Et_2O, and the eluent evaporated to yield a white solid (22 mg, 20% ee). NMR analysis of the residue revealed full conversion to *C*-acylated oxindole **9Da**. HPLC (Regis (*R*,*R*)-Whelk-O, 4.6 mm x 25 cm, 99:1 hexanes/isopropanol, 0.5 mL/min) T_R = 24.3 min (major), T_R = 27.0 min (minor).

Chiral DMAP 14A catalyzed rearrangement of enol acetate 9Ba to 1,3-diacetyl-3-methyloxindole (9Da). Following the representative prodecure for the chiral nucleophile catalyzed rearrangement of enol acetate **9Ba** (23 mg, 0.10 mmol), chiral DMAP **14A** (3.6 mg, 0.010 mmol, 10 mol%) in THF (0.5 mL) afforded full conversion to *C*-acylated oxindole **9Da** (22 mg, 97%, 27% ee) in 4 h.

AcOVaDMAP 14B catalyzed rearrangement of enol acetate 9Ba to 1,3-diacetyl-3-methyloxindole (9Da). Following the representative prodecure for the chiral nucleophile catalyzed rearrangement of enol acetate **9Ba** (24 mg, 0.10 mmol), AcOVaDMAP **14B** (3.6 mg, 0.010 mmol, 10 mol%) in THF (0.5 mL) afforded full conversion to *C*-acylated oxindole **9Da** (23 mg, 97%, 55% ee) in 4 h.

AcOLeDMAP catalyzed rearrangement of protected enol acetates. 1,3-Diacetyl-3-methyloxindole (9Da). Enol acetate **9Ba** (21 mg, 0.1 mmol) and AcOLeDMAP (3.7 mg, 0.01 mmol, 10 mol%) were stirred in THF (0.5 mL) at rt. After 3.5 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure white solid **9Da** was isolated (21 mg, 99%, 61% ee). HPLC (Regis (*R*,*R*)-Whelk-O, 4.6 mm x 25 cm, 99:1 hexanes/isopropanol, 0.5 mL/min) T_R = 24.3 min (major), T_R = 27.0 min (minor).

AcOLeDMAP (14C) catalyzed rearrangement of protected enol acetates. 3-Acetyl-3-methyl-1-*p*-toluenesulfonyloxindole (9De). Enol acetate **9Be** (15 mg, 0.05 mmol) and AcOLeDMAP (**14C**) (1.7 mg, 0.005 mmol, 10 mol%) were stirred in THF (0.25 mL) at rt. After 20 h, the catalyst was quenched with MeI (0.1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure clear oil **9De** was isolated (46% ee). HPLC (Chiracel AD, 4.6 mm x 25 cm, 90:10 hexanes/isopropanol, 0.5 mL/min) T_R = 13.5 min (major), T_R = 15.7 min (minor).

AcOLeDMAP (14C) catalyzed rearrangement of protected enol acetates. 3-Acetyl-3-methyl-1-*p*-nitrophenylsulfonyloxindole (9Df). Enol acetate **9Bf** (37 mg, 0.1 mmol) and AcOLeDMAP (**14C**) (4.0 mg, 0.01 mmol, 10 mol%) were stirred in THF (0.5 mL) at rt. After 2 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure white solid **9Df** was isolated (30 mg, 81%, 57% ee). HPLC (Chiracel OD, 4.6 mm x 25 cm, 90:10 hexanes/isopropanol, 0.5 mL/min) T_R = 28.4 min (minor), T_R = 48.0 min (major).

AcOLeDMAP (14C) catalyzed rearrangement of protected enol acetates. 3-Acetyl-3-methyl-1-*o*-nitrophenylsulfonyloxindole (9Dg). Enol acetate **9Bg** (38 mg, 0.1 mmol) was

treated with a solution of AcOLeDMAP in THF (0.02 M, 0.5 mL, 10 mol%). After 2 h at rt, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure light yellow solid **9Dg** was isolated (31 mg, 83%, 58% ee). HPLC (Chiracel AS, 4.6 mm x 25 cm, 90:10 hexanes/isopropanol, 0.5 mL/min) T_R = 27.0 min (major), T_R = 40.5 min (minor).

AcOLeDMAP (14C) catalyzed rearrangement of protected enol acetates. 3-Acetyl-1-*iso*butyryl-3-methyloxindole (9Dj). Enol acetate **9Bj** (25 mg, 0.1 mmol) and AcOLeDMAP (4.0 mg, 0.01 mmol, 10 mol%) were stirred in THF (0.5 mL) at rt. After 2 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure clear oil **9Dj** was isolated (23 mg, 92%, 77% ee). HPLC (Chiracel OB, 4.6 mm x 25 cm, hexanes, 1 mL/min) T_R = 22.5 min (minor), T_R = 33.3 min (major).

AcOLeDMAP catalyzed rearrangement of protected enol acetates. 3-Acetyl-3-methyl-1-pivaloyloxindole (9Dk). Enol acetate **9Bk** (27 mg, 0.1 mmol) was treated with a solution of AcOLeDMAP in THF (0.02 M, 0.5 mL, 10 mol%). After 24 h at rt, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure clear oil **9Dk** was isolated (26 mg, 98%). Oxindole **9Dk** could not be resolved by chiral phase HPLC, however upon standing at room temperature for a week in hexanes and *iso*propanol, deprotected 3-acetyl-3-methyloxindole (**10A**) was obtained and the enantiomeric excess was determined (77% ee). HPLC for **10A** (Chiralcel AS, 4.6 mm x 25 cm, 90:10 hexanes/isopropanol, 1.0 mL/min) T_R = 21.4 min (minor), T_R = 30.0 min (major).

AcOLeDMAP catalyzed rearrangement of protected enol acetates. 3-Acetyl-3-methyl-1-phenylacetyloxindole (9Di). Enol acetate **9Bi** (31 mg, 0.1 mmol) was treated with a solution of AcOLeDMAP in THF (0.02 M, 0.5 mL, 10 mol%) at rt. After 2.5 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure clear oil **9Di** was

isolated (30 mg, 96%, 75% ee). HPLC (Chiracel OD, 4.6 mm x 25 cm, 90:10 hexanes/isopropanol, 1 mL/min) T_R = 7.7 min (minor), T_R = 9.3 min (major).

AcOLeDMAP catalyzed rearrangement of protected enol acetates. 3-Acetyl-1-diphenylacetyl-3-methyloxindole (5g). Enol acetate **4g** (38 mg, 0.1 mmol) was treated with a solution of AcOLeDMAP in THF (0.02 M, 0.5 mL, 10 mol%). After 24 h at rt, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure clear oil **5g** was isolated (34 mg, 89%, 86% ee). HPLC (Chiralcel OD, 4.6 mm x 25 cm, 99:1 hexanes/isopropanol, 1.0 mL/min) T_R = 9.6 min (minor), T_R = 12.7 min (major).

Representative Procedure for Synthesis of 1-Diphenylacetyloxindoles: 1-Diphenylacetyl-3-Methyloxindole (20Ba). 3-Methyloxindole (4.00 g, 27.2 mmol) and diphenylacetyl chloride (7.50 g, 32.5 mmol, 1.2 equiv) were heated to 150 °C with stirring. The reaction was monitored by taking a drop and diluting with $CDCl_3$ and following by NMR. After 4 h, the reaction was quenched with water (2 mL). After allowing to cool for five minutes, EtOH was added (50 mL) and the solution was allowed to cool to rt. The resulting precipitate was filtered and washed with ethanol (20 mL) and water (20 mL) to yield **20Ba** as a cream-colored powder (7.38 g, 80%). A second precipitate was filtered from the mother liquor containing **20Ba** and diphenylacetic acid. Recrystallization of the second precipitate from EtOH yielded an additional 470 mg (5%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.54. Molecular ion calcd for $C_{23}H_{19}NO_2$: 364.1308; [M+Na], ESMS found *m/z*= 364.1310; IR (neat, cm^{-1}) 1754, 1704; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.27 (1H, d, *J*= 8.2 Hz) 7.35-7.16 (13H, m) 6.62 (1H, s) 3.54 (1H, q, *J*= 7.4 Hz) 1.44 (3H, d, *J*= 7.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 178.5, 173.1, 140.4, 138.5, 138.4, 129.6, 129.3, 129.2, 128.6, 128.5, 128.3, 127.3, 127.2, 125.2, 123.2, 116.7, 108.1, 57.4, 41.3, 15.9.

1-Diphenylacetyl-3-Ethyloxindole (20Bb). Following the general procedure for the synthesis of 1-diphenylacetyloxindoles, 3-ethyloxindole (1.024 g, 6.4 mmol) and diphenylacetyl chloride (2.87 g, 12.4 mmol, 2.0 equiv) were heated. When NMR analysis revealed full

conversion (2.5 h), the reaction was quenched, diluted with EtOH and allowed to cool and filtered to yield **20Bb** as a cream-colored powder (1.89 g, 84%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.56. Molecular ion calcd for $C_{24}H_{21}NO_2$: 378.1470; [M+Na], ESMS found *m/z*= 378.1467; IR (neat, cm^{-1}) 1750, 1706; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.27 (1H, d, *J*= 8.2 Hz) 7.34-7.17 (13H, m) 6.63 (1H, s) 3.54 (1H, t, *J*= 5.5 Hz) 2.05-1.86 (2H, m) 0.65 (3H, t, *J*= 7.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 177.8, 173.1, 141.1, 138.4, 138.4, 129.3, 129.3, 128.5, 128.5, 128.2, 127.9, 127.2, 127.2, 125.1, 123.4, 116.5, 57.6, 47.2, 24.4, 9.3.

3-Benzyl-1-diphenylacetyloxindole (20Bc). Following the general procedure for the synthesis of 1-diphenylacetyloxindoles, 3-benzyloxindole (1.61 g, 7.21 mmol) and diphenylacetyl chloride (2.01 g, 8.7 mmol, 1.2 equiv) were heated. When NMR analysis revealed full conversion (3 h), the reaction was quenched and allowed to cool. Residue was purified by flash chromatography (silica gel, 5% acetone in hexanes) to yield **20Bc** as a clear oil (2.49 g, 83%). Analytical tlc, 5% acetone in hexanes, Rf= 0.19. Molecular ion calcd for $C_{29}H_{23}NO_2$: 440.1626; [M+Na], ESMS found *m/z*= 440.1633; IR (neat, cm^{-1}) 1750, 1706; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.19 (1H, d, *J*= 8.3 Hz) 7.34-7.11 (10H, m) 7.05 (1H, dd, *J*= 7.4, 7.4 Hz) 6.96-6.93 (2H, m) 6.84 (1H, d, *J*= 7.4 Hz) 6.59 (1H, s) 3.80 (1H, dd, *J*= 7.8, 5.0 Hz) 3.31 (1H, dd, *J*= 13,7, 5.0 Hz) 2.97 (1H, dd, *J*= 13.7, 7.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 177.0, 172.9, 140.7, 138.5, 138.3, 136.5, 129.3, 129.2, 129.2, 128.5, 128.5, 128.4, 128.3, 127.3, 127.2, 127.2, 126.8, 124.8, 124.0, 116.6, 57.4, 47.7, 37.4.

3-(2-(*tert*-Butyldiphenylsilanyloxy)ethyl)-1-diphenylacetyloxindole (20Bd). To a solution of 3-(2-hydroxyethyl)oxindole (1.52 g, 8.56 mmol) in DMF (44) was added imidazole (729 mg, 10.7 mmol, 1.25 equiv), then *tert*-butyldiphenylsilyl chloride (2.5 mL, 9.6 mmol, 1.1 equiv). After 1 h, the solution extracted from H_2O (100 mL) with ether (3x 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and dried over $MgSO_4$. After concentration, the yellow oil was purified by crystallization from ethanol/water to yield 3-(2-(*tert*-butyldiphenylsilanyloxy)ethyl)oxindole (**B)** as white crystals (2.15 g, 5.17 mmol, 60%). The mother liquor was purified by flash chromatography (10% acetone in hexanes) to yield additional **B** as a white crystalline solid (305 mg, 0.734 mmol, 9%). Analytical tlc, 50% Et_2O in hexanes, Rf=

0.3. Molecular ion calcd for $C_{26}H_{29}NO_2Si$: 438.1865; [M+Na], ESMS found *m/z*= 438.1848; IR (neat, cm^{-1}) 1706; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.67 (1H, br s) 7.66 (2H, dd, *J*= 7.8, 1.6 Hz) 7.51 (2H, dd, *J*= 8.2, 1.6 Hz) 7.44-7.30 (16H, m) 7.22 (1H, dd, *J*= 7.8, 7.4 Hz) 7.10 (1H, d, *J*= 7.0 Hz) 6.99 (1H, ddd, *J*= 7.4, 7.4, 0.8 Hz) 6.90 (1H, d, *J*= 7.8 Hz) 3.89-3.73 (2H, m) 3.69 (1H, dd, *J*= 6.6, 6.3 Hz) 2.32-2.10 (2H, m) 1.01 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 180.6, 141.7, 135.6, 135.5, 133.5, 133.4, 129.6, 129.5, 129.3, 127.8, 127.7, 127.6, 124.4, 122.1, 109.7, 60.4, 42.9, 32.7 26.7, 19.1.

Following the general procedure for the synthesis of 1-diphenylacetyloxindoles, **B** (175 mg, 0.42 mmol) and diphenylacetyl anhydride (259 mg, 0.64 mmol, 1.5 equiv) were heated. When NMR analysis revealed full conversion (3 h), the reaction was quenched with H_2O (0.2 mL) and allowed to cool. Recrystallization of the residue from EtOH/H_2O yielded **20Bd** as white crystals (185 mg, 72%). Analytical tlc, 5% acetone in hexanes, Rf= 0.14. Molecular ion calcd for $C_{40}H_{39}NO_3Si$: 632.2597; [M+Na], ESMS found *m/z*= 632.2601; IR (neat, cm^{-1}) 1754, 1706; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.31 (1H, d, *J*= 8.2 Hz) 7.63 (2H, d, *J*= 7.8 Hz) 7.47-7.09 (21H, m) 6.61 (1H, s) 3.76-3.63 (3H, m) 2.13 (2H, q, *J*= 6.0 Hz) 0.97 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 177.9, 173.0, 140.9, 138.6, 138.5, 135.5, 135.5, 133.3, 133.2, 129.7, 129.6, 129.4, 129.2, 128.6, 128.3, 128.2, 127.7, 127.7, 127.7, 127.2, 127.1, 125.0, 123.7, 116.7, 60.0, 57.5, 43.0, 33.2, 26.7, 19.0.

3-Allyl-1-diphenylacetyloxindole (20Be). According to the method developed by Wenkert[11], methyl magnesium bromide (1.7 mL, 3.0 M in Et_2O, 5.7 mmol) was added dropwise over 5 min to a solution of 3-allylindole (787 mg, 5.0 mmol) in THF (36 mL). After 30 min tosyl chloride was added in portions over 5 min and solution was stirred for 2 h. The mixture was poured into $NaHCO_3$ (sat., 100 mL) and diluted with DCM (100 mL). Layers were separated and organic layer was dried over $MgSO_4$, filtered and evaporated. The dark orange residue was purified by flash chromatography (silica gel, 50% Et_2O in hexanes) to yield 3-Allyloxindole **(C)** as an orange solid (554 mg, 64%). Analytical tlc, 50% Et_2O in hexanes, Rf= 0.12. Molecular ion calcd for $C_{11}H_{11}NO$: 196.0738; [M+Na], ESMS found *m/z*= 196.0743; IR (neat, cm^{-1}) 1689; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.10 (1H, br s) 7.26 (1H, d, *J*= 7.4 Hz) 7.20 (1H, ddd, *J*= 7.4, 7.4,

0.8 Hz) 7.01 (1H, ddd, *J*= 7.8, 7.4, 0.8 Hz) 6.91 (1H, d, *J*= 7.8 Hz) 5.78 (1H, dddd, *J*= 16.8, 10.2, 7.8, 6.3 Hz) 5.12 (1H, ddd, *J*= 16.8, 3.1, 1.6 Hz) 5.05 (1H, dd, *J*= 10.2, 1.6 Hz) 3.53 (1H, dd, *J*= 7.8, 5.1 Hz) 2.88-2.80 (1H, m) 2.64-2.56 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 180.1, 141.6, 133.9, 129.2, 127.9, 124.4, 122.2, 118.1, 109.8, 45.8, 34.7.

Following the general procedure for the synthesis of 1-diphenylacetyloxindoles, 3-allyloxindole (**C**, 520 mg, 3.0 mmol) and diphenylacetyl chloride (1.04 g, 4.5 mmol, 1.5 equiv) were heated. When NMR analysis revealed full conversion (2.5 h), the reaction was quenched and allowed to cool. Residue was purified by flash chromatography (silica gel, 5% Et_2O in hexanes) to yield **20Be** as a clear oil (817 mg, 74%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.57. Molecular ion calcd for $C_{25}H_{21}NO_2$: 390.1470; [M+Na], ESMS found *m/z*= 390.1458; IR (neat, cm^{-1}) 1750, 1704; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.26 (1H, d, *J*= 8.5 Hz) 7.34-7.19 (11H, m) 7.14 (1H, ddd, *J*= 7.3, 7.3, 1.0 Hz) 6.62 (1H, s) 5.41 (1H, dddd, *J*= 17.1, 10.3, 7.8, 6.3 Hz) 4.92 (1H, ddd, *J*= 17.1, 2.9, 1.5 Hz) 4.87 (1H, dd, *J*= 10.3, 1.5 Hz) 3.56 (1H, dd, *J*= 6.3, 5.4 Hz) 2.70-2.64 (1H, m) 2.59-2.53 (1H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 177.0, 173.0, 140.8, 138.4, 138.3, 132.4, 129.2, 128.5, 128.4, 128.3, 127.5, 127.2, 127.1, 125.0, 123.6, 118.7, 116.4, 57.4, 46.0, 35.4.

1-Diphenylacetyl-3-*iso*propyloxindole (20Bf). Following the general procedure for the synthesis of 1-diphenylacetyloxindoles, 3-*iso*propyloxindole (855 mg, 4.9 mmol) and diphenylacetyl chloride (2.29 g, 9.9 mmol, 2.0 equiv) were heated. When NMR analysis revealed full conversion (3 h), the reaction was quenched, diluted with EtOH, allowed to cool, and filtered to yield **20Bf** as off-white crystals (1.50 g, 83%). Analytical tlc, 5% acetone in hexanes, Rf= 0.28. Molecular ion calcd for $C_{25}H_{23}NO_2$: 392.1626; [M+Na], ESMS found *m/z*= 392.1629; IR (neat, cm^{-1}) 1750, 1704; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.27 (1H, d, *J*= 8.2 Hz) 7.32-7.15 (13H, m) 6.64 (1H, s) 3.44 (1H, d, *J*= 4.3 Hz) 2.36 (1H, qqd, *J*= 7.3, 6.8, 4.3 Hz) 0.85 (3H, d, *J*= 7.3 Hz) 0.75 (3H, d, *J*= 6.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 177.3, 173.1, 141.3, 138.4, 138.4, 129.3, 129.3, 128.5, 128.5, 128.2, 127.2, 127.2, 127.1, 124.9, 123.8, 116.4, 57.6, 52.1, 32.2, 18.9, 18.1.

1-Diphenylacetyl-3-phenyloxindole (20Bg). Following the general procedure for the synthesis of 1-diphenylacetyloxindoles, 3-phenyloxindole (805 mg, 3.9 mmol) and diphenylacetyl

chloride (1.34 g, 5.8 mmol, 1.5 equiv) were heated. When NMR analysis revealed full conversion (3.5 h), the reaction was quenched and allowed to cool. Residue was purified by flash chromatography (silica gel, 5% Et_2O in hexanes) to yield **20Bg** as a white solid (876 mg, 56%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.48. Molecular ion calcd for $C_{28}H_{21}NO_2$: 426.1470; [M+Na], ESMS found *m/z*= 426.1472; IR (neat, cm^{-1}) 1752, 1708; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.33 (1H, d, *J*= 8.2 Hz) 7.39-7.17 (17H, m) 7.13 (1H, d, *J*= 7.4 Hz) 7.02-6.97 (2H, m) 6.57 (1H, s) 4.70 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.8, 173.2, 141.0, 138.3, 138.1, 136.2, 129.3, 129.2, 129.0, 128.8, 128.6, 128.5, 128.3, 128.0, 127.3, 127.2, 125.5, 124.7, 116.6, 57.5, 52.8.

5-Bromo-1-diphenylacetyl-3-methyloxindole (23C). Following the general procedure for the synthesis of 1-diphenylacetyloxindoles, 5-bromo-3-methyloxindole (314 mg, 1.4 mmol) and diphenylacetyl chloride (424 mg, 1.8 mmol, 1.3 equiv) were heated. When NMR analysis revealed full conversion (4 h), the reaction was quenched, diluted with EtOH, allowed to cool, and filtered to yield **23C** as an off-white powder (361 mg, 61%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.5. Molecular ion calcd for $C_{23}H_{18}BrNO_2$: 419.0521; [M+], EI+ found *m/z*= 419.0513; IR (neat, cm^{-1}) 1756, 1706; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.17 (1H, d, *J*= 8.6 Hz) 7.44 (1H, dd, *J*= 7.8, 1.2 Hz) 7.38-7.22 (11H, m) 6.57 (1H, s) 3.55 (1H, q, *J*= 7.4 Hz) 1.44 (3H, d, *J*= 7.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 177.5, 173.0, 139.3, 128.3. 138.1, 131.7, 131.3, 129.3, 129.2, 128.6, 128.5, 127.4, 127.3, 126.4, 118.3, 118.2, 57.4, 41.1, 15.8.

Representative Procedure for Synthesis of Enol Acetates: 2-Acetoxy-1-diphenylacetyl-3-methylindole (20Ca). To a slurry of **20Ba** (5.01 g, 14.7 mmol) in Et_2O (72 mL) was added Et_3N (10 mL, 136 mmol, 10 equiv) and the solution was agitated with a mechanical stirrer and placed in a water bath at rt. AcCl (5 mL, 70.3 mmol, 5 equiv) was added dropwise over 5 min (caution: exotherm). After 1 h, solution was poured over water (100 mL) and extracted with DCM (200 mL). Organic layer was washed with $NaHCO_3$ (sat., 75 mL), and brine (75 mL) and dried over $MgSO_4$, filtered and concentrated. Recrystallization from ethyl acetate yielded

enol acetate **20Ca** as clear white crystals (4.50 g from 3 crops, 80%). Spectral data matched characterization for 2-acetoxy-1-diphenylacetyl-3-methylindole obtained via protection of indole **7**.

2-Acetoxy-1-diphenylacetyl-3-ethylindole (20Cb). Following the general procedure for the synthesis of enol acetates, **20Bb** (989 mg, 2.8 mmol) was treated with Et_3N (2.0 mL, 14.3 mmol, 5 equiv) and AcCl (1.0 mL, 14.1 mmol, 5 equiv). After workup, recrystallization of the residue from EtOH yielded **20Cb** as off-white needles (825 mg, 75%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.45. Molecular ion calcd for $C_{26}H_{23}NO_3$: 420.1576; [M+Na], ESMS found *m/z*= 420.1575; IR (neat, cm^{-1}) 1791, 1702; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.31-8.26 (1H, m) 7.52-7.48 (1H, m) 7.34-7.22 (12H, m) 5.90 (1H, s) 2.49 (2H, q, *J*= 7.4 Hz) 1.95 (3H, s) 1.21 (3H, t, *J*= 7.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.6, 167.7, 139.3, 136.1, 133.3, 129.2, 128.7, 127.6, 127.4, 124.9, 123.7, 118.7, 116.3, 111.8, 58.5, 20.1, 16.4, 12.9.

2-Acetoxy-3-benzyl-1-diphenylacetylindole (20Cc). Following the general procedure for the synthesis of enol acetates, **20Bc** (207 mg, 0.5 mmol) was treated with Et_3N (0.34 mL, 2.4 mmol, 5 equiv) and AcCl (0.18 mL, 2.5 mmol, 5 equiv). After workup, recrystallization of the residue from EtOH yielded **20Cc** as white needles (136 mg, 60%). Additional material was isolated from the mother liquor by preparatory thin layer chromatography (5% acetone in hexanes) to give **15c** (23 mg, 10%). Analytical tlc, 5% acetone in hexanes, Rf= 0.13. Molecular ion calcd for $C_{31}H_{25}NO_3$: 482.1732; [M+Na], ESMS found *m/z*= 482.1728; IR (neat, cm^{-1}) 1791, 1704; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.27 (1H, d, *J*= 8.3 Hz) 7.34-7.16 (18H, m) 5.90 (1H, s) 3.84 (2H, s) 1.81 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.7, 167.5, 139.1, 138.2, 137.4, 133.2, 129.1, 128.7, 128.6, 128.5, 127.7, 127.4, 126.4, 125.0, 123.8, 119.1, 116.1, 108.7, 58.7, 29.3, 20.0.

2-Acetoxy-3-(2-(*tert*-Butyldiphenylsilanyloxy)ethyl)-1-diphenylacetylindole (20Cd). Following the general procedure for the synthesis of enol acetates, **20Bd** (184 mg, 0.3 mmol) was treated with Et_3N (0.21 mL, 1.5 mmol, 5 equiv) and AcCl (0.11 mL, 1.5 mmol, 5 equiv). After workup, recrystallization of the residue from EtOH yielded **15d** as white needles (104 mg, 53%). Additional material was isolated from the mother liquor by preparatory thin layer chromatography (5% acetone in hexanes) to give **20Cd** (29 mg, 15%). Analytical tlc, 5% acetone in hexanes, Rf=

0.08. Molecular ion calcd for $C_{42}H_{41}NO_4Si$: 674.2703; [M+Na], ESMS found *m/z*= 674.2705; IR (neat, cm^{-1}) 1791, 1706; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.22 (1H, d, *J*= 8.3 Hz) 7.61-7.60 (4H, m) 7.41-7.37 (2H, m) 7.33-7.13 (17H, m) 5.83 (1H, s) 3.83 (2H, t, *J*= 7.3 Hz) 2.73 (2H, t, *J*= 7.3 Hz) 1.83 (3H, s) 1.04 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.6, 167.6, 139.2, 137.4, 135.5, 133.6, 133.0, 129.6, 129.1, 128.7, 127.7, 127.7, 127.4, 124.9, 123.7, 118.8, 116.1, 107.1, 62.3, 58.6, 26.8, 26.7, 20.0, 19.2.

2-Acetoxy-3-allyl-1-diphenylacetylindole (20Ce). Following the general procedure for the synthesis of enol acetates, **20be** (305 mg, 0.83 mmol) was treated with Et_3N (0.59 mL, 4.2 mmol, 5 equiv) and AcCl (0.29 mL, 4.1 mmol, 5 equiv). After workup, recrystallization of the residue from EtOH yielded **20Ce** as white needles (227 mg, 67%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.51. Molecular ion calcd for $C_{27}H_{23}NO_3$: 432.1576; [M+Na], ESMS found *m/z*= 432.1566; IR (neat, cm^{-1}) 1789, 1704; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.31-8.27 (1H, m) 7.50-7.46 (1H, m) 7.34-7.22 (12H, m) 5.91 (1H, s) 5.88 (1H, ddt, *J*= 17.2, 10.2, 6.3 Hz) 5.14 (1H, ddd, *J*= 17.2, 1.6, 1.6 Hz) 5.08 (1H, ddd, *J*= 10.2, 1.6, 1.6 Hz) 3.24 (2H, dt, *J*= 6.3, 1.6 Hz) 1.92 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.6, 167.4, 139.2, 136.9, 134.4, 133.1, 129.1, 128.7, 127.7, 127.4 125.0, 123.8, 118.9, 116.4, 116.2, 107.8, 58.6, 27.6, 20.1.

2-Acetoxy-1-diphenylacetyl-3-*iso*propylindole (20Cf). Following the general procedure for the synthesis of enol acetates, **20Bf** (752 mg, 2.0 mmol) was treated with Et_3N (1.4 mL, 10 mmol, 5 equiv) and AcCl (0.18 mL, 9.8 mmol, 5 equiv). After workup, product was purified by flash chromatography (silica gel, 5% acetone in hexanes) and then recrystallization from EtOH yielded **20Cf** as white needles (357 mg, 43%). Analytical tlc, 5% acetone in hexanes, Rf= 0.17. Molecular ion calcd for $C_{27}H_{25}NO_3$: 434.1732; [M+Na], ESMS found *m/z*= 434.1738; IR (neat, cm^{-1}) 1791, 1702; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.26 (1H, m) 7.61 (1H, m) 7.34-7.23 (12H, m) 5.89 (1H, s) 2.86 (1H, septet, *J*= 7.0 Hz) 1.91 (3H, s) 1.34 (6H, d, *J*= 7.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.7, 168.1, 139.3, 135.4, 133.4, 129.2, 128.7, 127.4, 126.7, 124.6, 123.4, 119.8, 116.3, 115.3, 58.6, 25.0, 21.2, 20.1.

2-Acetoxy-1-diphenylacetyl-3-phenylindole (20Cg). Following the general procedure for the synthesis of enol acetates, **20Bg** (201 mg, 0.5 mmol) was treated with Et_3N (0.35 mL, 2.5

mmol, 5 equiv) and AcCl (0.18 mL, 2.5 mmol, 5 equiv). After workup, recrystallization of the residue from Et_2O/hexanes yielded **20Cg** as white needles (191 mg, 86%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.45. Molecular ion calcd for $C_{30}H_{23}NO_3$: 468.1576; [M+Na], ESMS found *m/z*= 468.1570; IR (neat, cm^{-1}) 1794, 1706; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.34 (1H, d, *J*= 7.7 Hz) 7.63 (1H, d, *J*= 7.5 Hz) 7.52-7.49 (2H, m) 7.46-7.43 (2H, m) 7.36-7.27 (13H, m) 5.98 (1H, s) 1.76 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.9, 167.3, 139.1, 136.5, 133.2, 131.1, 129.1, 128.8, 128.8, 128.7, 127.6, 127.5, 127.0, 125.3, 124.2, 119.4, 116.3, 111.8, 58.8, 20.2.

2-Acetoxy-5-bromo-1-diphenylacetyl-3-methylindole (23D). Following the general procedure for the synthesis of enol acetates, **23C** (466 mg, 1.1 mmol) was treated with Et_3N (0.77 mL, 5.5 mmol, 5 equiv) and AcCl (0.39 mL, 5.5 mmol, 5 equiv). After workup, recrystallization of the residue from EtOH yielded **23D** as white needles (228 mg, 44%). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.37. Molecular ion calcd for $C_{25}H_{20}BrNO_3$: 484.0524; [M+Na], ESMS found *m/z*= 484.0514; IR (neat, cm^{-1}) 1789, 1698; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.22 (1H, d, *J*= 8.6 Hz) 7.56 (1H, d, *J*= 2.0 Hz) 7.38 (1H, dd, *J*= 9.0, 2.0 Hz) 7.35-7.19 (10H, m) 5.88 (1H, s) 1.97 (3H, s) 1.95 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.5, 166.6, 139.0, 137.4, 131.7, 130.2, 129.1, 128.8, 127.8, 127.5, 121.2, 117.9, 117.2, 105.5, 58.6, 20.0, 7.6.

Representative Procedure for the AcOLeDMAP-Catalyzed Rearrangement of Enol Acetates: 3-Acetyl-1-diphenylacetyl-3-methyloxindole (21Aa). To a solution of enol acetate **20Ca** (1.00 g, 2.61 mmol) in EtOAc (10 mL) at 0 °C was added a precooled solution of AcOLeDMAP (**14C**, 10.0 mg, 0.026 mmol, 1 mol%) in EtOAc (3 mL). After 24 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (10 mL) and solution was applied to a plug of silica (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O. After concentration, the pure white crystalline product **21Aa** was isolated (999 mg, 99%, 92% ee). Enantioenriched product was obtained by crystallization from ether/hexanes by slow diffusion to give 593 mg white crystals enriched in racemate and the mother liquor was concentrated to give 395 mg of 99% ee crystals. Spectral data matched characterization for 3-acetyl-1-diphenylacetyl-3-methyloxindole obtained via DMAP catalysis; mp = 120-122 °C (98% ee). $[\alpha]_D$ = -214 (c= 0.0071, 98% ee, DCM). HPLC (Chiralcel OD, 4.6 mm x

25 cm, 99:1 hexanes/isopropanol, 1.0 mL/min) T_R = 9.6 min (minor), T_R = 12.7 min (major, (*S*) according to the negative optical rotation response by the in-line polarimetry detector).

3-Acetyl-1-diphenylacetyl-3-ethyloxindole (21Ab). To a solution of enol acetate **20Cb** (40 mg, 0.1 mmol) in EtOAc (0.4 mL) at 0 °C was added a precooled solution of AcOLeDMAP (**14C**) in EtOAc (0.1 mL, 0.1 M, 10 mol%). After 2.5 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure colorless oil product **21Ab** was isolated (39 mg, 98%, 91% ee). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.45. HPLC (Chiralcel OD, 4.6 mm x 25 cm, 99.95:0.05 hexanes/isopropanol, 1.0 mL/min) T_R = 32.0 min (minor), T_R = 41.9 min (major, (*S*) according to the negative optical rotation response by the in-line polarimetry detector). Molecular ion calcd for $C_{26}H_{23}NO_3$: 420.1576; [M+Na], ESMS found *m/z*= 420.1584; IR (neat, cm^{-1}) 1750, 1715; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.31 (1H, d, *J*= 8.3 Hz) 7.38 (1H, ddd, *J*= 8.3, 7.8, 1.5 Hz) 7.35-7.21 (11H, m) 6.61 (1H, s) 2.17 (1H, dq, *J*= 13.9, 7.3 Hz) 2.10 (1H, dq, *J*= 13.9, 7.3 Hz) 1.62 (3H, s) 0.41 (3H, t, *J*= 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 199.6, 175.3, 173.0, 141.2, 137.7, 129.5, 129.3, 128.7, 128.5, 127.5, 127.4, 126.4, 125.8, 123.3, 116.5, 67.8, 58.1, 27.4, 26.3, 7.7.

3-Acetyl-3-benzyl-1-diphenylacetyloxindole (21Ac). To a solution of enol acetate **20Cc** (46 mg, 0.1 mmol) in EtOAc (0.4 mL) at 0 °C was added a precooled solution of AcOLeDMAP (**14C**) in EtOAc (0.1 mL, 0.1 M, 10 mol%). After 3 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure white solid product **21Ac** was isolated (44 mg, 96%). The enantiomeric excess of product was determined on the deprotected oxindole **19c**. Analytical tlc, 5% acetone in hexanes, Rf= 0.17. Molecular ion calcd for $C_{31}H_{25}NO_3$: 482.1732; [M+Na], ESMS found *m/z*= 482.1748; IR (neat, cm^{-1}) 1748, 1713; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.09 (1H, d, *J*= 8.2 Hz) 7.33-7.20 (11H, m) 7.17-7.14 (2H, m) 7.01 (1H, dd, *J*= 7.4, 7.4 Hz) 6.91 (2H, dd, *J*= 7.8, 7.0 Hz) 6.67 (2H, d, *J*= 7.0 Hz) 6.48 (1H, s) 3.44 (2H, s) 1.66 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 199.1, 174.8, 172.5, 141.0, 138.0,

137.8, 134.1, 129.7, 129.6, 129.3, 128.7, 128.5, 128.0, 127.4, 127.3, 127.0, 126.0, 125.6, 123.7, 116.9, 68.6, 57.6, 39.8, 26.5.

1-Acetyl-3-(2-(*tert*-Butyldiphenylsilanyloxy)ethyl)-1-diphenylacetyloxindole (21Ad). To a solution of enol acetate **20Cd** (65 mg, 0.1 mmol) in EtOAc (0.4 mL) at 0 °C was added a precooled solution of AcOLeDMAP (**14C**) in EtOAc (0.1 mL, 0.1 M, 10 mol%). After 3 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure white crystalline product **21Ad** was isolated (62 mg, 94%, 91% ee). Analytical tlc, 5% acetone in hexanes, Rf= 0.08. HPLC (Chiralcel OD, 4.6 mm x 25 cm, 99.9:0.1 hexanes/isopropanol, 1.0 mL/min) T_R = 14.9 min (minor), T_R = 19.4 min (major, (*S*) according to the negative optical rotation response by the in-line polarimetry detector). Molecular ion calcd for $C_{42}H_{41}NO_4Si$: 674.2703; [M+Na], ESMS found *m/z*= 674.2712; IR (neat, cm^{-1}) 1758, 1715; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.43 (1H, d, *J*= 8.3 Hz) 7.58-7.55 (2H, m) 7.45 (1H, ddd, *J*= 8.3, 7.8, 1.5 Hz) 7.42-7.14 (18H, m) 7.01 (1H, dd, *J*= 7.3, 1.0 Hz) 6.94 (1H, s) 3.44 (1H, ddd, *J*= 10.7, 5.7, 3.4 Hz) 3.26 (1H, ddd, *J*= 11.2, 10.7, 3.4 Hz) 2.62 (1H, ddd, *J*= 14.6, 11.2, 5.7 Hz) 2.43 (1H, dt, *J*= 14.6, 3.4 Hz) 1.26 (3H, s) 0.89 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 198.8, 175.3, 172.8, 141.5, 137.9, 137.6, 135.5 135.2, 132.8, 132.7, 129.7, 129.6, 129.5, 129.5, 129.4, 128.9, 128.2, 127.7, 127.6, 127.5, 127.2, 125.6, 125.5, 123.8, 117.0, 65.6, 59.8, 58.1, 34.9, 26.6, 25.0, 18.8.

3-Acetyl-3-allyl-1-diphenylacetyloxindole (21Ae). To a solution of enol acetate **20Cd** (42 mg, 0.1 mmol) in EtOAc (0.4 mL) at 0 °C was added a precooled solution of AcOLeDMAP (**14C**) in EtOAc (0.1 mL, 0.1 M, 10 mol%). After 2.5 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure white crystalline product **21Ae** was isolated (41 mg, 98%, 85% ee). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.55. HPLC (Chiracel OD, 4.6 mm x 25 cm, 99.5:0.5 hexanes/isopropanol, 1.0 mL/min) T_R = 12.7 min (minor), T_R = 15.1 min (major, (*S*) according to the negative optical rotation response by the in-line polarimetry detector). Molecular ion calcd for $C_{27}H_{23}NO_3$: 432.1576; [M+Na], ESMS found *m/z*= 432.1569; IR (neat, cm^{-1}) 1750, 1717; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.29 (1H, d, *J*= 8.1 Hz) 7.41-7.20 (11H, m) 7.13

(1H, dd, *J*= 7.0, 0.8 Hz) 6.58 (1H, s) 5.48 (1H, dddd, *J*= 17.2, 10.2, 7.8, 7.0 Hz) 4.84 (1H, dd, *J*= 17.2, 1.6 Hz) 4.85 (1H, d, *J*= 10.3 Hz) 2.86 (1H, dd, *J*= 14.0, 7.0 Hz) 2.81 (1H, dd, *J*= 14.0, 7.8 Hz) 1.67 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 198.9, 174.7, 172.9, 141.0, 137.8, 137.7, 130.3, 129.7, 129.4, 129.3, 128.7, 128.5, 127.5, 127.4, 126.1, 125.8, 123.4, 120.2, 116.7, 67.0, 58.0, 38.3, 26.2.

3-Acetyl-1-diphenylacetyl-3-*iso*propyloxindole (21Af). To a solution of enol acetate **20Cf** (41 mg, 0.1 mmol) in EtOAc (0.4 mL) at 0 °C was added a precooled solution of AcOLeDMAP (**14C**) in EtOAc (0.1 mL, 0.1 M, 10 mol%). After 41.5 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). The residue was purified by preparatory thin layer chromatography (2.5 % acetone in hexanes) run twice to yield **21Af** as a colorless oil (34 mg, 82%, 94% ee). Analytical tlc, 5% acetone in hexanes, Rf= 0.19. HPLC (Regis (*R*,*R*)-Whelk-O, 4.6 mm x 25 cm, 99:1 hexanes/isopropanol, 1.0 mL/min) T_R = 16.1 min (major, (*S*) according to the negative optical rotation response by the in-line polarimetry detector), T_R = 21.7 min (minor). Molecular ion calcd for $C_{27}H_{25}NO_3$: 434.1732; [M+Na], ESMS found *m/z*= 434.1732; IR (neat, cm^{-1}) 1748, 1713; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.28 (1H, ddd, *J*= 8.2, 0.8, 0.8 Hz) 7.39-7.19 (13H, m) 6.61 (1H, s) 2.73 (1H, qq, *J*= 7.0, 6.6 Hz) 1.81 (3H, s) 0.81 (3H, d, *J*= 6.6 Hz) 0.57 (3H, d, *J*= 7.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 200.6, 174.7, 173.0, 140.8, 137.9, 137.8, 129.4, 129.3, 129.2, 128.6, 128.6, 127.4, 127.4, 126.3, 125.5, 124.1, 116.2, 70.3, 58.1, 35.6, 27.7, 17.0.

3-Acetyl-1-diphenylacetyl-3-phenyloxindole (21Ag). To a solution of enol acetate **20Cg** (47 mg, 0.1 mmol) in EtOAc (0.4 mL) at 0 °C was added a precooled solution of AcOLeDMAP (**14C**) in EtOAc (0.1 mL, 0.1 M, 10 mol%). After 2 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure white crystalline product **21Ag** was isolated (46 mg, 98%, 66% ee). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.42. HPLC (Chiralcel AD, 4.6 mm x 25 cm, 99:1 hexanes/isopropanol, 1.0 mL/min) T_R = 21.1 min (major, (*S*) according to the negative optical rotation response by the in-line polarimetry detector), T_R = 27.7

min (minor). Molecular ion calcd for $C_{30}H_{23}NO_3$: 468.1576; [M+Na], ESMS found *m/z*= 468.1571; IR (neat, cm^{-1}) 1752, 1713; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.36 (1H, d, *J*= 8.2 Hz) 7.44 (1H, ddd, *J*= 7.3, 6.8, 2.0 Hz) 7.36-7.20 (15H, m) 7.08-7.05 (2H, m) 6.54 (1H, s) 1.88 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 199.7, 173.6, 173.1, 140.9, 137.8, 137.8, 135.6, 129.9, 129.3, 129.3, 128.9, 128.7, 128.5, 128.5, 128.1, 127.4, 127.3, 125.7, 125.7, 125.6, 116.9, 71.7, 58.1, 26.7.

3-Acetyl-5-bromo-1-diphenylacetyl-3-methyloxindole (23E). To a solution of enol acetate **23D** (92 mg, 0.2 mmol) in EtOAc (0.8 mL) at 0 °C was added a precooled solution of AcOLeDMAP (**14C**) in EtOAc (0.2 mL, 0.1 M, 10 mol%). After 20 min, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and solution was applied to a plug of silica gel (5 cm x 1 cm) and flushed with 3:1 Hex:Et_2O (50 mL). After concentration, the pure white crystalline product **23E** was isolated (88 mg, 95%, 86% ee). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.5. HPLC (Chiralcel OD, 4.6 mm x 25 cm, 95:5 hexanes/isopropanol, 1.0 mL/min) T_R = 10.2 min (minor), T_R = 17.6 min (major, (*S*) according to the negative optical rotation response by the in-line polarimetry detector). Molecular ion calcd for $C_{25}H_{20}BrNO_3$: 484.0524; [M+Na], ESMS found *m/z*= 484.0518; IR (neat, cm^{-1}) 1756, 1715; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.20 (1H, d, *J*= 9.0 Hz) 7.51 (1H, dd, *J*= 8.6, 2.3 Hz) 7.36-7.23 (11H, m) 6.54 (1H, s) 1.52 (3H, s) 1.52 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 198.4, 175.1, 172.9, 139.2, 137.5, 137.4, 132.5, 130.3, 129.3, 129.2, 128.8, 128.5, 127.6, 127.5, 126.3, 118.9, 118.2, 62.2, 58.1, 25.5, 19.8.

3-Acetyl-3-methyloxindole (24A). To a solution of oxindole **21Aa** (200 mg, 0.522 mmol) in MeCN (2.2 mL) was added Et_2NH (1.1 mL, 10.6 mmol, 20 equiv). The solution was heated to 60 °C. After 2 h, the solution was cooled, diluted with chloroform (10 mL) and concentrated. Purification by flash chromatography (20% acetone in hexanes) followed by recrystallization from Et_2O/hexanes yielded **24A** as a colorless crystalline solid (75 mg, 75%). Analytical tlc, 50% Et_2O in hexanes, Rf= 0.21. HPLC (Chiralcel AS, 4.6 mm x 25 cm, 90:10 hexanes/isopropanol, 1.0 mL/min) T_R = 21.4 min (minor), T_R = 30.0 min (major). Molecular ion calcd for $C_{11}H_{11}NO_2$: 212.0687; [M+Na], ESMS found *m/z*= 212.0697; IR (neat, cm^{-1}) 3265, 1723, 1698; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.20 (1H, br s) 7.30 (1H, dd, *J*= 7.8, 7.4 Hz) 7.15 (1H, d, *J*= 7.4 Hz) 7.08

(1H, dd, *J*= 7.4, 7.4 Hz) 7.02 (1H, d, *J*= 7.8 Hz) 2.06 (3H, s) 1.62 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 200.7, 178.5, 141.0, 130.1, 129.2, 123.8, 123.3, 110.5, 62.6, 26.0, 18.9.

3-Acetyl-3-benzyloxindole (e7A). To a solution of oxindole **21Ac** (319 mg, 0.69 mmol) in MeCN (3.5 mL) was added Et_2NH (1.4 mL, 13.5 mmol, 20 equiv). The solution was heated to 50 °C. After 4 h, the solution was cooled, diluted with chloroform (10 mL) and concentrated. Purification by flash chromatography (50% Et_2O in hexanes) yielded **e7A** as a clear, colorless oil (120 mg, 65%, 94% ee). Analytical tlc, 50% Et_2O in hexanes, Rf= 0.31. HPLC (Chiralcel AD, 4.6 mm x 25 cm, 90:10 hexanes/isopropanol, 1.0 mL/min) T_R = 7.6 min (major), T_R = 10.0 min (minor). Molecular ion calcd for $C_{17}H_{15}NO_2$: 288.1000; [M+Na], ESMS found *m/z*= 288.1005; IR (neat, cm^{-1}) 3251, 1721, 1704, ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.84 (1H, br s) 7.26-7.19 (2H, m) 7.11-7.00 (3H, m) 6.86 (2H, d, *J*= 6.6 Hz) 6.73 (2H, d, *J*= 7.8 Hz) 3.48 (1H, d, *J*= 13.8 Hz) 3.46 (1H, d, *J*= 13.8 Hz) 2.08 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 200.5, 176.0, 141.2, 135.0, 129.9, 129.3, 127.7, 127.3, 126.7, 124.7, 122.9, 109.9, 68.4, 38.7, 26.8.

3-Acetoxy-1-diphenylacetyl-3-methyloxindole (e8A). A solution of oxindole **21Aa** (38 mg, 0.10 mmol) in DCM (1 mL) was treated with $NaHCO_3$ (20 mg, 0.24 mmol, 2.4 equiv) and *m*-CPBA (49 mg, 0.20 mmol, 2 equiv). The solution was heated to reflux. The reaction was monitored by TLC and allowed to cool after consumption of the starting material (8 h). The excess peracid was quenched with $NaHSO_3$ (sat., 1 mL) and stirred for 10 min. The solution was diluted with H_2O (10 mL) and DCM (10 mL) and the layers were separated. The aqueous layer was extracted with DCM (2x, 10 mL) and combined organic layers were washed with $NaHCO_3$ (sat., 10 mL), dried ($MgSO_4$), filtered and condensed. The crude oil was purified by preparatory TLC (25% Et_2O in Hexanes) to afford **e8A** as a white solid (29.2 mg, 73%, 87% ee) HPLC (Chiralcel OD, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 8.2 min (major), T_R = 10.3 min (minor). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.31. IR (neat, cm^{-1}) 1767, 1744, 1710; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.30 (1H, d, *J*= 8.2 Hz) 7.37-7.16 (13H, m) 6.54 (1H, s) 2.02 (3H, s) 1.40 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.0, 172.9, 169.0, 139.8, 138.5, 138.2, 130.1, 129.3, 129.3, 128.6, 128.5, 128.4, 127.3, 127.1, 125.5, 121.6, 116.9, 77.1, 57.5, 23.7, 20.3.

Representative Procedure for the Synthesis of *N*-Acetyl-Protected Oxindole Enol Carbonates 25A: 1-Acetyl-2-phenoxycarbonoxy-3-methylindole (25Aa). A solution of 1-acetyl-3-methyloxindole (**9C**, 373 mg, 1.97 mmol) in THF (8 mL) was treated with triethylamine (0.27 mL, 1.94 mmol, 1.0 equiv) and cooled to 0 °C. Phenyl chloroformate (0.27 mL, 2.2 mmol, 1.1 equiv) was added dropwise. The solution was allowed to warm to rt and after 30 min the solvent was removed with a stream of nitrogen. The residue was taken up in H_2O (2 mL), stirred for 2 h at 0 °C and the white precipitate was filtered and recrystallized from EtOH/H_2O to yield enol carbonate **25Aa** as a white crystalline solid (373 mg, 81%). Molecular ion calcd for $C_{18}H_{15}NO_4$: 332.0899; [M+Na], ESMS found *m/z*= 332.0894; IR (neat, cm^{-1}) 1787, 1704, 1646, 1194; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23 (1H, d, *J*= 8.4 Hz) 7.51-7.43 (3H, m) 7.38-7.29 (5H, m) 2.71 (3H, s) 2.21 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.0, 150.8, 150.6, 137.2, 132.3, 129.8, 128.0, 126.8, 125.2, 123.7, 120.6, 118.8, 115.9, 105.8, 25.1, 7.2.

1-Acetyl-2-methoxycarbonoxy-3-methylindole (25Ab). A solution of 1-acetyl-3-methyloxindole (**9C**, 375 mg, 1.98 mmol) in THF (10 mL) was treated with triethylamine (0.31 mL, 2.2 mmol, 1.1 equiv) and cooled to 0 °C. Methyl chloroformate (0.18 mL, 2.3 mmol, 1.2 equiv) was added dropwise. The solution was allowed to warm to rt and after 30 min the solvent was removed with a stream of nitrogen. The residue was taken up in H_2O (2 mL), stirred for 2 h at 0 °C and the white precipitate was filtered and recrystallized from EtOH to yield **25Ab** as a colorless crystalline solid (147 mg, 30%). Analytical tlc, 20% Et_2O in hexanes, Rf= 0.41. Molecular ion calcd for $C_{13}H_{13}NO_4$: 270.0742; [M+Na], ESMS found *m/z*= 270.0737; IR (neat, cm^{-1}) 1777, 1704; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.28 (1H, dd, *J*= 8.2, 1.2 Hz) 7.46 (1H, dd, *J*= 7.8, 1.6 Hz) 7.34 (1H, ddd, *J*= 8.2, 7.4, 1.6 Hz) 7.29 (1H, ddd, *J*= 7.8, 7.4, 1.2 Hz) 3.99 (3H, s) 2.58 (3H, s) 2.13 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.0, 152.6, 137.2, 132.3, 128.0, 125.1, 123.7, 118.6, 116.2, 105.5, 56.5, 25.9, 7.1.

1-Acetyl-2-ethoxycarbonoxy-3-methylindole (25Ac). Using the general procedure outlined above for the synthesis of enol carbonates, oxindole **9C** (387 mg, 2.05 mmol) yielded enol carbonate **25Ac** after recrystallization from EtOH/H_2O as a white crystalline solid (392 mg,

73%). IR (neat, cm^{-1}) 1773, 1706, 1646, 1219; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.30 (1H, dd, *J*= 7.4, 1.2 Hz) 7.46 (1H, dd, *J*= 7.4, 1.9 Hz) 7.34 (1H, td, *J*= 7.4, 1.9 Hz) 7.29 (1H, td, *J*= 7.4, 1.2 Hz) 4.41 (2H, q, *J*= 7.0 Hz) 2.59 (3H, s) 2.13 (3H, s) 1.43 (3H, s).

1-Acetyl-2-benzoxycarbonoxy-3-methylindole 25Ad. Using the general procedure outlined above for the synthesis of enol carbonates, oxindole **9C** (369 mg, 1.95 mmol) yielded enol carbonate **25Ad** after recrystallization from EtOH/H_2O as a white crystalline solid (376 mg, 59%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.29 (1H, d, *J*= 7.8 Hz) 7.46-7.37 (6H, m) 7.35-7.23 (2H, m) 5.33 (2H, s) 2.47 (3H, s) 2.09 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.0, 152.0, 137.1, 134.1, 132.4, 129.2, 128.8, 128.7, 128.0, 125.2, 123.7, 118.5, 116.3, 105.5, 71.6, 25.7, 7.1.

1-Acetyl-2-*iso*-propoxycarbonoxy-3-methylindole (25Ae). Using the general procedure outlined above for the synthesis of enol carbonates, oxindole **9C** (378 mg, 2.00 mmol) yielded enol carbonate **25Ae** after recrystallization from EtOH/H_2O as a white crystalline solid (292 mg, 53%). IR (neat, cm^{-1}) 1766, 1704, 1648, 1237; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.31 (1H, dd, *J*= 8.2, 1.2 Hz) 7.46 (1H, dd, *J*= 7.0, 1.6 Hz) 7.34 (1H, dd, *J*= 8.2, 7.8, 1.6 Hz) 7.29 (1H, dd, *J*= 7.8, 7.0, 1.2 Hz) 5.05 (1H, septet, *J*= 6.3 Hz) 2.58 (3H, s) 2.13 (3H, s) 1.42 (6H, d, *J*= 6.3 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 168.0, 151.4, 137.3, 132.4, 128.1, 125.1, 123.6, 118.5, 116.3, 105.4, 74.9, 25.8, 21.6, 7.1.

1-Acetyl-3-methyl-3-phenoxycarbonyloxindole (25Ba). Enol carbonate **25Aa** (31 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 10 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a white solid (27 mg). NMR analysis of the residue revealed full conversion to *C*-carboxylated oxindole **25Ba**. IR (neat, cm^{-1}) 1787, 1704, 1646, 1194; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.30 (1H, d, *J*= 8.3 Hz) 7.44-7.38 (2H, m) 7.35-7.30 (2H, m) 7.28 (2H, ddd, *J*= 7.8, 7.3, 1.0 Hz) 7.23-7.19 (1H, m) 6.95-6.92 (1H, m) 2.74 (3H, s) 1.84 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.4, 170.8, 167.6, 150.2, 140.1, 129.7, 129.5, 128.6, 126.4, 125.7, 122.6, 121.0, 117.1, 56.0, 26.7, 20.7.

***rac*-1-Acetyl-3-methoxycarbonyl-3-methyloxindole (25Bb).** Enol carbonate **25Ab** (12 mg, 0.05 mmol) was treated with a solution of DMAP in THF (6 mM, 0.25 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a white solid (11 mg). NMR analysis of the residue revealed full conversion to *C*-carboxylated oxindole **25Bb**. Analytical tlc, 20% Et_2O in hexanes, Rf= 0.33. Molecular ion calcd for $C_{13}H_{13}NO_4$: 270.0742; [M+Na], ESMS found *m/z*= 270.0739; IR (neat, cm^{-1}) 1744, 1713; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.26 (1H, d, *J*= 8.2 Hz) 7.37 (1H, ddd, *J*= 8.2, 7.4, 1.6 Hz) 7.28 (1H, dd, *J*= 7.4, 1.6 Hz) 7.22 (1H, ddd, *J*= 7.4, 7.4, 1.2 Hz) 3.69 (3H, s) 2.71 (3H, s) 1.74 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 199.4, 176.6, 170.7, 140.0, 129.5, 128.5, 125.8, 123.1, 117.0, 62.6, 26.7, 26.1, 20.0.

1-Acetyl-3-ethoxycarbonyl-3-methyloxindole (25Bc). Enol carbonate **25Ac** (26 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a white solid (23 mg). NMR analysis of the residue revealed 97% conversion to *C*-carboxylated oxindole **25Bc**. IR (neat, cm^{-1}) 1760, 1740, 1715; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25 (1H, d, *J*= 8.2 Hz) 7.37 (1H, ddd, *J*= 8.2, 7.4, 1.6 Hz) 7.29 (1H, dd, *J*= 7.8, 1.6 Hz) 7.22 (1H, ddd, *J*= 7.8, 7.4, 0.8 Hz) 4.18 (1H, dq, *J*= 10.9, 7.0 Hz) 4.12 (1H, dq, *J*= 10.9, 7.0 Hz) 2.71 (3H, s) 1.73 (3H, s) 1.16 (3H, dd, *J*= 7.0, 7.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.9, 170.8, 168.9, 139.9, 129.3, 129.1, 125.5, 122.6, 116.8, 62.3, 55.8, 26.6, 20.7, 13.8.

1-Acetyl-3-benzoxycarbonyl-3-methyloxindole (25Bd). A solution of enol carbonate **25Ad** (32 mg, 0.1 mmol) in THF (0.25 mL) was treated with a solution of DMAP in THF (12 mM, 0.25 mL, 3 mol%). After 30 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a white solid (24 mg). NMR analysis of the residue revealed full conversion to *C*-carboxylated oxindole **25Bd**. IR (neat, cm^{-1}) 1760, 1744, 1713; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25 (1H, d, *J*= 8.2 Hz) 7.36 (2H, ddd, *J*= 8.2, 7.4, 1.6 Hz) 7.30-7.22 (4H, m) 7.19 (2H, ddd, *J*= 7.4, 7.4, 0.8

Hz) 7.13-7.10 (2H, m) 5.15 (1H, d, *J*= 12.5 Hz) 5.09 (1H, d, *J*= 12.5 Hz) 2.67 (3H, s) 1.75 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.7, 170.8. 168.7, 139.9, 135.0, 129.4, 128.8, 128.5, 128.3, 127.4, 125.5, 122.7, 116.9, 67.6, 55.9, 26.6, 20.5.

1-Acetyl-3-methyl-3-*iso*-propoxycarbonyloxindole (25Be). Enol carbonate **25Ae** (27 mg, 0.1 mmol) was treated with a solution of DMAP in THF (6 mM, 0.5 mL, 3 mol%). After 20 min at rt, DMAP was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a white solid (23 mg). NMR analysis of the residue revealed 69% conversion to *C*-carboxylated oxindole **25Be**. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25 (1H, d, *J*= 8.2 Hz) 7.36 (1H, ddd, *J*= 8.2, 7.8, 1.6 Hz) 7.28 (1H, dd, *J*= 7.8, 1.6 Hz) 7.21 (2H, ddd, *J*= 7.8, 7.8, 1.2 Hz) 4.99 (1H, qq, *J*= 6.3, 5.9 Hz) 2.70 (3H, s) 1.72 (3H, s) 1.19 (3H, d, *J*= 6.3 Hz) 1.08 (3H, d, *J*= 5.9 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 176.0, 170.9, 168.4, 139.9, 129.3, 129.2, 125.5, 122.5, 116.8, 70.1, 56.0, 26.6, 21.4, 21.2, 20.5.

Representative procedure for Table 2-26: AcOLeDMAP (14C) catalyzed rearrangement of enol carbonate 25Aa to form 4-*tert*-Butyl-5-(4-dimethylaminopyridin-3-yl)-2-phenyloxazoline (f7A). A solution of enol carbonate **25Aa** (31 mg, 0.1 mmol) in THF (0.5 mL) was treated with AcOLeDMAP (**14C**, 3.6 mg, 10 mol%) and the reaction turned purple. After 1 h at rt, catalyst was quenched with methyl iodide (0.1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a colorless oil (22 mg). NMR analysis of the residue revealed *C*-carboxylated oxindole **25Ba** (93%, 29% ee), along with 1-acetyl-3-methyloxindole (**9C**, 7%). HPLC conditions for **25Ba** (Chiralcel AD, 4.6 mm x 25 cm, 95:5 hexanes/isopropanol, 1.0 mL/min) T_R = 7.8 min (major), T_R = 9.9 min (minor). Flushing the silica plug with EtOAc yielded a purple oil containing AcOLeDMAP (**14C**, ~16% by NMR), oxazoline **f7A** and an unidentified purple impurity (1.5 mg). Spectral data for **f7A**: Molecular ion calcd for $C_{20}H_{25}N_3O$: 324.2076; [M+1], ESMS found *m/z*= 324.2064; IR (neat, cm^{-1}) 1711, 1640; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.45 (1H, s) 8.36 (1H, d, *J*= 5.9 Hz) 7.99 (2H, m) 7.48 (1H, td, *J*= 7.3, 1.5 Hz) 7.41 (2H, m) 6.86 (1H, d, *J*= 5.9 Hz) 5.67 (1H, d, *J*= 6.8 Hz) 4.10 (1H, d, *J*= 6.8

Hz) 2.93 (6H, s) 2.16 (3H, s) 0.95 (9H, s). ^{13}C NMR (126 MHz, $CDCl_3$, ppm) δ 162.3, 158.8, 151.1, 150.1, 131.3, 129.0, 128.4, 128.3, 127.9, 112.9, 84.8, 76.7, 44.2, 34.8, 25.9.

2-Benzoxycarbonoxy-1-diphenylacetyl-3-methylindole (26A). A solution of oxindole **20Ba** (683 mg, 1.98 mmol) in THF (10 mL) was treated with triethylamine (0.42 mL, 3.0 mmol, 1.5 equiv) and cooled to 0 °C. Benzyl chloroformate (0.46 mL, 3.1 mmol, 1.5 equiv) was added dropwise. The solution was allowed to warm to rt and after 30 min the solution was diluted with EtOAc (20 mL) and washed with water (15 mL). The aqueous layer was extracted with EtOAc (1x, 10 mL) and combined organic layers were washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was recrystallized from EtOH to yield **26A** as a colorless crystalline solid (711 mg, 74%, 2 batches). Molecular ion calcd for $C_{31}H_{25}NO_4$: 476.1862; [M+H], ESMS found *m/z*= 476.1862; IR (neat, cm^{-1}) 1779, 1702, 1644; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.42 (1H, d, *J*= 7.6 Hz) 7.44-7.20 (18H, m) 5.94 (1H, s) 4.97 (2H, s) 2.00 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.4, 151.1, 138.8, 136.9, 134.0, 133.0, 129.1, 129.1, 128.8, 128.6, 128.5, 128.2, 127.3, 125.3, 123.9, 118.5, 116.7, 105.9, 71.4, 58.3, 7.4.

Monitoring AcOLeDMAP (14C) decomposition over time in the rearrangement of enol carbonate 25Aa. A solution of enol carbonate **25Aa** (31 mg, 0.1 mmol) in $CDCl_3$ (0.7 mL) in an NMR tube was treated with AcOLeDMAP (**14C**, 3.8 mg, 10 mol%) at rt and the solution turned purple. The reaction was monitored by ^{1}H NMR spectroscopy every 5 min, and the results are tabulated in Table 2-27.

Monitoring AcOLeDMAP (14C) decomposition over time in the rearrangement of enol carbonate 25Aa. A solution of enol carbonate **25Ad** (32 mg, 0.1 mmol) in $CDCl_3$ (0.7 mL) in an NMR tube was treated with AcOLeDMAP (**14C**, 3.9 mg, 10 mol%) at rt and the solution turned purple. The reaction was monitored by ^{1}H NMR spectroscopy at the intervals specified in Table 2-28.

Representative procedures for screening catalysts for decomposition in the rearrangement of enol carbonate 26A. A solution of enol carbonate **26A** (48 mg, 0.1 mmol) in $CDCl_3$ (0.7 mL) in an NMR tube was treated with AcOLeDMAP (**14C**, 3.9 mg, 10 mol%) at rt and

the solution turned purple. The reaction was monitored by ^{1}H NMR spectroscopy every 5-10 minutes.

Acetic acid 1-(4-dimethylaminopyridin-3-yl)-3-methyl-2-toluenesulfonylaminobutyl ester (e12B). To a solution of *t*BuLi in hexane (8.0 mL, 1.7 M, 13.6 mmol, Acros) at –78 °C was added a solution of 3-bromo-4-dimethylaminopyridine (1.38 g, 6.85 mmol) in THF (65 mL) dropwise. The resulting solution was added dropwise to a solution of *N*-*p*-toluenesulfonyl-valinal **e12A** (0.791 g, 3.10 mmol) in THF (30 mL) at –78 °C. The solution was stirred at –78 °C for 1 h, then quenched with H_2O (5 mL). The solution was warmed to rt, and extracted from brine with CH_2Cl_2 (3x, 50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated (aspirator). The residue was taken up in CH_2Cl_2 (15 mL) and treated with Et_3N (2.0 mL, 14 mmol) and Ac_2O (1.6 mL, 14 mmol, Fluka). After stirring overnight at rt, the solution was poured into 2 M NaOH (10 mL) and extracted with CH_2Cl_2 (3x, 10mL), and the combined organic layers were dried over $MgSO_4$, filtered and evaporated yielding a yellow oil that was purified by flash chromatography to remove excess DMAP (silica gel; 5 x 15 cm column) using 20% acetone in hexanes as the eluent, yielding **e12B** as a yellow solid. This material was recrystallized from EtOAc yielding **e12B** as a white powder (0.364 g, 28%, >98:2 dr). Additional product was found in the mother liquor but not recovered. Molecular ion calcd for $C_{21}H_{29}N_3O_4S$: 420.1957; [M+H], ESMS found *m/z*= 420.1954; IR (neat, cm^{-1}) 3379 (br), 1737, 1594, 1229, 1152; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.29 (1H, s) 8.29 (1H, d, *J*= 5.5 Hz) 7.49 (2H, d, *J*= 8.0 Hz) 7.15 (2H, d, *J*= 8.0 Hz) 6.78 (1H, d, *J*= 5.5 Hz) 6.26 (1H, d, *J*= 4.6 Hz) 4.84 (1H, d, *J*= 9.8 Hz) 3.67 (1H, ddd, *J*= 9.8, 5.1, 4.6 Hz) 2.74 (6H, s) 2.39 (1H, s) 2.04 (1H, s) 1.73 (1H, qqd, *J*= 6.6, 6.6, 5.1 Hz) 0.92 (3H, d, *J*= 6.6 Hz) 0.86 (3H, d, *J*= 6.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.5, 158.5, 150.3, 149.1, 142.7, 138.5, 129.5, 127.2, 126.7, 114.1, 70.1, 62.3, 43.8, 30.7, 21.5, 21.0, 19.4, 18.3.

3-((2*R*,3S)-3-Isopropyl-1-*p*-tosylaziridin-2-yl)-4-dimethylaminopyridine (f9A): A solution of oxindole **26A** (48 mg, 0.10 mmol) in $CDCl_3$ (0.7 mL) was treated with *N*-tosyl catalyst **e12B** (4.2 mg, 0.010 mmol, 10 mol%). The reaction was monitored by NMR. After 2 d, the DMAP catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and the solution was applied to

a pipet silica plug, flushed with 3:1 Hex:Et_2O. Flushing the silica plug with 3% Et_3N in EtOAc (10 mL) yielded a clear oil containing aziridine **f9A** (4.0 mg). Molecular ion calcd for $C_{19}H_{25}N_3O_2S$: 360.1746; [M+H], ESMS found *m/z*= 360.1745; IR (neat, cm^{-1}) 1588, 1326, 1158; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.26 (1H, d, *J*= 5.6 Hz) 8.22 (1H, s) 7.88 (2H, d, *J*= 8.0 Hz) 7.32 (2H, d, *J*= 8.0 Hz) 6.67 (1H, d, *J*= 5.6 Hz) 4.08 (1H, d, *J*= 6.8 Hz) 2.94 (6H, s) 2.90 (1H, dd, *J*= 10.0, 6.8 Hz) 2.43 (3H, s) 1.49 (1H, qqd, *J*= 10.0, 7.2, 6.4 Hz) 0.84 (3H, d, *J*= 7.2 Hz) 0.81 (3H, d, *J*= 6.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 158.0, 150.2, 149.7, 144.6, 135.2, 129.7, 128.0, 118.0, 111.0, 52.8, 43.8, 42.7, 25.5, 21.7, 21.0, 19.2.

Acetic acid 2-phthaloylamino-1-(4-dimethylaminopyridin-3-yl)-3,3-dimethylbutyl ester (30D). A solution of *tert*-leucinol (344 mg, 2.9 mmol) in THF (35 mL) and water (10 mL) was treated with *N*-carbethoxyphthalimide (653 mg, 3.0 mmol). After stirring overnight at rt, $NaHCO_3$ (366 mg, 4.4 mmol) was added. After an additional 2 h, the THF was evaporated and the aqueous solution extracted with Et_2O (3x, 15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and evaporated. The residue contained (*S*)-*N*-phthalimide *tert*-leucinol (**30B**) and ethyl carbamate by ^1H NMR spectroscopy. The ethyl carbamate was removed under high vacuum to afford **30B** as a white solid (439 mg, 60%) which was taken on without further purification.

(*S*)-*N*-Phthalimide *tert*-leucinol (**30B**, 439 mg, 1.77 mmol) was taken up in DCM (3.5 mL) and treated with Et_3N (1.2 mL, 8.60 mmol). The solution was cooled to 0 °C and a solution of SO_3•pyridine (1.41 g, 8.87 mmol) in DMSO (5 mL) was added dropwise over 10 min. After 1 h, the solution was poured into H_2O and extracted with Et_2O. The combined organics were washed with 0.1 M HCl and brine, dried over $MgSO_4$, filtered and concentrated (aspirator). The residue was purified by flash chromatography (silica; 3 x 15 cm) with 25 % Et_2O in hexanes as the eluent yielding (*S*)-*N*-phthalimide-*tert*-leucinal as a white solid (**30C**, 351 mg, 81%) was isolated. In order to avoid possible racemization, this material was used promptly upon purification.

To a solution of *t*BuLi in hexane (0.8 mL, 1.1 M, 0.88 mmol, Acros) at –78 °C was added a solution of 3-bromo-4-dimethylaminopyridine (92 mg, 0.46 mmol) in THF (2 mL) dropwise. The resulting solution was added dropwise to a solution of (*S*)-*N*-phthalimide-*tert*-leucinal (49 mg, 0.20

mmol) in THF (5 mL) at –78 °C. The solution was stirred at –78 °C for 1 h, then quenched with Ac_2O (1 mL). The solution was warmed to rt, and the solution was poured into 2 M NaOH (10 mL) and extracted with CH_2Cl_2 (3x, 10mL), and the combined organic layers were dried over $MgSO_4$, filtered and evaporated yielding a yellow oil that was purified by flash chromatography to remove excess DMAP (silica gel; 5 x 15 cm column) using 5% Et_3N in EtOAc as the eluent, yielding **30D** as a yellow solid. This material was recrystallized from toluene/hexanes yielding **30D** as a white powder (8.9 mg, 11%, >98:2 dr).

2-Dibenzylamino-1-(4-dimethylaminopyridin-3-yl)-3-methylbutanol (30F). To a solution of *t*BuLi in hexane (2.8 mL, 1.6 M, 4.9 mmol, Acros) at –78 °C was added a solution of 3-bromo-4-dimethylaminopyridine (453 mg, 2.25 mmol) in THF (25 mL) dropwise. The resulting solution was added dropwise to a solution of *N*,*N*-dibenzylvalinal (**30E**, 429 mg, 1.50 mmol) in THF (15 mL) at –78 °C. The solution was stirred at –78 °C for 1 h, then quenched with Ac_2O (1.4 mL). The solution was warmed to rt, and extracted from 2 M NaOH with CH_2Cl_2 (3x, 50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated (aspirator). Purification by flash chromatography (30% acetone in hexanes) afforded **30F** as a clear oil (53 mg, 8%). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.39 (1H, d, *J*= 5.9 Hz) 8.37 (1H, s) 7.28-7.18 (10H, m) 6.87 (1H, d, *J*= 5.9 Hz) 6.59 (1H, d, *J*= 5.4 Hz) 3.78 (2H, d, *J*= 13.7 Hz) 3.58 (2H, d, *J*= 13.7 Hz) 2.86 (1H, dd, *J*= 5.4, 2.9 Hz) 2.78 (6H, s) 2.67 (6H, s) 2.18-2.11 (1H, m) 2.12 (3H, s) 1.12 (3H, d, *J*= 7.3 Hz) 0.74 (3H, d, *J*= 6.8 Hz).

2-Benzoylamino-1-(4-dimethylaminopyridin-3-yl)-3,3-dimethylbutanol (31B). To a solution of *t*BuLi in hexane (3.8 mL, 0.6 M, 2.3 mmol, Acros) at –78 °C was added a solution of 3-bromo-4-dimethylaminopyridine (232 mg, 1.15 mmol) in THF (11 mL) dropwise. The resulting solution was added dropwise to a solution of *N*- benzoyl-*tert*-leucinal (110 mg, 0.50 mmol) in THF (5 mL) at –78 °C. The solution was stirred at –78 °C for 1 h, then quenched with H_2O (5 mL). The solution was warmed to rt, and extracted from brine with CH_2Cl_2 (3x, 50 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated (aspirator). The residue was purified by flash chromatrography (40% acetone in hexanes) to yield alcohol **31B** as a white solid (120 mg, 70%, dr >98:2). Analytical tlc, 40% Et_2O in hexanes, Rf= 0.06. Molecular ion calcd for

$C_{20}H_{27}N_3O_2$: 342.2182; [M+H], ESMS found *m/z*= 342.2175; IR (neat, cm^{-1}) 3303, 1646, 1592, 1513, 1486; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51 (1H, s) 8.18 (1H, d, *J*= 5.5 Hz) 7.68-7.65 (2H, m) 7.46-7.34 (3H, m) 6.86 (1H, d, *J*= 5.5 Hz) 6.84 (1H, d, *J*= 10.2 Hz) 5.48 (1H, s) 5.40 (1H, s) 4.17 (1H, d, *J*= 10.2 Hz) 2.67 (6H, s) 1.09 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.4, 158.5, 149.1, 148.5, 135.0, 132.0, 131.1, 128.5, 126.8, 114.7, 67.1, 59.7, 44.2 35.8, 27.5.

Benzoic acid 2-benzoylamino-1-(4-dimethylaminopyridin-3-yl)-3,3-dimethylbutyl ester (31C). A solution of alcohol **31B** (46 mg, 0.13 mmol) in DCM (0.75 mL) was treated with Et_3N (0.05 mL, 0.4 mmol) and benzoic anhydride (69 mg, 0.30 mmol). After stirring for 20 h at rt, the solution was poured over $NaHCO_3$ (sat., 5 mL) and extracted with DCM (2x, 5 mL). The combined organic layers were washed with $NaHCO_3$ (sat., 5 mL), dried ($MgSO_4$), filtered and condensed. The residue contained product and BzOH by NMR and was taken up in Et_2O and washed with NaOH (2M, 10 mL). The aqueous layer was extracted with Et_2O (3x, 10 mL) and combined organic layers were dried ($MgSO_4$), filtered and condensed to afford the benzoate ester **31C**. The ester was purified by recrystallization from ether/hexanes to afford white crystals (35 mg, 58%). Analytical tlc, 5% MeOH in DCM, Rf= 0.41 Molecular ion calcd for $C_{27}H_{31}N_3O_3$: 446.2444; [M+H], ESMS found *m/z*= 446.2446; IR (neat, cm^{-1}) 3282 (br), 1717, 1661, 1590, 1264, 712; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (1H, s) 8.34 (1H, d, *J*= 5.5 Hz) 8.01-8.06 (2H, m) 7.66-7.61 (3H, m) 7.53-7.40 (5H, m) 6.95 (1H, d, *J*= 5.5 Hz) 6.83 (1H, d, *J*= 1.5 Hz) 6.50 (1H, d, *J*= 10.6 Hz) 4.47 (1H, dd, *J*= 10.6, 1.5 Hz) 2.94 (6H, s) 1.11 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.3, 165.4, 158.3, 150.3, 147.5, 134.9, 133.6, 131.4, 129.5, 128.8, 128.7, 128.5, 126.6, 114.4, 70.8, 59.0, 43.9, 35.3, 27.3.

2-Benzoylamino-1-(4-dimethylaminopyridin-3-yl)-3,3-dimethylbutyl methoxymethyl ether (32B). A solution of alcohol **31B** (34.1 mg, 0.10 mmol) in $(MeO)_2CH_2$ (1 mL) was added $TsOH \cdot H_2O$ (38.6 mg, 0.20 mmol) and a precipitate formed. DCM (0.5 mL) was added to dissolve the ppt and LiBr (3.0 mg) was added followed by P_2O_5 (~100 mg). After 2 h at rt, an additional batch of P_2O_5 (~100 mg) was added. After an additional 30 min, the reaction was quenched slowly with cold $NaHCO_3$ (sat., 1 mL). After ensuring the solution was basic by litmus paper, it was extracted with DCM (2x, 10 mL) and combined organic layers were washed with cold

$NaHCO_3$ (sat., 1x, 10 mL), dried ($MgSO_4$), filtered and condensed. The residue was purified by preparatory TLC (250 micron plate, 25% acetone, 5% Et_3N in hex, developed twice) to afford MOM ether **32B** as a clear oil (12 mg, 32%) Analytical tlc, 25% acetone, 5% Et_3N in hexanes, Rf= 0.25. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.33 (1H, s) 8.31 (1H, d, *J*= 5.5 Hz) 7.70-7.68 (2H, m) 7.50-7.39 (3H, m) 6.91 (1H, d, *J*= 5.5 Hz) 6.60 (1H, d, *J*= 10.2 Hz) 5.60 (1H, s) 4.67 (1H, d, *J*= 6.9 Hz) 4.64 (1H, d, *J*= 6.9 Hz) 4.05 (1H, d, *J*= 10.2 Hz) 3.44 (1H, s) 2.82 (6H, s) 1.14 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.2, 159.2, 149.6, 148.4, 135.0, 131.2, 128.7, 128.6, 126.7, 114.3, 95.2, 71.3, 59.9, 57.3, 44.1, 35.6, 27.4.

2-Benzoylamino-1-(4-dimethylaminopyridin-3-yl)-3,3-dimethylbutyl benzyl ether (32D). A solution of alcohol **31B** (50 mg, 0.15 mmol) in THF (1.0 mL) was cooled to -78 °C and added to sodium hexamethyldisilazide (65 mg, 0.35 mmol) at -78 °C and the solution turned yellow. The alcohol flask was rinsed with THF (0.5 mL) and this solution was added to the NaHMDS solution. After 15 min, a cooled solution of benzyl bromide (0.20 mL, 0.75M in THF) was added. The solution was allowed to warm gradually over 1.5 h, and then tetrabutylammonium iodide (5.5 mg, 0.015 mmol) was added. After 7 h, the reaction was poured over brine (10 mL) and extracted with DCM (3x, 10 mL). Combined organic layers were dried ($MgSO_4$), filtered and condensed. The residue was purified by flash chromatography (25% acetone in hexanes) to afford benzyl ether **32D** as a white solid (45 mg, 71%). The catalyst could be recrystallized from hot hexanes as fine needles. Analytical tlc, 25% acetone in hexanes, Rf= 0.14. mp = 132-135 °C. $[\alpha]_D$ = +22.8 (c= 0.0076, DCM). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.14. Molecular ion calcd for $C_{27}H_{33}N_3O_2$: 432.2651; [M+H], ESMS found *m/z*= 432.2640; IR (neat, cm^{-1}) 1667, 1586, 1509, 1484; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.49 (1H, s) 8.35 (1H, d, *J*= 5.5 Hz) 7.62 (2H, d, *J*= 7.0 Hz) 7.47-7.31 (8H, m) 6.96 (1H, d, *J*= 5.5 Hz) 6.65 (1H, d, *J*= 10.2 Hz) 5.29 (1H, s) 4.54 (1H, d, *J*= 11.0 Hz) 4.40 (1H, d, *J*= 11.0 Hz) 4.14 (1H, d, *J*= 10.2 Hz) 2.80 (6H, s) 1.09 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 167.3, 159.6, 149.7, 148.6, 137.2, 135.0, 131.1, 128.8, 128.6, 128.5, 128.1, 126.7, 114.7, 74.0, 71.0, 59.9, 44.3, 35.7, 27.6.

MOM ether catalyst 32B catalyzed rearrangement of enol carbonate 26A. A solution of enol carbonate **26A** (50 mg, 0.1 mmol) in $CDCl_3$ (0.7 mL) in an NMR tube was treated with

MOM ether catalyst **32B** (4.0 mg, 10 mol%) at rt and the solution remained colorless. The reaction was monitored by ^{1}H NMR spectroscopy every 5-10 minutes. After 2 h, catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield *C*-carboxylated oxindole **25Ba** as colorless oil (45 mg, 90%, 66% ee). Flushing the silica plug with 5% Et_3N in EtOAc recovered a light yellow oil containing MOM ether **32B** unchanged. **3-Benzoxycarbonyl-1-diphenylacetyl-3-methyloxindole 26B:** HPLC (Chiralcel AD, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 13.3 min (major), T_R = 15.8 min (minor). Molecular ion calcd for $C_{31}H_{25}NO_4$: 498.1681; [M+Na], ESMS found *m/z*= 498.1689; IR (neat, cm^{-1}) 1762, 1744, 1713; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.28 (1H, d, *J*= 8.2 Hz) 7.38-7.15 (16H, m) 6.99-6.96 (2H, m) 6.56 (1H, s) 4.98 (1H, d, *J*= 12.5 Hz) 4.91 (1H, d, *J*= 12.5 Hz) 1.62 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.0, 173.0, 168.5, 140.2, 138.2, 128.1, 125.0, 129.5, 129.3, 129.1, 128.8, 128.5, 128.5, 128.4, 128.1, 127.3, 127.2, 127.2, 125.6, 122.7, 116.8, 67.4, 57.6, 55.9, 20.3.

Benzyl ether catalyst 32D catalyzed rearrangement of enol carbonate 26A. A solution of enol carbonate **26A** (47 mg, 0.1 mmol) in $CHCl_3$ (0.7 mL) was treated with benzyl ether catalyst **32D** (3.9 mg, 10 mol%) at rt and the solution remained colorless. After 3 h, catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield *C*-carboxylated oxindole **25Ba** as colorless oil (46 mg, 97%, 61% ee). Flushing the silica plug with 5% Et_3N in EtOAc recovered a light yellow oil containing benzyl ether **32D** unchanged.

Representative procedure for the benzyl ether catalyst 32D catalyzed rearrangement of *N*-acetyl protected enol carbonates 25A. 1-Acetyl-3-methyl-3-phenoxycarbonyloxindole (25Ba). A solution of enol carbonate **25Aa** (31 mg, 0.1 mmol) in EtOAc (0.4 mL) was treated with a solution of benzyl ether catalyst **32D** in EtOAc (0.1 mL, 0.1 M, 10 mol%) at rt and the solution remained colorless. After 1 h, catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield *C*-carboxylated oxindole **25Ba** as colorless oil (30 mg, 97%,

5% ee). Flushing the silica plug with 5% Et_3N in EtOAc recovered a light yellow oil containing benzyl ether **32D** unchanged (4.5 mg).

1-Acetyl-3-methoxycarbonyl-3-methyloxindole (25Bb). Following the representative procedure outlined above, enol carbonate **25Ab** (24 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **25Bb** as a clear oil after 5 h (23 mg, 93%, 33% ee). HPLC (Chiralcel OJ, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 14.0 min (minor), T_R = 17.4 min (major).

1-Acetyl-3-benzyoxycarbonyl-3-methyloxindole (25Bd). Following the representative procedure outlined above, enol carbonate **25Ad** (32 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **25Bb** as a clear oil after 5 h (31 mg, 95%, 40% ee). HPLC (Regis (*R*,*R*)-Whelk-O, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 13.5 min (major), T_R = 15.4 min (minor).

Representative procedure for the synthesis of *N*-diphenylacetyl enol carbonates 35A: 1-Diphenylacetyl-2-methoxycarbonoxy-3-methylindole (35Aa). A solution of oxindole **20Ba** (512 mg, 1.50 mmol) in THF (7.5 mL) was treated with triethylamine (0.23 mL, 1.65 mmol, 1.1 equiv) and cooled to 0 °C. Methyl chloroformate (0.13 mL, 1.68 mmol, 1.1 equiv) was added dropwise. The solution was allowed to warm to rt and after 30 min the solution was diluted with EtOAc (20 mL) and washed with water (15 mL). The aqueous layer was extracted with EtOAc (1x, 10 mL) and combined organic layers were washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was recrystallized from EtOH to yield **35Aa** as a colorless crystalline solid (441 mg, 75%, 2 batches). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.44-8.40 (1H, m) 7.46-7.43 (1H, m) 7.35-7.23 (12H, m) 5.99 (1H, s) 3.61 (3H, s) 2.06 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.4, 151.7, 138.8, 136.9, 132.9, 129.2, 128.6, 128.2, 127.3, 125.3, 123.9, 118.5, 116.7, 105.9, 58.3, 56.2, 7.4.

1-Diphenylacetyl-3-methyl-2-(2,2,2-trichloro-1,1-dimethylethoxy)carbonoxyindole (35Ab). Using the general procedure outlined above for the synthesis of *N*-diphenylacetyl enol carbonates, oxindole **20Ba** (259 mg, 0.76 mmol) yielded enol carbonate **35Ab** after recrystallization from EtOH/H_2O as a white crystalline solid (134 mg, 32%). IR (neat, cm^{-1}) 1785, 1706, 1644; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.38 (1H, d, *J*= 7.8 Hz) 7.44 (1H, d, *J*= 7.0 Hz)

7.36-7.23 (12H, m) 5.99 (1H, s) 2.09 (2H, s) 1.83 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.5, 148.3, 138.7, 136.8, 133.0, 129.1, 128.7, 128.1, 127.4, 125.4, 123.9, 118.5, 116.6, 105.9, 104.6, 92.1, 77.2, 58.1, 20.9, 7.5.

1-Diphenylacetyl-3-methyl-2-phenoxycarbonoxyindole (35Ac). Using the general procedure outlined above for the synthesis of *N*-diphenylacetyl enol carbonates, oxindole **20Ba** (512 mg, 1.50 mmol) yielded enol carbonate **35Ac** after recrystallization from EtOH/H_2O as a white crystalline solid (606 mg, 88%). Molecular ion calcd for $C_{30}H_{23}NO_4$: 484.1525; [M+Na], ESMS found *m/z*= 484.1520; IR (neat, cm^{-1}) 1785, 1702, 1644, 1201; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.37 (1H, d, *J*= 8.6 Hz) 7.47 (1H, d, *J*= 7.4 Hz) 7.40-7.23 (15H, m) 7.01 (2H, d, *J*= 7.8 Hz) 6.09 (1H, s) 2.15 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.5, 150.7, 149.6, 138.8, 136.8, 132.8, 129.5, 129.1, 128.7, 128.2, 127.4, 126.6, 125.4, 124.0, 120.4, 118.7, 116.5, 106.1, 58.4, 7.6.

2-*iso*-Butoxycarbonoxy-1-diphenylacetyl-3-methylindole (35Ag). Using the general procedure outlined above for the synthesis of *N*-diphenylacetyl enol carbonates, oxindole **20Ba** (514 mg, 1.51 mmol) yielded enol carbonate **35Ag** after recrystallization from EtOH/H_2O as a white crystalline solid (548 mg, 82%). IR (neat, cm^{-1}) 1781, 1702, 1644; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.45-8.41 (1H, m) 7.46-7.42 (1H, m) 7.35-7.23 (12H, m) 6.00 (1H, s) 3.75 (2H, d, *J*= 6.7, 6.7 Hz) 2.06 (3H, s) 1.94 (1H, dseptet, *J*= 0.94 (6H, d, *J*= 6.7 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.5, 151.2, 138.8, 137.0, 133.0, 129.2, 128.6, 128.3, 127.3, 125.3, 123.9, 118.4, 116.7, 105.7, 75.8, 58.2, 27.6, 18.8 7.4.

1-Diphenylacetyl-3-methyl-2-(2,2,2-trichloroethoxy)carbonoxyindole (35Ab). Using the general procedure outlined above for the synthesis of *N*-diphenylacetyl enol carbonates, oxindole **20Ba** (255 mg, 0.75 mmol) yielded enol carbonate **35Ab** after recrystallization from EtOH/H_2O as a white crystalline solid (225 mg, 58%). IR (neat, cm^{-1}) 1793, 1706, 1644; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43 (1H, d, *J*= 7.8 Hz) 7.46 (1H, d, *J*= 7.0 Hz) 7.37-7.24 (12H, m) 5.97 (1H, s) 4.23 (2H, s) 2.08 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.2, 150.2,138.7, 136.4, 132.9, 129.2, 128.6, 128.0, 127.4, 125.6, 124.1, 118.7, 116.8, 106.3, 93.6, 77.4, 58.5, 7.4.

1-Diphenylacetyl-2-ethoxycarbonoxy-3-methylindole (35Af). Using the general procedure outlined above for the synthesis of *N*-diphenylacetyl enol carbonates, oxindole **20Ba** (514 mg, 1.51 mmol) yielded enol carbonate **35Af** after recrystallization from hexanes/Et_2O as a white crystalline solid (454 mg, 73%). IR (neat, cm^{-1}) 1779, 1702, 1644; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.42 (1H, d, *J*= 7.4 Hz) 7.46-7.42 (1H, m) 7.35-7.23 (12H, m) 6.00 (1H, s) 3.99 (2H, q, *J*= 7.0 Hz) 2.06 (3H, s) 1.27 (3H, t, *J*= 7.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.5, 151.0, 138.9, 137.0, 132.9, 129.1, 128.5, 128.3, 127.3, 125.3, 123.9, 118.5, 116.7, 105.8, 66.0, 58.2, 13.9, 7.4.

2-Allyloxycarbonoxy-1-diphenylacetyl-3-methylindole (35Ag). Using the general procedure outlined above for the synthesis of *N*-diphenylacetyl enol carbonates, oxindole **20Ba** (512 mg, 1.50 mmol) yielded enol carbonate **35Ag** after recrystallization from hexanes/Et_2O as a white crystalline solid (498 mg, 78%). IR (neat, cm^{-1}) 1781, 1702, 1644; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43 (1H, d, *J*= 7.4 Hz) 7.46-7.42 (1H, m) 7.35-7.23 (13H, m) 5.99 (1H, s) 5.89 (1H, ddd, *J*= 17.2, 10.2, 5.9 Hz) 5.38 (1H, dd, *J*= 17.2, 1.6 Hz) 5.32 (1H, dd, *J*= 10.2, 1.2 Hz) 4.41 (1H, ddd, *J*= 5.9, 1.6, 1.2 Hz) 2.06 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.5, 150.9, 138.8, 136.9, 132.9, 130.3, 129.2, 128.6, 128.2, 127.3, 125.3, 123.9, 120.1, 118.5, 116.7, 105.9, 70.127, 58.3, 7.4.

1-Diphenylacetyl-3-methyl-2-*p*-nitrobenzoxycarbonoxyindole (35Ah). Using the general procedure outlined above for the synthesis of *N*-diphenylacetyl enol carbonates, oxindole **20Ba** (256 mg, 0.75 mmol) yielded enol carbonate **35Ah** after recrystallization from EtOH/H_2O as a white crystalline solid (254 mg, 65%). IR (neat, cm^{-1}) 1783, 1702, 1644, 1212; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.34 (1H, d, *J*= 8.2 Hz) 8.21 (2H, d, *J*= 8.6 Hz) 7.48 (2H, d, *J*= 8.6 Hz) 7.45 (1H, dd, *J*= 6.6, 2.0 Hz) 7.35-7.21 (13H, m) 5.95 (1H, s) 5.01 (2H, s) 2.04 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.3, 151.1, 148.1, 141.0, 138.7, 136.8, 132.8, 129.1, 128.6, 128.4, 128.1, 127.4, 125.5, 124.0, 123.9, 118.7, 116.5, 106.1, 69.4, 58.4, 7.3.

1-Diphenylacetyl-3-methyl-2-(1-naphthyl)methoxycarbonoxyindole (35Ai). A solution of oxindole **20Ba** (468 mg, 1.40 mmol) in THF (7 mL) was treated with triethylamine (0.3 mL, 2.0 mmol, 1.4 equiv) and cooled to 0 °C. 1-Naphthylmethyl chloroformate (455 mg, 1.8 mmol, ~85%,

1.3 equiv) was added. The solution was allowed to warm to rt and after 1 h the solution was diluted with EtOAc (20 mL) and washed with water (15 mL). The aqueous layer was extracted with EtOAc (1x, 10 mL) and combined organic layers were washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was recrystallized from EtOH/H_2O to yield enol carbonate **35Ai** as a white crystalline solid (486 mg, 68%). Analytical tlc, 10% Et_2O in hexanes, Rf= 0.26. Molecular ion calcd for $C_{35}H_{27}NO_4$: 548.1891; [M+Na], ESMS found *m/z*= 548.1853; IR (neat, cm^{-1}) 1777, 1702, 1644; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.42 (1H, d, *J*= 7.5 Hz) 8.00-7.95 (1H, m) 7.93-7.83 (2H, m) 7.57-7.50 (3H, m) 7.47 (1H, dd, *J*= 7.1, 6.7 Hz) 7.43-7.40 (1H, m) 7.34-7.41 (13H, m) 5.87 (1H, s) 5.49 (2H, s) 1.94 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.4, 151.2, 138.7, 136.9, 133.7, 132.9, 131.4, 130.1, 129.5, 129.1, 128.9, 128.5, 128.2, 128.1, 127.2, 126.9, 126.2, 125.3, 125.2, 123.9, 123.2, 118.5, 116.7, 105.9, 69.7, 58.3, 7.3.

Representative procedure for the rearrangement of *N*-diphenylacetyl enol carbonates 35A using benzyl ether 32D: 1-Diphenylacetyl-3-methoxycarbonyl-3-methyloxindole (35Ba). A solution of enol carbonate **35Aa** (39 mg, 0.1 mmol) in $CHCl_3$ (0.5 mL) was treated with benzyl ether catalyst **32D** (4.3 mg, 10 mol%). After 4 h at rt, catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield *C*-carboxylated oxindole **35Ba** as a white solid (33 mg, 84%, 12% ee). The catalyst could be recovered by flushing the silica plug with 5% Et_3N in EtOAc (20 mL). HPLC (Chiralcel AS, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 6.9 min (minor), T_R = 9.3 min (major). IR (neat, cm^{-1}) 1762, 1739, 1702; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.29 (1H, d, *J*= 8.2 Hz) 7.38-7.18 (13H, m) 6.58 (1H, s) 3.45 (3H, s) 1.61 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.1, 173.1, 169.2, 140.2, 138.1, 138.0, 129.5, 129.3, 129.3, 128.9, 128.6, 128.5, 127.3, 127.2, 125.6, 122.7, 116.8, 57.7, 55.6, 53.1, 20.4.

1-Diphenylacetyl-3-methyl-3-(2,2,2-trichloro-1,1-dimethylethoxy)carbonyloxindole (35Bb). Following the representative procedure outlined above for rearrangement of *N*-diphenylacetyl enol carbonates **35A** using benzyl ether **32D**, enol carbonate **35Ab** (54 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **35Bb** as a clear oil after 6 h (54 mg, 99%, 18% ee).

HPLC (Chiralcel OD, 4.6 mm x 25 cm, 99.5:0.5 hexanes/isopropanol, 1.0 mL/min) T_R = 8.2 min (major), T_R = 10.3 min (minor). IR (neat, cm^{-1}) 1766, 1748, 1713; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.30 (1H, d, *J*= 8.2 Hz) 7.38-7.17 (13H, m) 6.54 (1H, s) 1.81 (3H, s) 1.67 (3H, s) 1.61 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 174.5, 172.8, 166.4, 140.6, 138.3, 138.3, 129.5, 129.4, 129.1, 128.8, 128.6, 128.5, 127.3, 127.3, 125.6, 122.3, 117.2, 105.1, 90.1, 57.4, 57.0, 21.2, 20.7, 19.6.

1-Diphenylacetyl-3-methyl-3-phenoxycarbonyloxindole (35Bc). Following the representative procedure outlined above for rearrangement of *N*-diphenylacetyl enol carbonates **35A** using benzyl ether **32D**, enol carbonate **35Ac** (46 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **35Bc** as a white solid after 2 h (44 mg, 96%, 32% ee). HPLC (Chiralcel AS, 4.6 mm x 25 cm, 99:1 hexanes/isopropanol, 1.0 mL/min) T_R = 10.0 min (minor), T_R = 11.4 min (major). IR (neat, cm^{-1}) 1766, 1752, 1717; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.34 (1H, d, *J*= 8.2 Hz) 7.40 (1H, ddd, *J*= 8.2, 7.4, 1.6 Hz) 7.37-7.10 (16H, m) 6.71-6.68 (2H, m) 6.62 (1H, s) 5.49 (2H, s) 1.70 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 174.7, 173.1, 167.3, 150.0, 140.4, 138.2, 137.9, 129.8, 129.4, 129.2, 129.1, 128.7, 128.6, 128.5, 127.4, 127.2, 126.2, 125.8, 122.6, 121.0, 117.1, 57.8, 56.0, 20.3.

3-*iso*-Butoxycarbonyl-1-diphenylacetyl-3-methyloxindole (35Bd). Following the representative procedure outlined above for rearrangement of *N*-diphenylacetyl enol carbonates **35A** using benzyl ether **32D**, enol carbonate **35Ad** (40 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **35Bd** as a white solid after 4 h (39 mg, 98%, 41% ee). HPLC (Chiralcel OD, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 17.3 min (major), T_R = 20.2 min (minor). Molecular ion calcd for $C_{28}H_{27}NO_4$: 464.1838; [M+Na], ESMS found *m/z*= 464.1830; IR (neat, cm^{-1}) 1762, 1740, 1713; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.29 (1H, d, *J*= 8.2 Hz) 7.37-7.17 (13H, m) 6.61 (1H, s) 5.49 (2H, s) 3.74 (1H, dd, *J*= 10.6, 6.6 Hz) 3.69 (1H, dd, *J*= 10.6, 6.6 Hz) 1.62 (1H, ddqq, *J*= 6.6, 6.6, 6.6, 6.6 Hz) 1.63 (3H, s) 0.66 (6H, d, *J*= 6.6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.2, 173.0, 168.7, 140.2, 138.3, 138.2, 129.4, 129.3, 129.2, 128.6,, 128.5, 127.3, 127.2, 125.6, 122.6, 116.9, 71.8, 57.5, 56.0, 27.5, 20.3, 18.6.

1-Diphenylacetyl-3-methyl-3-(2,2,2-trichloroethoxy)carbonyloxindole (35Be). Following the representative procedure outlined above for rearrangement of *N*-diphenylacetyl enol carbonates **35A** using benzyl ether **32D**, enol carbonate **35Ae** (53 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **35Be** as a white solid after HPLC (Chiralcel OD, 4.6 mm x 25 cm, 99.5:0.5 hexanes/isopropanol, 1.0 mL/min) T_R = 12.2 min (major), T_R = 14.3 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.31 (1H, d, *J*= 8.2 Hz) 7.39-7.18 (13H, m) 6.58 (1H, s) 4.71 (1H, d, *J*= 12.0 Hz) 4.44 (1H, dd, *J*= 12.0 Hz) 1.69 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 174.2, 172.8, 167.1, 140.4, 138.1, 129.8, 129.2, 129.2, 128.6, 128.1, 127.3, 127.3, 125.6, 122.9, 117.0, 94.0, 74.1, 57.5, 55.8, 20.0.

1-Diphenylacetyl-3-ethoxycarbonyl-3-methyloxindole (35Bf). Following the representative procedure outlined above for rearrangement of *N*-diphenylacetyl enol carbonates **35A** using benzyl ether **32D**, enol carbonate **35Af** (42 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **35Bf** as a white solid after 4 h (40 mg, 95%, 48% ee). HPLC (Chiralcel OD, 4.6 mm x 25 cm, 99.8:0.2 hexanes/isopropanol, 1.0 mL/min) T_R = 34.5 min (major), T_R = 45.3 min (minor). IR (neat, cm^{-1}) 1760, 1739, 1711; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.29 (1H, d, *J*= 8.2 Hz) 7.38-7.18 (13H, m) 6.60 (1H, s) 4.00 (1H, dq, *J*= 10.5, 7.4 Hz) 3.92 (1H, dq, *J*= 10.5, 7.0 Hz) 1.61 (3H, s) 0.96 (3H, dd, *J*= 7.4, 7.0). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.2, 173.1, 168.7, 140.2, 138.2, 138.2, 129.4, 129.3, 129.2, 129.1, 128.5, 128.5, 127.3, 127.3, 125.6, 122.6, 116.6, 62.2, 57.6, 55.8, 20.5, 13.7.

3-Allyloxycarbonyl-1-diphenylacetyl-3-methyloxindole (35Bg). Following the representative procedure outlined above for rearrangement of *N*-diphenylacetyl enol carbonates **35A** using benzyl ether **32D**, enol carbonate **35Ag** (43 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **35Bg** as a white solid after 4 h (39 mg, 91%, 52% ee). HPLC (Chiralcel OD, 4.6 mm x 25 cm, 99.8:0.2 hexanes/isopropanol, 1.0 mL/min) T_R = 39.3 min (major), T_R = 53.7 min (minor). IR (neat, cm^{-1}) 1762, 1742, 1711, 1127; (400 MHz, $CDCl_3$, ppm) δ 8.29 (1H, d, *J*= 8.2 Hz) 7.38-7.18 (13H, m) 6.59 (1H, s) 5.57 (1H, dddd, *J*= 17.2, 10.5, 5.5, 5.1 Hz) 5.07 (1H, ddd, *J*= 10.5, 1.6, 1.2 Hz) 4.99 (1H, ddd, *J*= 17.2, 1.6, 1.2 Hz) 4.40 (1H, dd, *J*= 5.1, 1.6, 1.2 Hz) 4.40 (1H, dd, *J*= 5.4, 1.6, 1.2 Hz) 1.62 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 175.0, 173.1, 168.4, 140.2,

138.2, 138.1, 130.9, 129.5, 129.3, 129.2, 129.0, 128.6, 127.3, 127.2, 125.6, 122.7, 118.,2, 116.9, 66.2, 57.6, 55.8, 20.4.

1-Diphenylacetyl-3-methyl-3-*p*-nitrobenzoxycarbonyloxindole (35Bh). Following the representative procedure outlined above for rearrangement of *N*-diphenylacetyl enol carbonates **35A** using benzyl ether **32D**, enol carbonate **35Ah** (53 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **35Bh** as a white solid after 4 h (49 mg, 92%, 55% ee). HPLC (Chiralcel AD, 4.6 mm x 25 cm, 90:10 hexanes/isopropanol, 1.0 mL/min) T_R = 14.8 min (major), T_R = 18.3 min (minor). IR (neat, cm^{-1}) 1760, 1744, 1711; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.32 (1H, dd, *J*= 8.2, 0.8 Hz) 8.06 (2H, d, *J*= 8.8 Hz) 7.40 (1H, ddd, *J*= 8.2, 6.6, 2.3 Hz) 7.36-7.16 (13H, m) 7.03 (2H, d, *J*= 8.8 Hz) 6.59 (1H, s) 5.49 (2H, s) 1.65 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 1174.8, 173.0, 168.3, 147.6, 142.2, 140.3, 138.1, 130.0, 129.8, 129.3, 129.1, 128.6, 128.5, 128.5, 127.4, 127.4, 127.3, 125.8, 123.7, 122.6, 117.0, 65.7, 57.6, 55.9, 20.2.

1-Diphenylacetyl-3-methyl-3-(1-naphthyl)methoxycarbonyloxindole (35Bi). Following the representative procedure outlined above for rearrangement of *N*-diphenylacetyl enol carbonates **35A** using benzyl ether **32D**, enol carbonate **35Ai** (53 mg, 0.1 mmol) yielded *C*-carboxylated oxindole **35Bi** as a viscous oil after 4 h (53 mg, 99%, 71% ee). Analytical tlc, 10% Et_2O in hexanes, Rf= 0.22. HPLC (Chiralcel AD, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 15.4 min (major), T_R = 19.7 min (minor). Molecular ion calcd for $C_{35}H_{27}NO_4$: 548.1891; [M+Na], ESMS found *m/z*= 548.1859; IR (neat, cm^{-1}) 1760, 1740, 1711; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.20 (1H, d, *J*= 8.2 Hz) 7.81 (1H, d, *J*= 7.8 Hz) 7.79 (1H, d, *J*= 8.2 Hz) 7.57-7.39 (3H, m) 7.38-7.04 (15H, m) 6.44 (1H, s) 5.44 (1H, d, *J*= 12.6 Hz) 5.37 (1H, d, *J*= 12.6 Hz) 1.61 (1H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 174.9, 173.0, 168.5, 138.22, 138.0, 133.5, 131.1, 130.2, 129.4, 129.3, 129.0, 128.7, 128.5, 128.4, 127.3, 127.1, 126.9, 126.5, 125.9, 125.5, 125.1, 123.1, 122.6, 116.8, 66.4, 57.5, 56.0, 20.1.

3-Benzyl-1-diphenylacetyl-2-(1-naphthyl)methoxycarbonoxyindole (36A). A solution of oxindole **20Bc** (263 mg, 0.63 mmol) in THF (3.2 mL) was treated with triethylamine (0.18 mL, 1.3 mmol, 2.1 equiv) and cooled to 0 °C. 1-Naphthylmethyl chloroformate (205 mg, 0.79 mmol, ~85%, 1.3 equiv) was added. The solution was allowed to warm to rt and after 1 h the solution

was diluted with EtOAc (20 mL) and washed with water (15 mL). The aqueous layer was extracted with EtOAc (1x, 10 mL) and combined organic layers were washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was recrystallized from EtOH/H_2O to yield enol carbonate **36A** as small white needles (267 mg, 70%). Analytical tlc, 10% Et_2O in hexanes, Rf= 0.19. Molecular ion calcd for $C_{41}H_{31}NO_4$: 624.2151; [M+Na], ESMS found *m/z*= 624.2154; IR (neat, cm^{-1}) 1779, 1706, 1636, 1200; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.38 (1H, d, *J*= 8.1 Hz) 7.93-7.86 (3H, m) 7.53-7.41 (4H, m) 7.30-7.05 (18H, m) 5.85 (1H, s) 5.40 (2H, s) 3.79 (2H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.6, 151.4, 138.6, 138.1, 137.5, 133.7, 133.1, 131.4, 130.1, 129.4, 129.1, 128.8, 128.5, 128.5, 128.4, 128.2, 127.5, 127.3, 126.9, 126.3, 126.2, 125.3, 125.2, 123.9, 123.2, 119.2, 116.5, 108.7, 69.8, 58.4, 29.0.

3-(2-(*tert*-Butyldiphenylsilanyloxy)ethyl)-1-diphenylacetyl-2-(1-naphthyl)methoxy carbonoxyindole (36B). A solution of oxindole **20Bd** (608 mg, 1.00 mmol) in THF (5 mL) was treated with triethylamine (0.21 mL, 1.5 mmol, 1.5 equiv) and cooled to 0 °C. 1-Naphthylmethyl chloroformate (336 mg, 1.3 mmol, ~85%, 1.3 equiv) was added. The solution was allowed to warm to rt and after 1 h the solution was diluted with EtOAc (20 mL) and washed with water (15 mL). The aqueous layer was extracted with EtOAc (1x, 10 mL) and combined organic layers were washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (10% Et_2O in hex) to yield enol carbonate **36B** as a viscous oil that solidified on standing (569 mg, 72%). Analytical tlc, 10% Et_2O in hexanes, Rf= 0.22. Molecular ion calcd for $C_{52}H_{47}NO_5Si$: 816.3121; [M+Na], ESMS found *m/z*= 816.3148; IR (neat, cm^{-1}) 1779, 1706, 1638; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.34 (1H, d, *J*= 8.2 Hz) 7.95-7.86 (3H, m) 7.59-7.06 (27H, m) 5.81 (1H, s) 5.42 (2H, s) 3.77 (2H, t, *J*= 7.2 Hz) 2.70 (2H, t, *J*= 7.2 Hz) 1.00 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.5, 151.6, 138.6, 137.5, 135.5, 133.7, 133.6, 132.9, 131.3, 130.0, 129.6, 129.5, 129.0, 128.8, 128.5, 127.9, 127.6, 127.6, 127.2, 126.9, 126.2, 125.2, 125.1, 123.8, 123.1, 119.0, 116.5, 107.0, 69.7, 62.3, 58.3, 26.8, 26.5, 19.1.

1-Diphenylacetyl-2-(1-naphthyl)methoxycarbonoxy-3-phenylindole (36C). A solution of oxindole **20Bg** (101 mg, 0.25 mmol) in THF (1.3 mL) was treated with triethylamine (0.05 mL,

0.36 mmol, 1.4 equiv) and cooled to 0 °C. 1-Naphthylmethyl chloroformate (123 mg, 0.47 mmol, ~85%, 1.9 equiv) was added. The solution was allowed to warm to rt and after 1 h the solution was diluted with EtOAc (10 mL) and washed with water (10 mL). The aqueous layer was extracted with EtOAc (1x, 10 mL) and combined organic layers were washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (10% Et_2O in hex) to yield enol carbonate **36C** as a viscous oil that solidified on standing (120 mg, 81%). Analytical tlc, 10% Et_2O in hexanes, Rf= 0.38. Molecular ion calcd for $C_{40}H_{29}NO_4$: 610.1994; [M+Na], ESMS found *m/z*= 610.1984; IR (neat, cm^{-1}) 1781, 1706, 1644, 1196; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.48 (1H, d, *J*= 8.3 Hz) 7.88 (1H, d, *J*= 8.2 Hz) 7.86 (1H, d, *J*= 9.4 Hz) 7.73 (1H, d, *J*= 8.2 Hz) 7.61 (1H, d, *J*= 7.8 Hz) 7.55-7.19 (21H, m) 5.97 (1H, s) 5.19 (2H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.8, 150.7, 138.6, 136.5, 133.7, 133.1, 131.3, 130.5, 130.0, 129.2, 129.1, 128.8, 128.7, 128.6, 128.6, 128.5, 128.1, 127.6, 127.3, 126.9, 126.7, 126.1, 125.6, 125.1, 124.3, 123.1, 119.4, 116.8, 111.2, 77.2, 69.6, 58.7.

5-Bromo-1-diphenylacetyl-3-methyl-2-(1-naphthyl)methoxycarbonoxyindole (36D). Using the general procedure outlined above for the synthesis of *N*-diphenylacetyl enol carbonates, oxindole **23B** (105 mg, 0.25 mmol) yielded enol carbonate **36D** after recrystallization from EtOH/H_2O as small white needles (105 mg, 70%). Analytical tlc, 15% DCM in hexanes, Rf= 0.25. Molecular ion calcd for $C_{35}H_{26}BrNO_4$: 626.0943; [M+Na], ESMS found *m/z*= 626.0941; IR (neat, cm^{-1}) 1781, 1706, 1642, 1198; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.34 (1H, d, *J*= 9.0 Hz) 7.96 (1H, dd, *J*= 5.9, 3.5 Hz) 7.94-7.88 (1H, m) 7.57-7.51 (4H, m) 7.47 (1H, dd, *J*= 7.8, 7.0 Hz) 7.40 (1H, dd, *J*= 9.0, 2.0 Hz) 7.27-7.20 (7H, m) 7.15-7.10 (4H, m) 5.82 (1H, s) 5.50 (2H, s) 1.92 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 170.4, 151.0, 138.4, 137.5, 133.8, 131.6, 131.4, 130.3, 130.0, 129.4, 129.0, 128.9, 128.6, 128.2, 128.1, 127.4, 127.0, 126.3, 125.2, 123.1, 121.3, 118.3, 117.2, 105.2, 69.9, 58.3, 7.3.

Representative procedure for the optimized benzyl ether catalyst 32D promoted rearrangement of enol carbonates 26Ai and 36A-36D: 1-Diphenylacetyl-3-methyl-3-(1-naphthyl)methoxycarbonyloxindole (35Bi). Enol carbonate **35Ai** (105 mg, 0.20 mmol) and benzyl ether catalyst **32D** (8 mg, 0.019M, 9 mol%) were dissolved in a cooled (-20 °C) solution of

$CHCl_3$ (0.25 mL). The solution was stirred at -20 °C in a Cryocool. After 22.5 h, the catalyst was quenched with TsOH (20 mg) in Et_2O (2 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield *C*-carboxylated oxindole **35Bi** as a viscous oil (96 mg, 91%, 90% ee). The catalyst could be recovered by flushing the silica plug with 5% Et_3N in EtOAc (20 mL). $[\alpha]_D$ = +11.7 (c= 0.0069, 90% ee, DCM). HPLC (Chiralcel AD, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 15.4 min (major, (*S*) according to the positive optical rotation response by the in-line polarimetry detector), T_R = 19.7 min (minor).

3-Benzyl-1-diphenylacetyl-3-(1-naphthyl)methoxycarbonyloxindole (36E). Enol carbonate **36A** (116 mg, 0.19 mmol) and benzyl ether catalyst **32D** (9 mg, 0.02 mmol, 10 mol %) were dissolved in a cooled (-20 °C) solution of $CHCl_3$ (0.25 mL). The solution was stirred at -20 °C in a Cryocool. After 22.5 h, the catalyst was quenched with TsOH (20 mg) in Et_2O (2 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield *C*-carboxylated oxindole **36E** as a viscous oil (114 mg, 98%, 92% ee). The catalyst could be recovered by flushing the silica plug with 5% Et_3N in EtOAc (20 mL). Analytical tlc, 25% Et_2O in hexanes, Rf= 0.37. HPLC (Regis (*R*,*R*)-Whelk-O, 4.6 mm x 25 cm, 90:10 hexanes/isopropanol, 1.0 mL/min) T_R = 13.7 min (major, (*S*) according to the positive optical rotation response by the in-line polarimetry detector), T_R = 19.5 min (minor). Molecular ion calcd for $C_{41}H_{31}NO_4$: 624.2151; [M+Na], ESMS found *m/z*= 624.2143; IR (neat, cm^{-1}) 1760, 1740, 1713; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.02 (1H, d, *J*= 8.2 Hz) 7.83 (1H, d, *J*= 9.0 Hz) 7.80 (1H, d, *J*= 9.4 Hz) 7.64 (1H, d, *J*= 8.2 Hz) 7.47-7.04 (17H, m) 6.96 (1H, dd, *J*= 7.4, 7.4 Hz) 6.82 (1H, d, *J*= 7.8 Hz) 6.80 (1H, d, *J*= 7.4 Hz) 6.59 (1H, d, *J*= 7.0 Hz) 6.39 (1H, s) 5.52 (1H, d, *J*= 12.5 Hz) 5.49 (1H, d, *J*= 12.5 Hz) 3.57 (1H, d, *J*= 13.4 Hz) 3.50 (1H, d, *J*= 13.4 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 173.7, 172.5, 168.2, 140.8, 138.3, 138.0, 133.6, 133.5, 131.2, 130.2, 129.7, 129.5, 129.4, 129.2, 129.2, 128.6, 128.6, 128.4, 128.0, 127.2, 127.1, 127.0, 126.6, 126.2, 126.0, 125.2, 125.1, 123.4, 123.2, 116.9, 66.6, 61.9, 57.3, 40.1.

3-(2-(*tert*-Butyldiphenylsilanyloxy)ethyl)-1-diphenylacetyl-3-(1-naphthyl)methoxy carbonyloxindole (36F). Enol carbonate **36B** (155 mg, 0.20 mmol) and benzyl ether catalyst **32D** (9 mg, 0.02 mmol, 10 mol %) were dissolved in a cooled (-20 °C) solution of $CHCl_3$ (0.25

mL). The solution was stirred at -20 °C in a Cryocool. After 22.5 h, the catalyst was quenched with TsOH (20 mg) in Et_2O (2 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield *C*-carboxylated oxindole **36F** as a viscous oil (154 mg, 99%, 94% ee). The catalyst could be recovered by flushing the silica plug with 5% Et_3N in EtOAc (20 mL). Analytical tlc, 5% acetone in hexanes, Rf= 0.21. HPLC (Chiralcel AD, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 10.2 min (minor), T_R = 17.0 min (major, (*S*) according to the positive optical rotation response by the in-line polarimetry detector). Molecular ion calcd for $C_{52}H_{47}NO_5Si$: 816.3121; [M+Na], ESMS found *m/z*= 816.3152; IR (neat, cm^{-1}) 1764, 1740, 1710; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.32 (1H, d, *J*= 8.3 Hz) 7.80 (1H, d, *J*= 9.0 Hz) 7.75 (1H, d, *J*= 8.3 Hz) 7.53-7.49 (2H, m) 7.46-7.16 (22H, m) 7.12-7.00 (5H, m) 6.94 (1H, dd, *J*= 7.8, 1.1 Hz) 6.52 (1H, s) 5.38 (1H, d, *J*= 12.5 Hz) 5.09 (1H, d, *J*= 12.5 Hz) 3.40-3.26 (2H, m) 2.74 (1H, ddd, *J*= 14.5, 9.4, 5.9 Hz) 2.47 (1H, ddd, *J*= 14.5, 4.7, 3.9 Hz) 0.82 (9H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 174.2, 172.8, 168.1, 141.3, 138.2, 135.5, 135.5, 135.3, 135.3, 133.4, 132.9, 132.8, 130.9, 130.3, 129.7, 129.5, 129.5, 129.3, 129.0, 129.0, 128.9, 128.5, 128.5, 128.3, 128.1, 127.7, 127.6, 127.5, 127.1, 127.0, 126.4, 126.2, 126.1, 125.9, 125.8, 125.1, 125.0, 123.2, 122.9, 117.0, 66.1, 59.4, 58.8, 57.5, 44.7, 35.1, 26.6, 26.5, 18.8, 8.7.

1-Diphenylacetyl-3-(1-naphthyl)methoxycarbonyl-3-phenyloxindole (36G). Enol carbonate **36C** (59 mg, 0.1 mmol) was treated with a cooled (-20 °C) solution of benzyl ether catalyst **32D** in $CHCl_3$ (0.5 mL, 0.02M, 10 mol %). The solution was stirred at -20 °C in a Cryocool. After 2 h, the catalyst was quenched with TsOH (10 mg) in Et_2O (1 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a viscous oil. The residue was purified by preparatory tlc (10% Et_2O in hexanes) to afford *C*-carboxylated oxindole **36G** (57 mg, 97%, 92% ee). The catalyst could be recovered by flushing the silica plug with 5% Et_3N in EtOAc (20 mL). Analytical tlc, 10% Et_2O in hexanes, Rf= 0.28. HPLC (Chiralcel AD, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 32.8 min (major, (*S*) according to the positive optical rotation response by the in-line polarimetry detector), T_R = 41.3 min (minor). Molecular ion calcd for $C_{40}H_{29}NO_4$: 610.1994; [M+Na], ESMS found *m/z*= 610.1990; IR (neat, cm^{-1}) 1764, 1744,1711; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.26 (1H, d, *J*= 8.2

Hz) 7.81 (1H, d, *J*= 7.8 Hz) 7.79 (1H, d, *J*= 8.2 Hz) 7.54 (1H, d, *J*= 8.6 Hz) 7.44 (1H, t, *J*=7.4 Hz) 7.36-7.06 (22H, m) 6.45 (1H, s) 5.53 (1H, d, *J*= 12.5 Hz) 5.46 (1H, d, *J*= 12.5 Hz). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 173.1, 172.4, 168.1, 141.0, 138.1, 137.9, 135.0, 133.5, 131.2, 130.1, 129.9, 129.4, 129.2, 129.1, 128.6, 128.5, 128.5, 128.5, 128.4, 128.1, 127.3, 127.2126.5, 126.0, 125.9. 125.5, 125.3, 125.1, 123.2, 116.8, 77.2, 66.7, 65.0, 57.5.

5-Bromo-1-diphenylacetyl-3-methyl-3-(1-naphthyl)methoxycarbonyloxindole (36H). Enol carbonate **36D** (242 mg, 0.4 mmol) was treated with a cooled (-20 °C) solution of benzyl ether catalyst **32D** in $CHCl_3$ (2 mL, 0.02M, 10 mol %). The solution was stirred at -20 °C in a Cryocool. After 5 h, the catalyst was quenched with TsOH (40 mg) in Et_2O (4 mL) and the solution was applied to a silica plug, flushed with 3:1 Hex:Et_2O, and the eluent evaporated to yield a viscous oil. The oil was purified by flash chromatography (15% DCM in hexanes) to afford the pure oxindole **36H** as a viscous oil (222 mg, 92%, 90% ee). The catalyst could be recovered by flushing the silica plug with 5% Et_3N in EtOAc (20 mL). Analytical tlc, 15% DCM in hexanes, Rf= 0.16. HPLC (Chiralcel AD, 4.6 mm x 25 cm, 98:2 hexanes/isopropanol, 1.0 mL/min) T_R = 14.9 min (major, (*S*) according to the positive optical rotation response by the in-line polarimetry detector), T_R = 21.1 min (minor). Molecular ion calcd for $C_{35}H_{26}BrNO_4$: 626.093; [M+Na], ESMS found *m/z*= 626.0949; IR (neat, cm^{-1}) 1764, 1744, 1713, 1111; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.05 (1H, d, *J*= 8.6 Hz) 7.84 (1H, d, *J*= 7.0 Hz) 7.81 (1H, d, *J*= 5.6 Hz) 7.53 (1H, d, *J*= 8.6 Hz) 7.45 (1H, dd, *J*= 7.8, 7.0 Hz) 7.40-7.08 (15H, m) 6.41(1H, s) 5.47 (1H, d, *J*= 12.3 Hz) 5.37 (1H, d, *J*= 12.3 Hz) 1.58 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 174.1, 173.8, 167.9, 139.1, 138.0, 137.8, 133.6, 132.4, 131.1, 130.6, 129.9, 129.6, 129.2, 129.1, 128.6, 128.6, 128.5, 127.4, 127.3, 126.6, 126.0, 125.7, 125.0, 122.9, 118.5, 118.3, 77.2, 66.8, 57.5, 55.9, 20.0.

5-Bromo-3-methyl-3-(1-naphthyl)methoxycarbonyloxindole (e13A). To a solution of oxindole **36H** in MeCN (0.75 mL, 0.2M, 0.15 mmol) was added Et_2NH (0.31 mL, 3.0 mmol, 20 equiv). The solution was heated to 50 °C. After 30 min, the solution was cooled, diluted with chloroform (10 mL) and concentrated. Purification by flash chromatography (15% acetone in hexanes) yielded **e13A** as a white crystalline solid (58 mg, 94%). Taking the solid up in ether (10 mL) and hexanes (10 mL) and allowing slow evaporation of the solvent over 3 days resulted in

the formation of fine needles (30 mg, 99% ee). Analytical tlc, 15% acetone in hexanes, Rf= 0.17. mp = 120-122 °C (99% ee material, grown from benzene/hexanes). $[\alpha]_D$ = -43.3 (c= 0.007, 99% ee, DCM). HPLC (Chiralcel AS, 4.6 mm x 25 cm, 80:20 hexanes/isopropanol, 1.0 mL/min) T_R = 14.7 min (major, giving a negative optical rotation response by the in-line polarimetry detector), T_R = 24.3 min (minor). Molecular ion calcd for $C_{21}H_{16}BrNO_3$: 432.0211; [M+Na], ESMS found *m/z*= 432.0221; IR (neat, cm^{-1}) 3228, 1739, 1715, ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.15 (1H, br s) 7.84-7.78 (2H, m) 7.70-7.67 (1H, m) 7.46-7.35 (4H, m) 7.31 (1H, dd, *J*= 8.2, 2.0 Hz) 7.23 (1H, d, *J*= 2.0 Hz) 6.68 (1H, d, *J*= 8.2 Hz) 5.60 (1H, d, *J*= 12.5 Hz) 5.54 (1H, d, *J*= 12.5 Hz) 1.68 (3H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 177.2, 168.7, 139.9, 133.6, 132.2, 131.9, 131.3, 130.4, 129.5, 128.6, 127.3, 126.5, 125.9, 125.0, 123.2, 115.3, 111.9, 66.5, 55.9, 19.8.

Probing the temperature effect on the formation of pyridinium salt f13A. A frozen solution of enol acetate (**20Ca**, 38 mg, 0.1 mmol) or enol carbonate (**35Aa**, 40 mg, 0.1 mmol) in $CHCl_3$ (0.4 mL) was treated with a cooled solution of DMAP in $CHCl_3$ (0.2 mL, 0.05M, 10 mol%). The NMR instrument was cooled to -50 °C and the reaction was thawed and inserted into the instrument. The ^1H NMR spectrum only revealed starting material, product and DMAP. Upon refreezing the solution the enol carbonate reaction turned a deep purple color while the enol acetate reaction remained white. The purple color faded over time in the frozen solution or if the solution was thawed. The ^1H NMR spectrum of the re-thawed solution showed rearranged oxindole and DMAP.

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Chapter 3

Dual Catalytic Parallel Kinetic Resolution under Homogeneous Reaction Conditions

I. Introduction.

As described in Chapter 1, the kinetic resolution of racemic mixtures is a classic and powerful method for obtaining enantioenriched organic molecules.[1] In a highly selective kinetic resolution (**s** >200), both the starting material and product can be recovered in >95% ee in 50% yield (maximum theoretical yield). Unfortunately, this level of selectivity is beyond the capabilities of most synthetic catalysts.[2] For a less selective kinetic resolution (**s**<200), highly enantioenriched starting material can be recovered at higher conversion albeit in low yield, or highly enantioenriched products can be obtained at low conversion. During these less selective kinetic resolutions, the enantiomeric excess of the product starts high but decreases significantly as conversion increases (Table 3-1). The higher enantiomeric excess of the product at low conversions is a result of the inherent relative reactivity of the two enantiomers. At higher conversions the relative concentration of the less reactive enantiomer increases as the more reactive enantiomer is converted to product. Consequently, the rate of conversion of the less reactive enantiomer increases and the product enantiomeric excess decreases.

Table 3-1. Product % ee as a Function of Conversion *C* and Enantioselectivity **s**.[a]

s	*C* = 1%	*C* = 10%	*C* = 20%	*C* = 30%	*C* = 40%	*C* = 50%
2	33.2	31.8	30.1	28.2	26.1	23.6
5	66.5	64.7	62.3	59.4	55.7	50.9
10	81.7	80.3	78.5	75.9	72.4	67.1
20	90.4	89.6	88.3	86.6	83.9	78.7
50	96.0	95.5	95.1	94.2	92.7	88.7
100	98.0	97.8	97.5	97.0	96.2	93.3
200	99.0	98.9	98.7	98.5	98.1	96.1
500	99.6	99.6	99.5	99.4	99.2	98.1

[a] adapted from reference 1c

Two strategies have been developed to obtain highly enantiomerically enriched products from moderately selective kinetic resolutions by maintaining the 1:1 ratio of enantiomers throughout the reaction. The first strategy, dynamic kinetic resolution (DKR), involves a rapid equilibration of the enantiomers during the resolution (Figure 3-1).[3] As the fast reacting enantiomer (*R*)-A is converted to product (*R*)-X by resolving agent M, the 1:1 ratio of the enantiomers of A is maintained by this equilibration. In this manner, both enantiomers of the reactant can be converted to a single enantioenriched product ((*R*)-X). However, this strategy is limited to enantiomers that can equilibrate under conditions compatible with the kinetic resolution. Parallel kinetic resolution (PKR) is the second strategy used to maintain a 1:1 ratio of the enantiomers of the starting material.[4] In PKR, a second kinetic resolution, by resolving agent N, is performed simultaneously to convert the less reactive enantiomer (*S*)-A to a distinct product (*S*)-Y (Figure 3-2). If the two kinetic resolutions convert the two reactant enantiomers to products at the same rate, then the starting material will remain racemic throughout the reaction. A successful PKR requires that the two resolutions be mutually non-interfering, occur with similar rates and enantioselectivities, and afford readily separated products.

Figure 3-1. Dynamic Kinetic Resolution

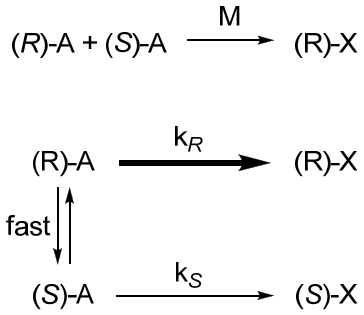
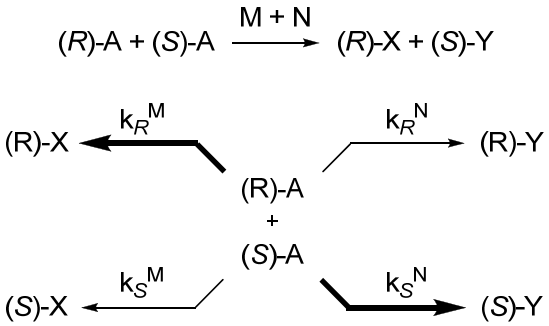
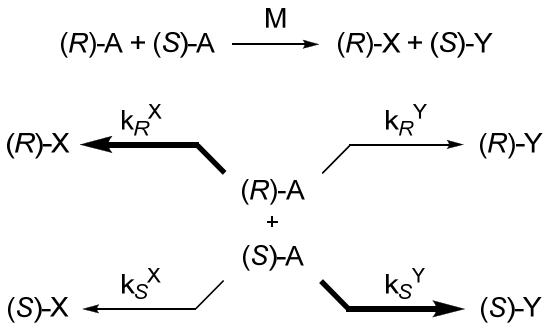


Figure 3-2. Parallel Kinetic Resolution

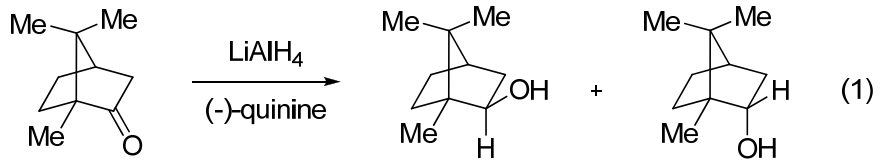


PKR is one of two types of reactions that convert racemic mixtures into two stereoenriched products coined “divergent reactions of a racemic mixture” (RRM) by Kagan.[5] The other type involves a single reagent or catalyst that converts the enantiomers into two distinct stereoenriched products (Figure 3-3). The stereoenrichment of the products obtained from divergent RRM is dependent on the inherent selectivity of each enantiomer with the chiral reagent or catalyst (i.e. $k_R^X > k_s^X$ and $k_R^Y > k_s^Y$) and not on the relative concentrations of the reactant enantiomers. The term PKR is commonly used in the literature to describe these single reagent/catalyst systems, but this usage is inaccurate because the stereoenrichment of the products does not depend on a kinetic resolution. Therefore we will reserve the term parallel kinetic resolution (PKR) for the two reagent/catalyst systems.

Figure 3-3. Divergent Reactions of a Racemic Mixture: One Reagent/Catalyst Approach.



A report by Guetté and Horeau in 1967 is significant among the early examples of divergent RRM because it describes the conceptual principles behind these reactions.[6] In this report, reduction of racemic camphor (**e1A**) with $LiAlH_4$/(-)-quinine affords isoborneol (**e1B**) as the major product with 2.5% ee (equation 1). In addition, a second isomeric alcohol (**e1C**) was isolated in low yield, but 21% ee. The authors derived a mathematical expression that relates the molar fraction of each product (X_2 and X_3) to the observed enantiomeric excesses (ee_2 and ee_3, equation 2). The two enantiomeric excess values, ee_2 and ee_3, are assigned opposite signs, based on the sign of optical rotation of the predominant enantiomer of that product. Therefore, at full conversion of a racemic mixture ($X_2+X_3=1$) the sum of the terms X_2ee_2 and X_3ee_3 is zero. A further expansion of this equation was reported by Kagan for divergent RRM that are not taken to completion. In this case, X_1 and ee_1 represent the molar fraction and enantiomeric excess of the recovered starting material, respectively.[7] As can be seen from these equations, if the two products are obtained in equal ratios, then the enantiomeric excesses should be equal. Conversely, when the two products are not obtained in equal ratios, the major product will have a lower enantiomeric excess than the minor product as seen in the reduction of (±)-camphor. Equations 2 and 3 can be applied to all divergent RRM, since they rely on both the material balance and the definition of ee, and therefore are independent of the reaction mechanism.

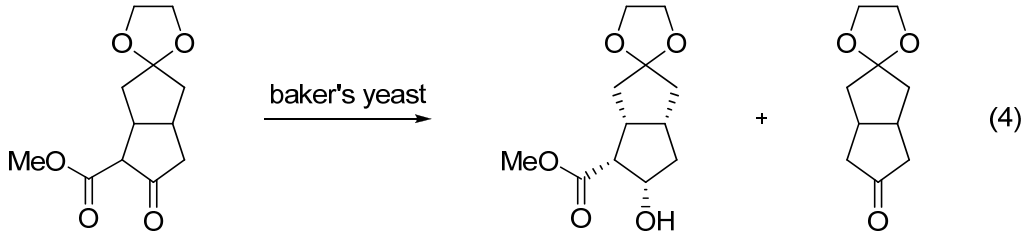


(±)-camphor **e1A** | isoborneol **e1B** 90% 2.5% ee | borneol **e1C** 10% 21% ee (1)

$$X_2(ee_2) + X_3(ee_3) = 0 \quad (2)$$

$$X_1(ee_1) + X_2(ee_2) + X_3(ee_3) = 0 \quad (3)$$

The first known example of what has come to be known as PKR was reported in 1987 when Brooks published the "dual kinetic resolution of a racemic pair."[8] Treatment of racemic ketone **e4A** with baker's yeast afforded the expected reduced product **e4B** in 43% yield and >99% ee. However, instead of recovering starting material from the resolution, achiral ketone **e4C** was recovered in 45% yield. The authors hypothesized that this product results from a second resolution by an enzymatic saponification of ester **e4A** followed by decarboxylation. When the resolution was stopped at partial conversion, the starting ketone **e4A** was enriched in the (+) enantiomer indicating that the rates of these two resolutions are unequal. Despite the inequality of the rates, alcohol **e4B** is obtained in very high % ee, suggesting that the enzymatic reduction is sufficiently stereoselective in a kinetic resolution to not need the added benefit of a PKR. However, the authors recognized that "dual kinetic resolution" could have potential benefits in other systems.

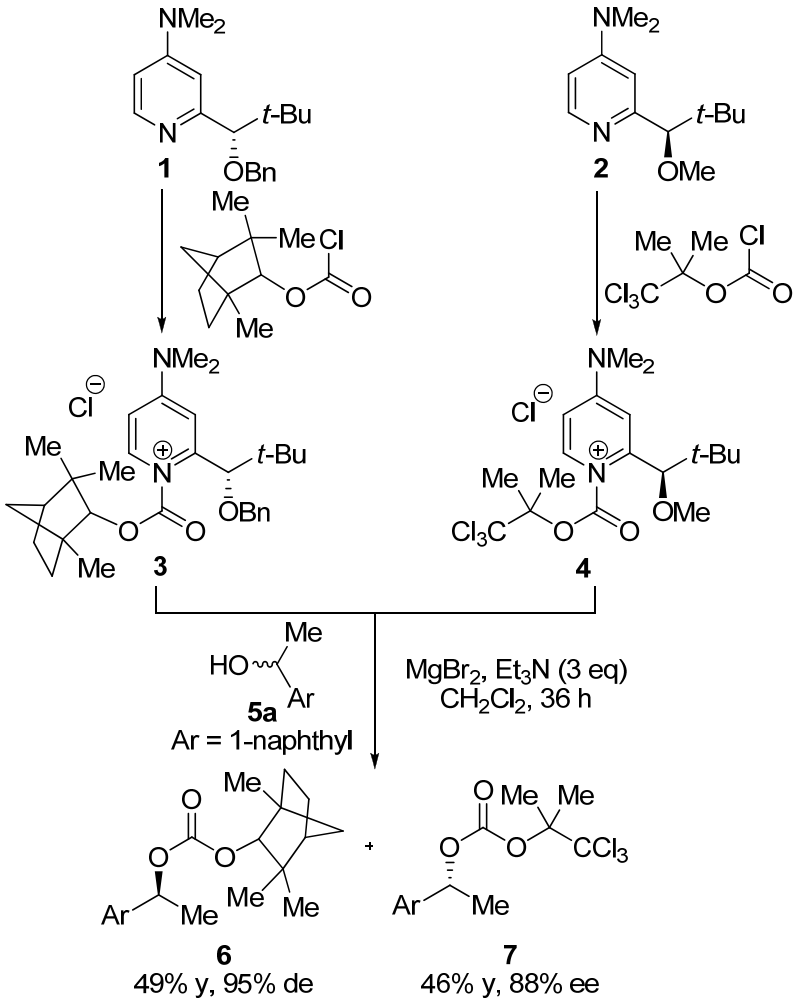


(±)-**e4A** | **e4B** 43% yield >99% ee | **e4C** 45% yield (4)

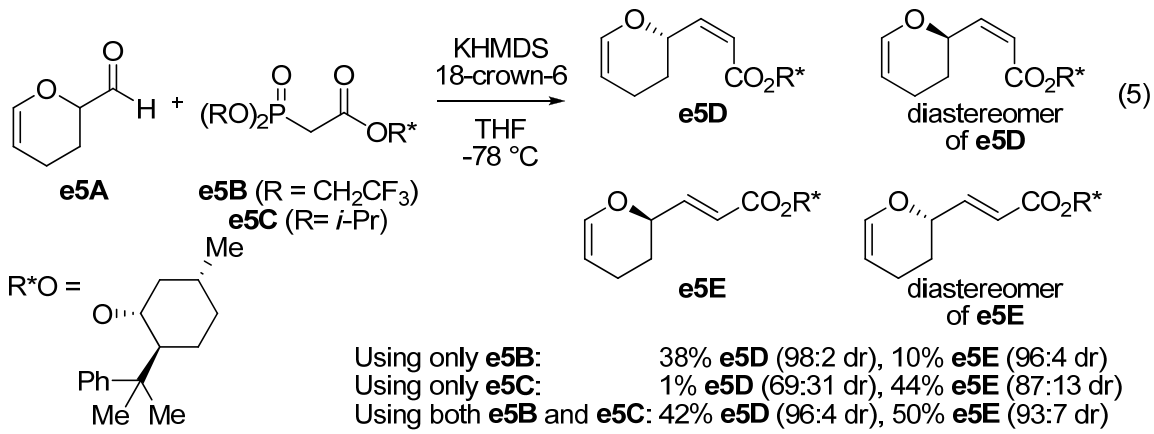
The first explicitly designed PKR experiment reported in the literature was described by Vedejs and Chen in 1997.[9] Quasienantiomeric pyridines **1** and **2** were treated with different

chloroformates to form pyridinium salts **3** and **4**. Treatment of alcohol **5** with equimolar amounts of these two pyridinium salts in the presence of $MgBr_2$ and Et_3N afforded two mixed carbonates **6** and **7** in high yields and enantiomeric excesses. Recovery of carbonate **6** in 49% yield and 95% de corresponds to **s** = 125 in a standard kinetic resolution. This selectivity is remarkable considering that both the individual kinetic resolutions of alcohol **5** with these pyridinium salt reagents have **s** = 41-42. The lower than optimal enantiomeric excess of carbonate **7** was attributed to some crossover between the two resolutions, but for the most part, the pre-formation of the pyridinium salt reagents allowed the resolutions to occur simultaneously without mutual interference.

Scheme 3-1. Dual Reagent Acyl Transfer PKR.



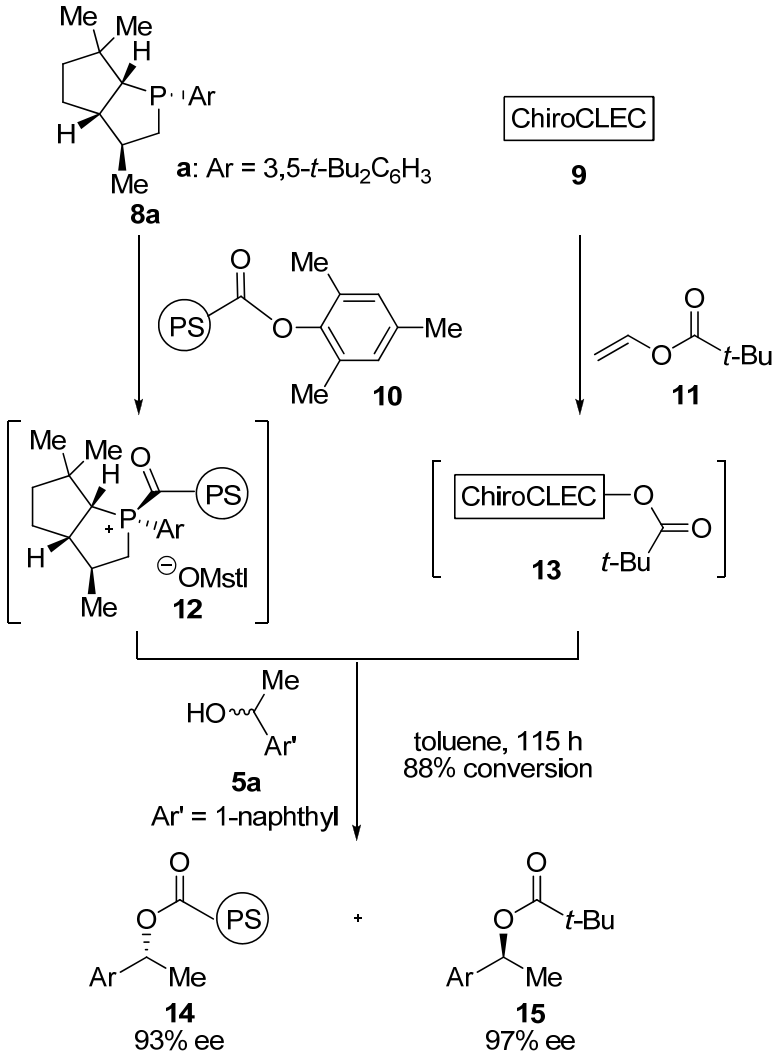
Subsequent reports of PKR have also focused on the use of quasienantiomeric reagents to separate racemic mixtures including nitrone cycloaddition,[10] Horner-Wadsworth-Emmons (HWE) olefination,[11] Michael addition,[12] reactions of lithiated oxazolidinones,[13,14] and transesterification.[15] The general concepts of PKR will be explained with the HWE olefination example.[11] Unlike the study by Chen and Vedejs, the PKR experiments listed above all incorporate the source of chirality into the products forming two quasidiastereomers. For example, HWE reagents **e5B** and **e5C** react with aldehydes to form olefins with the chiral ester incorporated into the product. In a standard kinetic resolution of aldehyde **e5A** using the electron poor *Z*-selective HWE reagent **e5B**, a 4:1 ratio of *Z*-olefin **e5D** and *E*-olefin **e5E** is obtained along with trace amounts of the diastereomers of each olefin. If the *E*-selective HWE reagent **e5C** is used instead, *E*-olefin **e5E** is formed almost exclusively, but a significant amount of the diastereomer is also formed. When the two resolutions are run in parallel, both of the olefin isomers are obtained in good diastereoselectivity, as the PKR enhanced the resolution of the racemic aldehyde to afford products in much higher yields and diastereoselectivities than could be obtained in the standard kinetic resolutions. The yield of the *Z*-olefin in the PKR experiment is higher than in the individual resolution with just **e5B**. In addition, the diastereoselectivity of the E-olefin is increased in the PKR experiment. The incorporation of the chirality into the product olefins deserves further mention. If this source of chirality is later cleaved, then the same objective could be accomplished by reaction of the racemic mixture with a single enantiomeric reagent followed by separation of the diastereomers, such as **e5D** and its diastereomer. On the other hand, since alkenes **e5D** and **e5E** are diastereomeric with respect to the two chiral centers as well as the olefin geometry, the separation of the products from the PKR experiment should be more facile than the simple diastereomers.



(5)

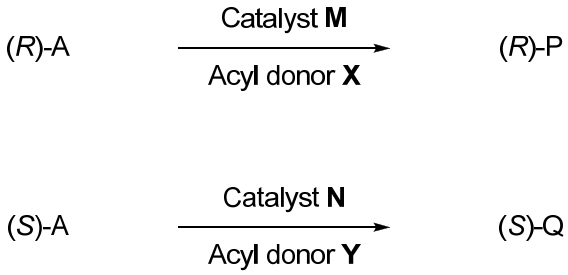
All of the preceeding examples of PKR involve stoichiometric chiral reagents. An analogous non-enzymatic catalytic example of PKR would be more practical, but so far, only one example is known, as reported by Vedejs and Rozners in 2001.[16] It was envisioned that chiral *P*-aryl-2-phophabicyclo[3.3.0]octane (PBO) **8a** might catalyze a resolution of benzylic alcohols via acyl transfer that would be complementary to a lipase-catalyzed resolution. However, a successful PKR requires that the two resolutions are mutually non-interfering, so the achiral stoichiometric acyl donors have to be carefully chosen. The insoluble lipase **9** is capable of acylating alcohols with vinyl pivalate (**s=** 83), an acyl donor that is unreactive with the chiral nucleophilic catalyst PBO **8a**. On the other hand, the typical anhydride acyl donors used with PBO **8a** are also activated by lipases. In order to prevent activation of the anhydride by the enzyme, an insoluble mixed anhydride **10** was chosen as the second acyl donor for PBO catalysis (**s=** 34). Mixed anhydride **10** is derived from polymer-bound cyclohexanecarboxylic acid and mesitoic acid. PBO **8a** only activates the less hindered cyclohexanecarbonyl for acyl transfer. This three-phase PKR experiment yields the two enantioenriched product esters **14** and **15**. Since ester **14** is bound to the polymer, the esters are readily separated by filtration. The esters are then saponified to afford the highly enantioenriched alcohols in good yields. Even though the selectivities of the two kinetic resolutions are not matched, the conditions for a successful PKR are met.

Scheme 3-2. Dual Catalytic Acyl Transfer PKR.



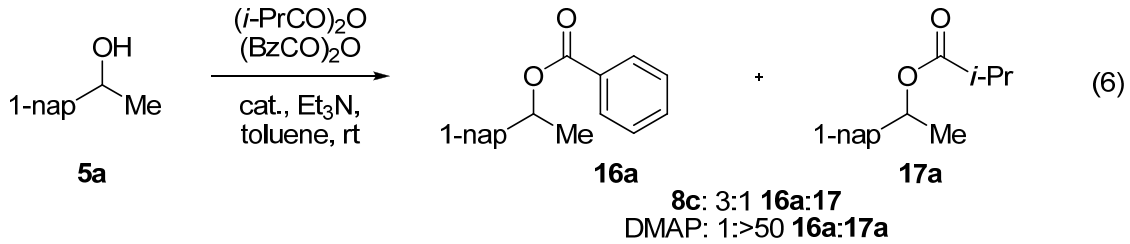
A catalytic acyl transfer PKR does not have to be performed in a heterogeneous solution. In fact, if the esters are the desired products, then the necessity of cleaving the alcohol from the solid support and re-acylating would be counterproductive. In addition, achieving exact loadings of the catalysts and acyl donors would be easier in a homogeneous solution. For the homogeneous PKR experiment, catalyst **M** would only activate achiral acyl donor **X** to convert (*R*)-A to (*R*)-P while catalyst **N** would only activate achiral acyl donor **Y** to convert (*S*)-A to (*S*)-Q (Figure 3-4). The challenge is to find a pair of complementary, mutually non-interfering kinetic resolutions that could be carried out under homogeneous conditions.

Figure 3-4. Catalytic PKR Scheme.

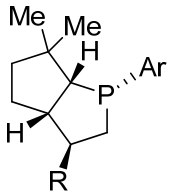


II. Results

As a part of the investigations into the application of chiral nucleophilic phosphine catalysts (**8**) in the Vedejs laboratories, it was recognized that phosphines catalyze the benzoylation of alcohols significantly faster than isobutyroylation. This effect was quantified by Harper in the kinetic analysis of PBO **8b**, and the benzoylation was found to occur approximately an order of magnitude faster than isobutyroylation.[17] A competition experiment between benzoic anhydride and isobutyric anhydride by MacKay demonstrated that this difference in reactivity results in the preferential benzoylation of alcohol **5a** catalyzed by PBO **8c** (3:1 selectivity, equation 6).[18] To take advantage of this inherent selectivity of the phosphine catalysts in PKR, a catalyst with complementary selectivity was needed. The chiral DMAP nucleophilic catalysts recently developed in the Vedejs laboratories[19] and elsewhere,[20] led MacKay to explore the selectivity of benzoylation versus isobutyroylation of alcohols catalyzed by DMAP. In a similar anhydride competition experiment with DMAP the sole product observed was the isobutyrate ester **17a** (equation 6). So, chiral DMAP-based catalysts should prove to be complementary to the chiral phosphine catalysts.



(6)



R = H, Ar= Ph: (**8b**)
R = Me, Ar = 3,5-*t*-Bu_2-4-MeOPh: (ArPBO, **8c**)
R = Me, Ar = Ph: (PhPBO, **8d**)

Therefore, we sought a chiral DMAP catalyst that was enantioselective in the kinetic resolution of alcohols to be used for the PKR experiment. Unfortunately, the resolution of alcohol **5a** with TADMAP (2,2,2-triphenyl-1-acetoxyethyl DMAP, **18a**), recently developed by Shaw, is poorly enantioselective (**s=** 1.4, Table 3-2, entry 1). In an effort to improve the kinetic resolution selectivity, the chirotopic environment of the catalyst was modified. The acetate of enantioenriched TADMAP could be cleaved under reductive conditions to afford the free alcohol **18b**. Since this hindered alcohol was unreactive to acylation by anhydrides in the presence of triethyl amine, more strongly basic conditions were investigated. Although, the lithium alkoxide of **18b** decomposed by C–C bond cleavage to afford 3-formyl DMAP and trityl anion,[19b] the magnesium alkoxide, generated by treating alcohol **18b** with EtMgBr, did not undergo this decomposition. Quenching the magnesium alkoxide with anhydrides afforded new enantioenriched TADMAP derivatives (**18c-e**). These catalysts were then screened for the kinetic resolution of alcohol **5**. The more hindered benzoate catalyst **18c** (TBDMAP) was more enantioselective (**s=** 3.4, Table 3-2, entry 2) than TADMAP, but the acylation was also slower. The enantioselectivity increased further when the solvent was switched to *t*-amyl alcohol (entry 3), with a slight increase in reaction rate. Lowering the temperature also increased the enantioselectivity (entry 4). Isobutyrate catalyst (**18d**) and formyl catalyst (**18e**) were less enantioselective than TBDMAP (**18c**), so attention was focused on TBDMAP. Due to the freezing point of *t*-amyl alcohol, the temperature could not be lowered further than 0 °C, but addition of a co-solvent allowed MacKay to run the resolution at -25 °C and the enantioselectivity increased to **s=** 6.1 (entry 7). This increase was not due to the co-solvent itself, since DCM was a poor solvent for the resolution (entry 8).

Scheme 3-3. Synthesis of New TADMAP Derivatives

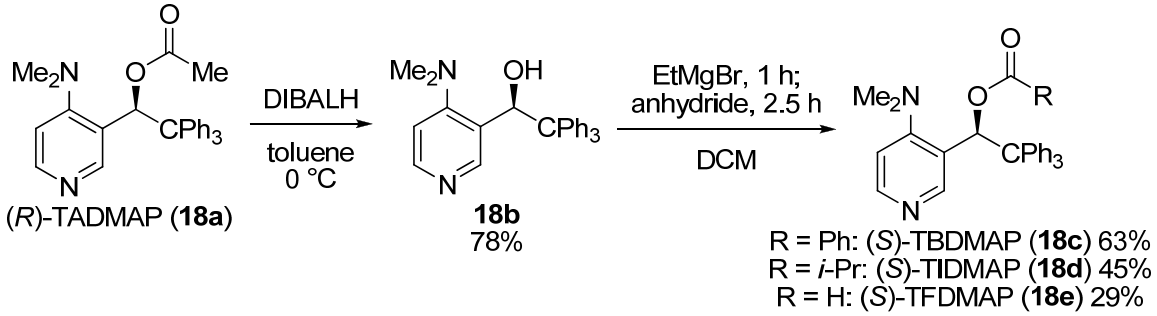


Table 3-2. Kinetic Resolution of Alcohol **5a** with TADMAP Derivatives.

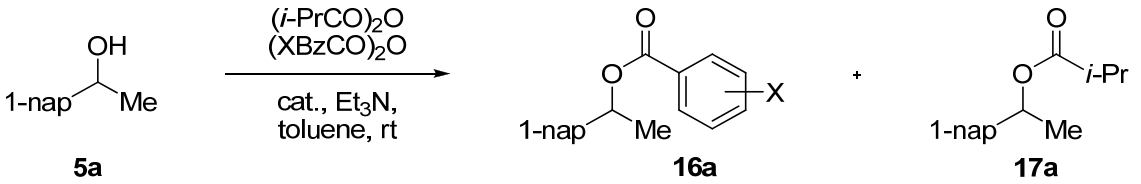
Entry	Cat. (%)	Solvent	temp	time	% conv	**s**
1	**18a** (1%)	toluene	rt	7 h	40%	1.4[b]
2	**18c** (1%)	toluene	rt	92 h	35%	3.4
3	**18c** (1%)	*t*-amyl alcohol	rt	48 h	40%	5.1
4	**18c** (1%)	*t*-amyl alcohol	0 °C	48 h	41%	5.3
5	**18d** (1%)	*t*-amyl alcohol	0 °C	24 h	52%	3.5
6	**18e** (1%)	*t*-amyl alcohol	0 °C	16 h	50%	2.3
7	**18c** (2%)	3:1 *t*-amyl alcohol:DCM	-25 °C	16 h	27%	6.1[c]
8	**18c** (4%)	DCM	-25 °C	28 h	21%	3.2[c]

[a] All reactions used 0.1 M **5a** in the given solvent with 1-4 mol% catalyst, 1 eq. of isobutyric anhydride, and 1.1 eq Et_3N [b] Experiment by S. A. Shaw [c] Experiment by J. A. MacKay.

Although catalysts **8c** and **18c** both catalyzed the acylation with opposite anhydride selectivity (Bz_2O vs $(i\text{-PrCO})_2O$), the moderate anhydride selectivity of the PBO catalyst **8c** (3:1) was non-ideal for a PKR experiment. Therefore, we sought a pair of anhydrides that might be activated more selectively by both ArPBO (**8c**) and TBDMAP (**18c**). Competition experiments between isobutyric anhydride and substituted benzoic anhydrides were conducted with both catalysts **8c** and **18c** for the acylation of alcohol **5a** (Table 3-3). Both TBDMAP (**18c**) and ArPBO (**8c**) favored the formation of the isobutyrate ester **17a** in competition experiments between isobutyric anhydride and *p*-methoxybenzoic anhydride (entry 2). On the other hand, in competition experiments with *m*-methoxybenzoic anhydride and 3,5-dimethoxybenzoic anhydride, PBO slightly favored formation of the aromatic ester **16a**, while TBDMAP (**18c**) still afforded isobutyrate **17a** exclusively (entry 3). The TBDMAP (**18c**) selectivity for isobutyrate **17a** formation decreased to 6:1 with the more electron-poor *m*-chlorobenzoic anhydride, but the PBO (**8c**) selectivity for aromatic ester formation increased dramatically (entry 5). A similar 6:1 selectivity was observed with nicotinic anhydride (Nic_2O) for TBDMAP catalysis, but PBO (**8c**) was

unselective affording a 1.6:1 ratio of esters **16a** and **17a** (entry 6). However, under conditions optimized for kinetic resolutions with TBDMAP (**18c**), PBO (**8c**) afforded only the nicotinic ester. Apparently, the selectivity of anhydride activation is sensitive to conditions, but this variable was not explored further.

Table 3-3. Anhydride Competition Experiments.



5a **16a** **17a**

Entry	Anhydride X =	ArPBO (**8c**) Ratio (**16**:**17**)	TBDMAP (**18c**) Ratio (**16**:**17**)
1	H	3 : 1 [a]	1 : 50 [a,b]
2	*p*-MeO	1 : 1.9	1 : 50
3	*m*-MeO	2.7 : 1	1 : 50
4	3,5-MeO_2	1.5 : 1	1 : 50
5	*m*-Cl	18 : 1	1 : 6 [a,b]
6	Nic_2O	1.6 : 1	1 : 6 [a,b]
7	Nic_2O	>50 : 1 [c]	1 : 6 [a,c]

[a] Data by J. A. MacKay [b] DMAP as catalyst [c] used 3:1 *t*-amyl alcohol:DCM, -25 °C.

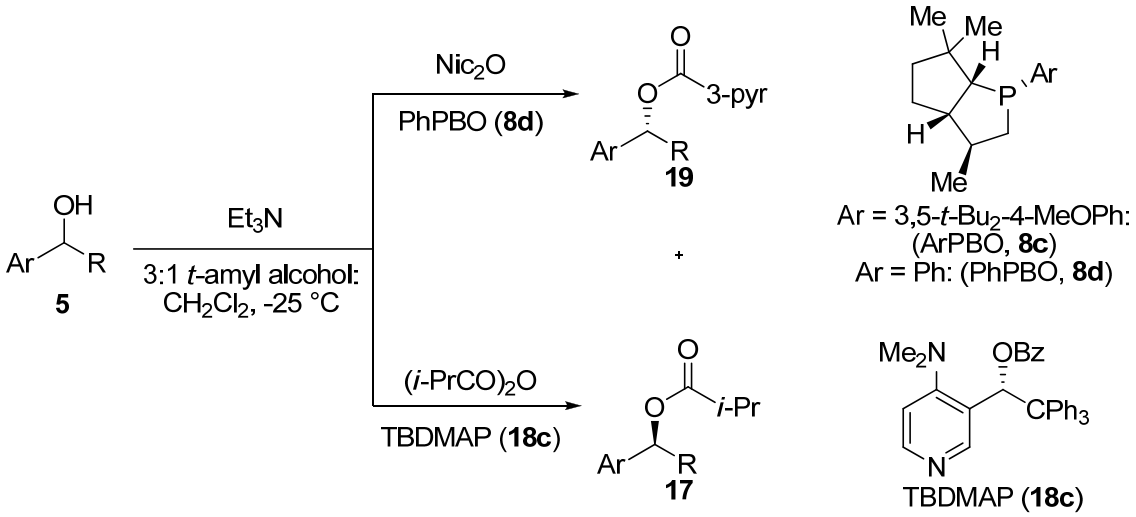
With a pair of complementary catalytic esterifications in hand (PBO **8c** with Nic_2O and TBDMAP **18c** with (*i*-$PrCO)_2O$), attention was turned to the enantioselectivity of the individual kinetic resolutions. Under optimized conditions MacKay found moderate enantioselectivity factors with both catalysts for the resolution of benzylic alcohols **5a**-**c** (Table 3-4). Phenyl substituted catalyst PhPBO (**8d**) proved to be more enantioselective than the more hindered (MeOdi-*t*-BuPh) PBO catalyst (**8c**) under the optimized conditions for TBDMAP (**18c**), so further experiments were carried out with this catalyst.

Table 3-4. Kinetic Resolutions of Alcohols Using Chiral Catalysts by J. A. MacKay.[a]

Entry	Alcohol	R	Ar	Cat. (mol%)	Anhydride	time	% conv.	**s**
1	**5a**	Me	1-nap	**8c** (2%)	nicotinic	3 h	79	7.5
2	**5a**	Me	1-nap	**8d** (4%)	nicotinic	3 h	68	11
3	**5a**	Me	1-nap	**18c** (4%)	isobutyric	16 h	27	6.1
4	**5b**	Me	2-MeC_6H_4	**8d** (2%)	nicotinic[b]	20 h	37	17
5	**5b**	Me	2-MeC_6H_4	**18c** (2%)	isobutyric[c]	96 h	50	14
6	**5c**	*t*-Bu	Ph	**8d** (2%)	nicotinic[b]	20 h	34	57
7	**5c**	*t*-Bu	Ph	**18c** (2%)	isobutyric[c]	96 h	43	9.9

[a] Experiments by J. A. MacKay. All reactions were conducted at -25 °C using 1 equiv **5a**, 1 equiv anhydride, 1.5 equiv Et_3N, 2-4 mol% catalyst, and were diluted to 0.1 M substrate in 3:1 *t*-amyl alcohol:DCM unless otherwise noted. [b] 0.6 equiv anhydride. [c] 2.5 equiv anhydride.

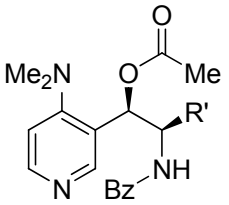
Table 3-5. Parallel Kinetic Resolutions of Alcohols by J. A. MacKay.[a]



				cat. (mol%)		ratio	**19**		**17**	
entry	alcohol	R	Ar	**8d**	**18c**	**19**:**17**	Yield	ee	yield	ee
1	**5a**	Me	1-nap	4.5	6.7	1.6 : 1.0	62%	62%	38%	-92%
2	**5a**	Me	1-nap	1.3	6.7	1.1 : 1.0	51%	65%	46%	-73%
3	**5a**	Me	1-nap	1.3	6.7	1.0 : 1.1	44%[b]	68%	46%	-63%
4	**5b**	Me	2-MeC_6H_4	6.0	3.0	1.2 : 1.0	52%	68%	44%	-82%
6	**5c**	*t*-Bu	Ph	4.0[c]	4.0	1.0 : 2.5	33%	84%	>39%	-38%
7	**5c**	*t*-Bu	Ph	6.0	5.0	1.0: 1.9	33%	79%	60%	-41%

[a] Experiments by J. A. MacKay. All reactions used 1 equiv **5a**, 1 equiv of each anhydride, 1.5 equiv Et_3N, 1.3-7 mol% of each catalyst, and were diluted to 0.1 M substrate in 3:1 *t*-amyl alcohol:DCM unless noted. [b] 0.75 equiv nicotinic anhydride. [c] Used the HBF_4 salt of **8d** as a precatalyst.

With the two complementary kinetic resolutions in hand, MacKay conducted the key PKR experiments with PhPBO (**8d**) and TBDMAP (**18c**). In these PKR experiments, PhPBO does selectively convert the (*R*)-**5** to nicotinic ester **19**, while TBDMAP converts the (*S*)-alcohol to isobutyrate **17** (Table 3-5). The phosphine catalyst is significantly more reactive than TBDMAP so the optimum 1:1 ratio of products **19a** and **17a** was achieved when a 1:5.2 ratio of the catalysts was used. As expected from the Horeau equation, when the products are obtained in nearly equal ratios, the enantiomeric excesses of the products are almost equal. In contrast, when one product is obtained in higher ratios, the %ee decreased. Thus, the enantiomeric excess decreased when the yield increased. Unfortunately, none of the enantiomeric excesses reached the theoretical limit of a PKR experiment even when the 1:1 ratio of products was obtained (optimal %ee: for **19a**: 83% ee; for **17a**: 71% ee). A possible explanation for these results will be discussed later.



R' = *i*-Pr (*S*,*S*)-AcOVaDMAP (*ent*-**20a**)
R' = *t*-Bu (*S*,*S*)-AcOLeDMAP (*ent*-**20b**)
R' = *t*-Bu (*R*,*R*)-AcOLeDMAP (**20b**)

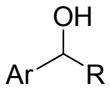


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Table 3-6. Kinetic Resolutions of Alcohols with Amino Acid Derived Catalysts.[a]

entry	alcohol	R	Ar	catalyst	solvent	temp	**s**
1	**5a**	Me	1-nap	*ent*-**20a**	*t*-amyl alcohol	rt	2.7
2	**5a**	Me	1-nap	*ent*-**20a**	toluene	rt	6.8[b]
3	**5a**	Me	1-nap	*ent*-**20b**	toluene	rt	8.9[b]
4	**5a**	Me	1-nap	*ent*-**20b**	toluene	-40 °C	20.5
5	**5a**	Me	1-nap	*ent*-**20b**	toluene	-70 °C	29
6	**5b**	Me	Ph	*ent*-**20b**	toluene	-40 °C	10.7
7	**5c**	*t*-Bu	Ph	*ent*-**20b**	toluene	-40 °C	1.8
8	**5d**	Me	2-MeC_6H_4	*ent*-**20b**	toluene	-40 °C	9.5

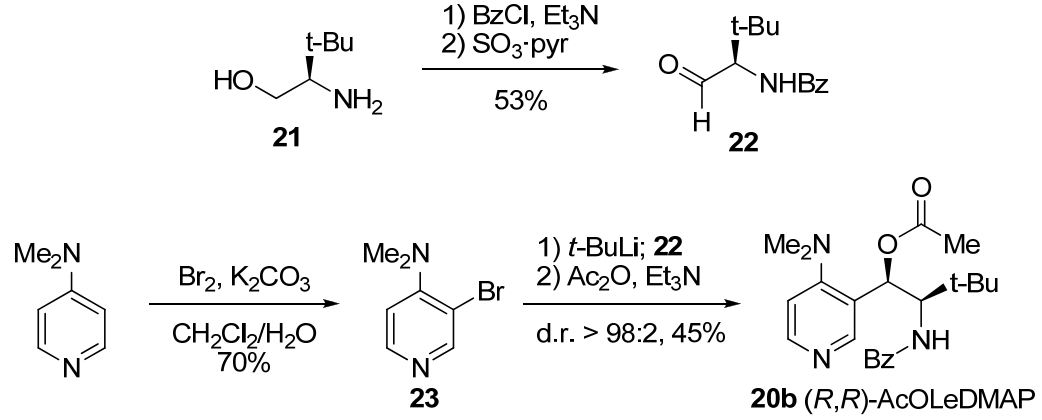
[a] All reactions were conducted using 1 equiv **5a**, 1 equiv anhydride, 1.5 equiv Et_3N, 1 mol% catalyst, and were diluted to 0.06 M substrate. [b] Experiment by S. A. Shaw.

At this point, the next generation amino acid-derived DMAP catalysts were developed by Shaw,[21] and proved to be much more enantioselective for the kinetic resolutions of benzylic alcohols. In contrast to TBDMAP, kinetic resolution of alcohol **5a** with valine-derived catalyst

AcOVaDMAP (*ent*-**20a**) and isobutyric anhydride was more enantioselective in toluene (**s=** 6.8) than *t*-amyl alcohol (**s=** 2.7) at rt (Table 3-6, entries 1 and 2). The more hindered *tert*-leucine derived catalyst AcOLeDMAP (*ent*-**20b**) proved even more enantioselective (**s=** 8.9, entry 3). At lower temperatures the selectivity increased to synthetically useful levels (**s=** 20.5 – 29, entries 4 and 5). However, at -70 °C the rate of acylation decreased dramatically, so further experiments were conducted at -40 °C. Unhindered alcohols **5b** and **5d** were also resolved with good enantioselectivity, but the kinetic resolution of *t*-butyl substituted alcohol **5c** failed (entries 6-8). In addition to increased enantioselectivity with the amino acid-derived catalysts *ent*-**20a** and *ent*-**20b**, the anhydride selectivity between isobutyric anhydride versus *m*-chlorobenzoic anhydride or nicotinic anhydride increased to 16:1 and 11:1, respectively (toluene, rt).

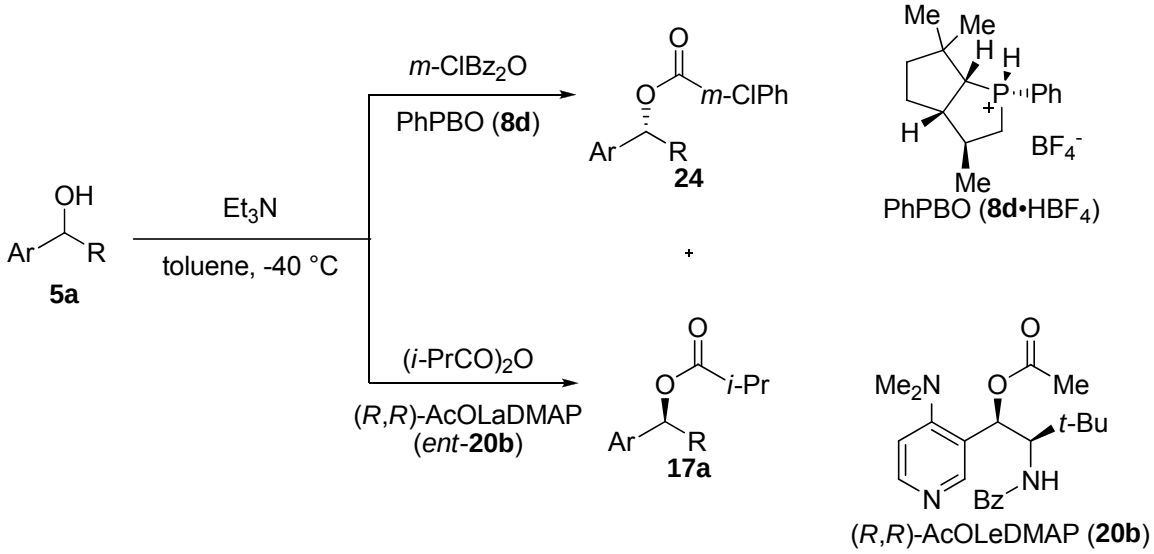
Since the kinetic resolution of alcohols using AcOLeDMAP (**20b**) was enantioselective under different conditions than TBDMAP **18c**, the PhPBO (**8d**) catalyzed kinetic resolution needed to be run under the optimized conditions. Fortuitously, the kinetic resolution of alcohol **5a** with PhPBO (**8d**) using *m*-chlorobenzoic anhydride was even more enantioselective under these conditions than those used above (**s** = 19.8, toluene, -40 °C). Unfortunately, both **8d** and *ent*-**20b** preferentially acylated the (*R*)-enantiomer of the alcohol. To achieve the desired complementarity, the enantiomeric catalyst (*R*,*R*)-AcOLeDMAP (**20b**) was synthesized from (*R*)-*tert*-leucinol according to the route developed by Shaw[21] (Scheme 3-4).

Scheme 3-4. Synthesis of (*R*,*R*)-AcOLeDMAP.



The similar and complementary enantioselectivities of PhPBO **8d** and AcOLeDMAP **20b**, in addition to high selectivities for activation of just one of the two anhydrides, met the enantioselectivity and mutual non-interference criteria for a PKR experiment. Thus the new catalyst combination was tested in the PKR of alcohol **5a** under the optimized kinetic resolution conditions. In contrast to TBDMAP, AcOLeDMAP (**20b**) proved to be more reactive than PhPBO **8d**. Therefore a 2.2:1 ratio of catalysts **8d** and **20b** was used to afford a 1:1.2 ratio of aromatic ester **24** and isobutyrate **17a** at approximately 92% conversion after 3 h (Table 3-7, entry 1). After isolation and saponification of the esters, the alcohols were assayed by HPLC on chiral support. The alcohol derived from *m*-chlorobenzoate **24** was obtained in 88% ee and the alcohol from isobutyrate **17a** in 75% ee. Increasing the catalyst loading of PhPBO **8d** in order to obtain a 1:1 ratio of the alcohols by NMR did not significantly affect the enantiomeric excesses of the products, but the recovered starting material was essentially racemic as desired for a PKR experiment (entry 2). Doubling the catalyst loading resulted in a slight increase in the enantiomeric excess of isobutyrate **17** at the expense of the % ee of aromatic ester **24** (entry 3). All of these PKR experiments use the HBF_4 salt of **8d** as a precatalyst for better control of catalyst loading.[22]

Table 3-7. Parallel Kinetic Resolutions of Alcohols with Amino Acid Derived Catalysts.



entry	**8d** (mol %)	**20b** (mol %)	Time	NMR Ratio (**24**:**17a**:**5a**)	**24** % ee	**17a** % ee	**5a** %ee
1	2.2	1	3 h	1.0:1.2:0.18	88	-75	27
2	2.6	1	3 h	1.0:1.0:0.5	87 (44% yield)	-76 (33% yield)	-8
3	5.2	2	2 h	1.0:1.2:0.53	86	-78	19

[a] All reactions used 1 equiv **5a**, 1 equiv of each anhydride, 1.5 equiv Et_3N, 1-5.2 mol% of each catalyst, and were diluted to 0.06 M substrate in toluene.

Under ideal PKR conditions, the product of a resolution with **s** = 20 would have 90% ee (defined as % ee at 1% conversion), so the recovery of aromatic ester **24** in 86-88% ee is nearly ideal. In addition, at 50% conversion, the product of a standard KR with **s** = 20 would be recovered in 79% ee (Table 3-1), so the PKR has significantly enhanced the efficiency of the resolution. However, the conditions for an ideal PKR were not fully satisfied because the enantiomeric excess of isobutyrate **17** was lower than the expected 90% ee (actual: 75-75% ee).

From the lower than expected enantiomeric excesses of the isobutyrate product, it is clear that the conditions for an ideal PKR have not been met. The criteria laid out earlier for an ideal PKR are: (1) mutual non-interference of the two competing KR's, (2) similar reaction rate, (3) similar enantioselectivity, and (4) formation of two distinct isolable products. In these experiments we have formed two distinct isolable products so that criterion (4) was met. The requirement for similar enantioselectivity of the two KR processes (3) was also met in the PKR

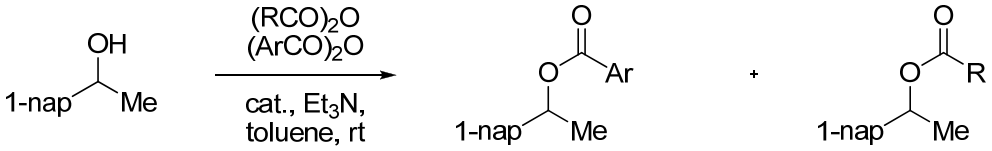
experiments using AcOLeDMAP. The two remaining criteria are similar reaction rate and mutual non-interference. Although we tried to match the catalyst loadings to achieve a 1:1 ratio of the products, it is possible that rates of the catalyzed reactions were not equal over the course of the reaction. In the three phase PKR experiment, Rozners noted that the enantiomeric excess of the recovered starting material did not remain constant over the course of the reaction, and the phosphine catalyzed resolution became slower at higher conversion.[16] This could arise from inactivation of the PBO catalyst by phosphine oxidation or by-product inhibition. Regardless of the cause, the phosphine catalyzed process may dominate at low conversions but as the catalyst is inhibited the other kinetic resolution becomes dominant. If this is the case, the starting material does not remain racemic throughout the course of the PKR.

The last criterion for an ideal PKR, is that the two resolutions must be mutually non-interfering (1). In the PKR experiments by MacKay, the anhydride selectivity of TBDMAP was only 6:1. Therefore, 15% of the time TBDMAP will be activating the wrong anhydride for acylation. The activation of the undesired anhydride would result in conversion of the wrong enantiomer to the aromatic ester. This problem was alleviated by switching to AcOLeDMAP which has increased anhydride selectivity. In the new PKR experiments, the aromatic ester was obtained in nearly ideal enantiomeric excess, indicating that the formation of the aromatic ester occurred almost exclusively by PhPBO catalysis.

This explanation does not address the lower enantiomeric excess of the aliphatic esters obtained in both sets of PKR data, since the anhydride selectivity of PhPBO was shown to be high for each of the electron poor aromatic anhydrides in competition studies. In an NMR study, MacKay found that DMAP and PhPBO each promoted the scrambling of a 1:1 mixture of benzoic and isobutyric anhydrides to form a statistical mixture of a new mixed anhydride and the symmetrical anhydrides. Several mixed anhydrides were independently synthesized to evaluate the effect of scrambling on the acyl activation process by each catalyst. DMAP catalysts remained selective for isobutyroylation regardless of which anhydrides were present (Table 3-8, entries 1, 2, 8 and 9). On the other hand, ArPBO was very sensitive to the nature of the anhydride. As shown previously, ArPBO preferentially forms the aromatic ester in the presence

of the two symmetrical anhydrides (entry 3). In contrast, the selectivity of ArPBO reverses with the mixed anhydrides, and isobutyrate (**17a**) becomes the major product (entries 4 and 5). To ensure that this change in anhydride selectivity was not due to a contaminant in the mixed anhydride, the highly crystalline biphenyl cyclohexyl mixed anhydride **25** was synthesized and thoroughly purified prior to the competition experiment. Even with this pure mixed anhydride, PhPBO selectively formed the aliphatic ester over the aromatic ester (entry 7), while a 1:1 ratio of the aliphatic and aromatic esters is formed from a mixture of the two symmetrical anhydrides (entry 6). If a mixed anhydride is formed during the course of the PKR experiment as indicated by the NMR experiments, then the PhPBO catalyst could begin forming the isobutyrate product. This would be detrimental to the enantiomeric excess of the isobutyrate **17a** since PhPBO would selectively form the undesired enantiomer. The decreased enantiomeric excess of isobutyrate **17a** in the PKR experiments with AcOLeDMAP (**20b**) corresponds to approximately 8% of the isobutyrate ester arising from PhPBO catalysis.

Table 3-8. Additional anhydride competition experiments.



5a **16a** **17a**

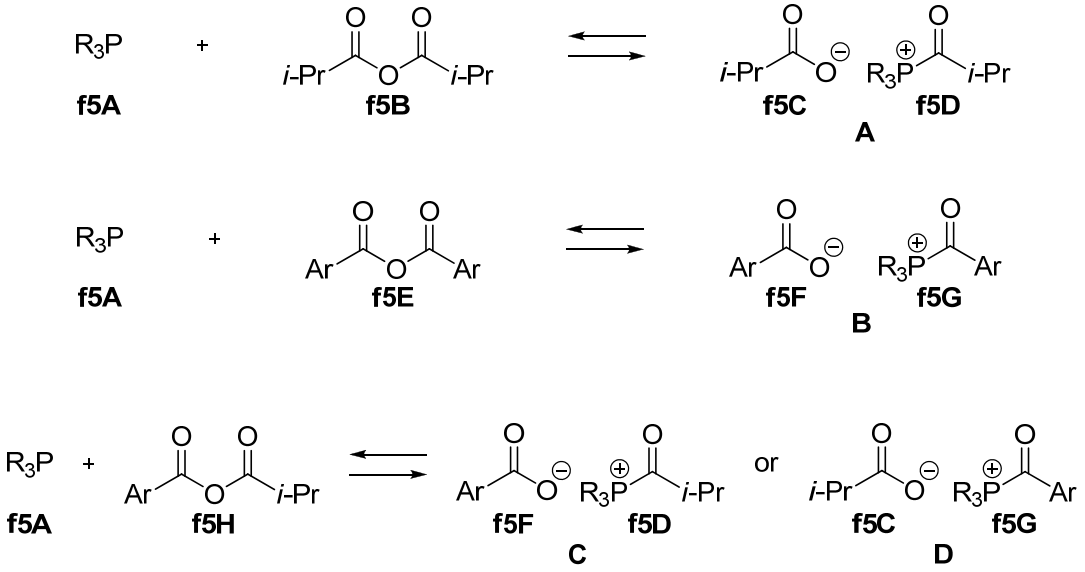
entry	Cat. (mol%)	R	Ar	**16**:**17**
1	DMAP (20%)	*i*-Pr	Ph	1:50[b]
2	DMAP (20%)	*i*-Pr/Ph mixed		1:50[b]
3	**8c** (6%)[c]	*i*-Pr	Ph	3:1[b]
4	**8c** (2%)[c]	*i*-Pr/Ph mixed		1:3[b]
5	**8c** (1%)[c]	*i*-Pr/3-Py mixed		1:4[b]
6	**8d** (5%)	Cyclohexyl	Biphenyl	1:1
7	**8d** (5%)	Cyclohexyl/Biphenyl mixed (**25**)		1:4
8	**18c** (5%)	Cyclohexyl	Biphenyl	1:50
9	**18c** (5%)	Cyclohexyl/Biphenyl mixed (**25**)		1:50

[a] All reactions used 1 equiv **5a**, 1-2 eq. of each anhydride (1:1 ratio), 1.5 equiv Et_3N, and were diluted to 0.2M substrate in toluene. [b] Experiment by J. A. MacKay. [c] ca. 0.1 equiv Et_3N.

The complementary anhydride selectivity of each of the catalysts deserves consideration. Nucleophiles catalyze acylations by forming an ion pair such as **A** (Figure 3-5). The rate of

nucleophile-catalyzed acylations depends on both the extent of formation of the ion pair and the reactivity of the ion pair. For phosphine catalysts, the anhydride selectivity is dependent on the extent of formation of the ion pair (Figure 3-5). In the competition experiments to determine anhydride selectivity for phosphine catalysts, the formation of ion pair **B** is favored over the formation of ion pair **A** for most aromatic anhydrides. The selectivity tends to increase as the carboxylate leaving group **f5C** or **f5F** becomes less basic, indicating that the formation of ion pair **B** becomes more favorable than ion pair **A** (Table 3-3). This trend is due to the mildly basic phosphine catalysts (Et_3P^+H: pK_a= 5.6 in MeOH, pK_a= 8.7 in $MeNO_2$)[23] more readily displacing the better leaving groups **f5F**, resulting in formation of a higher concentration of ion pair **B**. The increase in the phosphine catalyzed formation of aliphatic esters using the mixed anhydride **f5H** support this conclusion. The addition of the phosphine to the mixed anhydride **f5H** can form two ion pairs **C** and **D**, and the selective formation of the aliphatic ester suggests that ion pair **C** is favored over ion pair **D**. Comparing the favored ion pair **C** from the mixed anhydride with the favored ion pair **B** from the two symmetrical anhydrides, the common element is the carboxylate leaving group **f5F**.

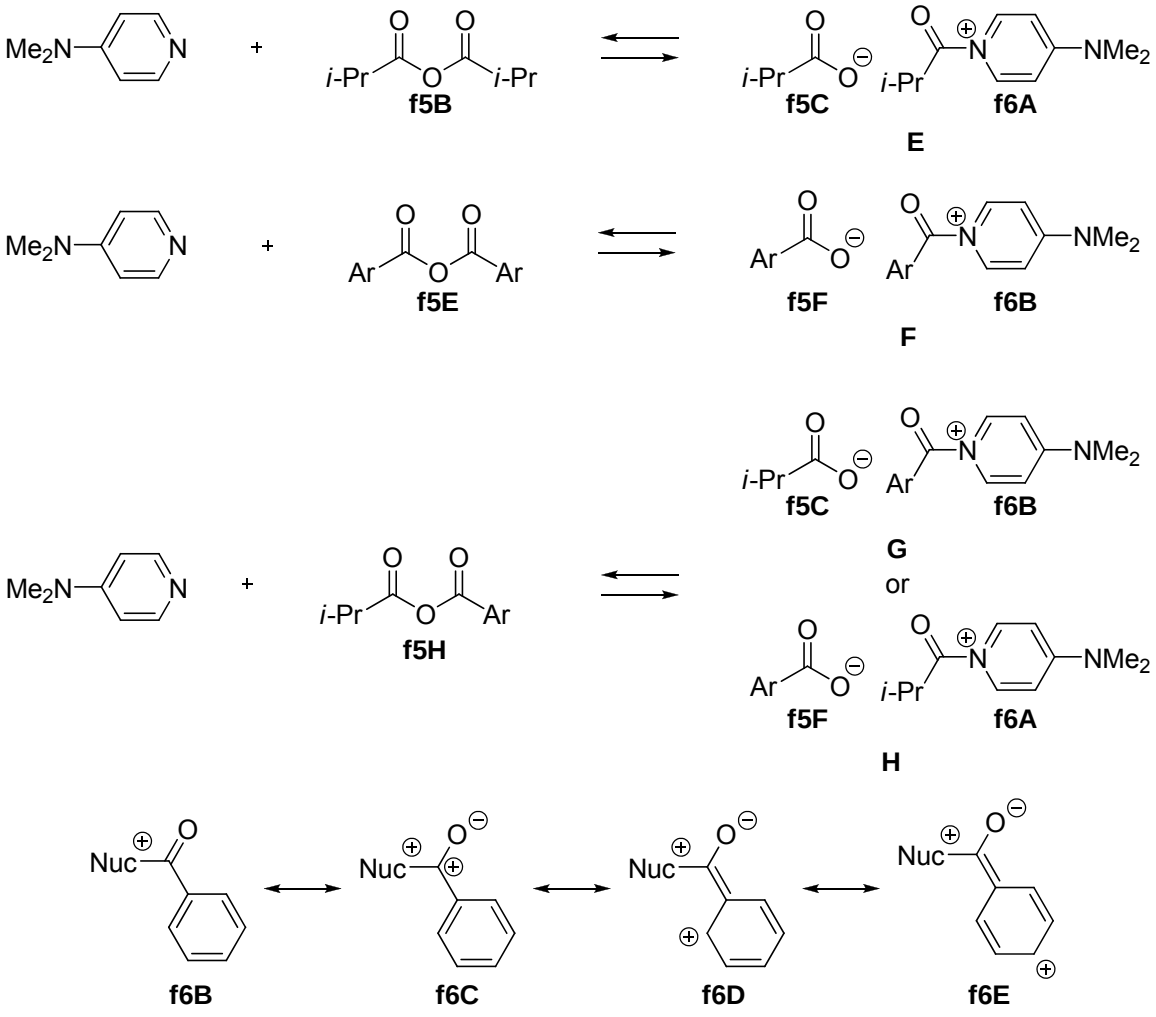
Figure 3-5. Proposed Intermediates in Phosphine Catalyzed Acyl Transfer Reactions.



A similar analysis of the DMAP catalyzed acyl transfer reactions leads to a different conclusion (Figure 3-6). Since DMAP selectively catalyzes the isobutyroylation of alcohols

regardless of the anhydride donor, ion pairs **E** and **H** are the active acylating agents. The common element between ion pairs **E** and **H** is the acylated pyridinium ion **f6A**. Since DMAP catalysts are more basic than the phosphine catalysts (DMAP: pK_a= 10.1 in MeOH, pK_a= 17.3 in $MeNO_2$)[24] all four ion pairs **E** – **H** are readily formed, so the selectivity arises from the reactivity of the intermediate acyl pyridinium salt. The additional resonance forms available with the arene ring stabilize the aromatic *N*-benzoyl pyridinium ion **f6B** over the corresponding aliphatic acyl pyridinium ion **f6A**. This additional stability decreases the reactivity of the pyridinium salt with the alcohol. The decrease in anhydride selectivity with electron poor aromatic anhydrides correlates to a decrease in this stabilization effect.

Figure 3-6. Proposed Intermediates in DMAP Catalyzed Acyl Transfer Reactions.



In conclusion, a dual catalytic homogeneous PKR with achiral acyl donors has been developed, and two distinct enantioenriched esters were isolated. The enantioenrichment of these products is solely due to the two chiral catalysts. This PKR was made possible by the complementary anhydride selectivity of phosphine and DMAP catalysts. Although the ideal enantiomeric excess of one of the products was not quite reached, this represents the first example of a catalytic PKR using non-enzymatic catalysts. Future work should focus on preventing the formation of the mixed anhydride (**f5H**), thereby limiting activation at the undesired acyl group by the PBO catalyst **8d**.

III. Experimental

General Experimental

Et_2O, THF and CH_2Cl_2 were dried by passing through a column of activated alumina. Ethyl acetate and Et_3N were distilled over CaH_2 prior to use. Et_2NH was distilled over KOH prior to use. *t*-Amyl alcohol was carefully distilled over molten sodium. Organolithium reagents were titrated with diphenylacetic acid in THF prior to use. All other reagents were used as received from the manufacturer. Analytical thin layer chromatography (tlc) was accomplished using Whatman 0.25 mm K6F Silica Gel 60 Å plates, and visualized with the aid of UV light or iodine vapor, or 10% PMA stain. Flash chromatography was accomplished according to the Still procedure[10] using Whatman Silica Gel: Puracil 60 Å (230-400 mesh). All reactions were performed under an atmosphere of nitrogen in oven-dried glassware.

1-(4-Dimethylaminopyridin-3-yl)-2,2,2-triphenylethanol (18b). (Preparation first reported in Ref 18.) To a solution of (-)-TADMAP (**18a**)[19] (175 mg, 0.41 mmol, 96.4% ee) in toluene (4.1 mL) cooled to 0 ^oC was added DIBAL (0.89 mL, 1M solution in toluene) via syringe. The mixture was stirred at 0 ^oC for 2 h, and then quenched with aqueous sodium potassium tartrate (sat., 4 mL) and stirred vigorously for 2 h to break up the emulsion. An additional 2 mL of saturated aqueous sodium potassium tartrate was added along with EtOAc (10 mL) and 10% HCl (0.5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and the aqueous later was extracted with EtOAc (10 mL). All aqueous layers were combined and extracted with DCM (2 x 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated (aspirator) to give 123 mg (78%) of a white solid (**18b**) that was used in the subsequent reaction without further purification. HRMS calcd for $C_{27}H_{26}N_2O$ [M+H], ESMS *m/z*= 395.2123; found *m/z*= 395.2127; IR (neat, cm^{-1}) 3417 (br); 1594; 700; ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 8.26 (1H, d, *J*= 5.3 Hz) 7.56 (1H, s) 7.38-7.33 (6H, m) 7.27-7.16 (9H, m) 6.88 (1H, d, *J*= 5.4 Hz) 6.75 (1H, s) 5.17 (1H, br s) 2.55 (6H, s). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 160.4, 151.1, 149.3, 144.5, 130.6, 129.9, 127.7, 126.4, 115.0, 73.1, 64.8, 44.5.

Representative Procedure for the synthesis of TADMAP derivatives: Benzoic acid 1-(4-dimethylaminopyridin-3-yl)-2,2,2-triphenylethyl ester (18c). (First reported in Ref 18.) Alcohol **18b** (121 mg, 0.31 mmol) was dissolved in DCM (1.5 mL). The solution was cooled to 0 ^{o}C, and EtMgBr (0.85 M in Et_2O, 0.54 mL, 0.46 mmol) was added via syringe. The cooling bath was removed and the mixture was stirred for 1 h at rt. The mixture was re-cooled to 0 ^{o}C and benzoic anhydride (208 mg, 0.92 mmol) was added as a solution in DCM (0.4 mL) via syringe. The solution immediately turned yellow, was stirred for 5 min, and warmed to room temperature. Then the mixture was stirred an additional 2.5 h and the solution turned orange. The reaction was quenched with H_2O (1 mL) followed by the addition of $NaHCO_3$ (sat., 10 mL) and extracted with DCM (4 x 10 mL). The combined organic layers were washed with $NaHCO_3$ (sat., 10 mL), dried ($MgSO_4$) and concentrated (aspirator). The crude product was purified by flash chromatography (3 x 14 cm) using 4:1 EtOAc/hexanes with a 1% Et_3N buffer as eluent and collecting 9 mL fractions. Impurities eluted in fractions 6-9. Fractions 10-17 were combined to yield 97 mg (63%) of **18c**, a pale yellow foam. HPLC assay was carried out on a Chiralpak AD analytical column, 5% isopropanol/hexanes, 1 mL/min flow rate. Retention times of enantiomers: 11.1 min (*R*), 20.0 min (*S*), 95% ee. HRMS calcd for $C_{34}H_{30}N_2O_2$ [M+H], ESMS *m/z*= 499.2386; found *m/z*= 499.2363; IR (neat, cm^{-1}) 1715; 1585; 1265; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.17 (1H, d, *J*= 5.9 Hz) 8.01 (1H, s) 7.88 (2H, d, *J*= 7.3 Hz) 7.51 (1H, t, *J*= 7.6 Hz) 7.40-7.34 (9H, m) 7.26-7.16 (9H, m) 6.73 (1H, d, *J*= 5.4 Hz) 2.79 (6H, s). ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 166.2, 159.5, 152.7, 149.9, 143.5, 133.4, 131.1, 130.3, 129.9, 128.7, 126.8, 126.5, 114.3, 73.1, 64.8, 43.8, 27.5.

Isobutyric acid 1-(4-dimethylaminopyridin-3-yl)-2,2,2-triphenylethyl ester (18e). Following the representative procedure for the synthesis of TADMAP derivatives, alcohol **18b** (26 mg, 0.066 mmol) was protected as the formate ester **18e** (8 mg, 29%) at 55% conversion using isobutyric anhydride (31 µL, 0.19 mmol). HRMS calcd for $C_{31}H_{32}N_2O_2$ [M+H], ESMS *m/z*= 465.2542; found *m/z*= 465.2542; IR (neat, cm^{-1}) 1731; 1586; 1148, 702; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.16 (1H, d, J= 5.4 Hz) 7.70 (1H, s) 7.34 (1H, s) 7.30-7.27 (6H, m) 7.23-7.17 (9H, m) 6.71 (1H, d, J= 5.4 Hz) 2.74 (6 H, s) 2.45 (1H, qq, *J*= 7.3, 6.8 Hz) 0.99 (1H, d, *J*= 6.8 Hz) 0.96

(1H, d, *J*= 7.3 Hz). ^{13}C NMR (125.7 MHz, $CDCl_3$, ppm) δ 176.1, 159.3, 151.5, 148.8, 143.2, 130.8, 127.3, 126.6, 113.8, 72.4, 64.4, 43.5, 34.3, 18.6, 18.6.

Formic acid 1-(4-dimethylaminopyridin-3-yl)-2,2,2-triphenylethyl ester (18d). Following the representative procedure for the synthesis of TADMAP derivatives, alcohol **18b** (24 mg, 0.062 mmol) was protected as the isobutryate ester **18d** (13 mg, 45%) at 56% conversion using formyl pivaloyl mixed anhydride (17 μL, 0.19 mmol). HRMS calcd for $C_{28}H_{26}N_2O_2$ [M+H], ESMS *m/z*= 423.2073; found *m/z*= 423.2063; IR (neat, cm^{-1}) 1723; 1588; 1162, 704; ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.21 (1H, d, J= 6.1 Hz) 8.01 (1H, s) 7.84 (1H, s) 7.47 (1H, s) 7.31-7.27 (6H, m) 7.24-7.19 (9H, m) 6.74 (1H, d, J= 6.1 Hz) 2.68 (6 H, s).

General procedure for kinetic resolutions using DMAP derivatives (A): Kinetic Resolution of 5a Using 18c. A solution of alcohol **5a** (17 mg, 0.1 mmol), DMAP **18c** (0.5 mg, 0.001 mmol, 91% ee), and Et_3N (15 μL, 0.1 mmol) in toluene (0.8 mL) was treated with isobutyric anhydride (17 μL, 0.1 mmol). The reaction was monitored by TLC to an estimated 50% conversion, and then was quenched by addition of *i*-$PrNH_2$ (0.1 mL). The mixture was concentrated (aspirator), and purified by flash chromatography. Ester fractions were concentrated, and 5% NaOH/MeOH (1 mL) was added to saponify the ester prior to assay. The solution was warmed gently for 5 min and then left at room temperature for 2 h. Methanol was evaporated, and the residue was filtered through an 8 cm x 1.2 cm pad of silica gel in DCM. After solvent removal (aspirator), HPLC assay was carried out on a chiral support. Conversion and selectivity of the kinetic resolution were calculated by a best fit method using both the ee of the recovered alcohol and ee of the hydrolyzed ester, correcting for the ee of the catalyst.[25]

Table 3-2, entry 2: Isobutyroylation of 5a with 18c. Following the general procedure **A**, racemic **5a** (17 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol) and catalyst **18c** (0.5 mg, 0.001 mmol, 91% ee) in toluene were stirred at rt for 20 h to afford unreacted alcohol *R*-**5a** 22.3% ee, and isobutyrate *S*-**17a** 40.7% ee (after hydrolysis); **s** = 3.4[25] and c = 35%. HPLC analysis: CHIRALCEL OD analytical column, 10% 2-propanol/hexanes, 1 mL/min flow rate. Retention times 9.8 min (*S*), according to (-) sign of opt. rotation ,[26] 15.0 min (*R*).

Table 3-2, entry 3: Isobutyroylation of 5a with 18c. Following the general procedure **A**, racemic **5a** (17 mg, 0.1 mmol), isobutyric anhydride (12 μL, 0.06 mmol) and catalyst **18c** (0.5 mg, 0.001 mmol, 91% ee) in *t*-amyl alcohol were stirred at rt for 48 h to afford unreacted alcohol *R*-**5a** 34.0% ee, and isobutyrate *S*-**17a** 49.8% ee (after hydrolysis); **s** = 5.1^{25} and c = 41%.

Table 3-2, entry 4: Isobutyroylation of 5a with 18c. Following the general procedure **A**, racemic **5a** (17 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst **18c** (0.5 mg, 0.001 mmol, 91% ee) in *t*-amyl alcohol were stirred at 0 °C for 48 h to afford unreacted alcohol *R*-**5a** 33.4% ee, and isobutyrate *S*-**17a** 51.1% ee (after hydrolysis); **s** = 5.3^{25} and c = 40%.

Table 3-2, entry 5: Isobutyroylation of 5a with 18d. Following the general procedure **A**, racemic **5a** (17 mg, 0.1 mmol), isobutyric anhydride (12 μL, 0.06 mmol), and catalyst **18d** (0.5 mg, 0.001 mmol, 93% ee) in *t*-amyl alcohol were stirred at 0 °C for 24 h to afford unreacted alcohol *R*-**5a** 40.0% ee, and isobutyrate *S*-**17a** 36.8% ee (after hydrolysis); **s** = 3.5^{25} and c = 52%.

Table 3-2, entry 6: Isobutyroylation of 5a with 18e. Following the general procedure, racemic **5a** (18 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst **18e** (0.1 mL, 0.01M in *t*-amyl alcohol, 0.001 mmol, 95.5% ee) in *t*-amyl alcohol were stirred at 0 °C for 16 h to afford unreacted alcohol *R*-**5a** 27.0% ee, and isobutyrate *S*-**17a** 26.7% ee (after hydrolysis); **s** = 2.3^{25} and c = 50%.

Table 3-6, entry 1: Isobutyroylation of 5a with *ent*-20a. Following the general procedure **A**, racemic **5a** (17 mg, 0.1 mmol), isobutyric anhydride (8 μL, 0.05 mmol), and catalyst *ent*-**20a** (0.05 mL, 0.02 M in *t*-amyl alcohol, 0.001 mmol) in *t*-amyl alcohol were stirred at rt for 4 h to afford unreacted alcohol *S*-**5a** 10.9% ee, and isobutyrate *R*-**17a** 41.8% ee (after hydrolysis); **s** = 2.7 and c = 21%.

Table 3-6, entry 4: Isobutyroylation of 5a with *ent*-20b. Following the general procedure **A**, racemic **5a** (17 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst *ent*-**20b** (0.05 mL, 0.02 M in toluene, 0.001 mmol) in toluene were stirred at -40 °C for 4 h to afford unreacted alcohol *S*-**5a** 19.2% ee, and isobutyrate *R*-**17a** 83.5% ee (after hydrolysis); **s** = 13.4 and c = 19%.

Table 3-6, entry 4: Isobutyroylation of 5a with *ent*-20b. Following the general procedure **A**, racemic **5a** (17 mg, 0.1 mmol), isobutyric anhydride (17 μL, 0.1 mmol), and catalyst *ent*-**20b** (0.4 mg, 0.001 mmol) in toluene were stirred at -40 °C for 4 h to afford unreacted alcohol *S*-**5a** 47.5% ee, and isobutyrate *R*-**17a** 85.5% ee (after hydrolysis); **s** = 20.5 and c = 36%.

Table 3-6, entry 5: Isobutyroylation of 5a with *ent*-20b. Following the general procedure **A**, racemic **5a** (17 mg, 0.1 mmol), isobutyric anhydride (8 μL, 0.05 mmol), and catalyst *ent*-**20b** (0.05 mL, 0.02 M in toluene, 0.001 mmol) in toluene were stirred at -70 °C for 8 h to afford unreacted alcohol *S*-**5a** 7.0% ee, and isobutyrate *R*-**17a** 92.9% ee (after hydrolysis); **s** = 29 and c = 7%.

Table 3-6, entry 6: Isobutyroylation of 5b with *ent*-20b. Following the general procedure **A**, racemic **5b** (0.1 mmol), isobutyric anhydride (8 μL, 0.05 mmol), and catalyst *ent*-**20b** (0.05 mL, 0.02 M in toluene, 0.001 mmol) in toluene were stirred at -40 °C for 4 h to afford unreacted alcohol *S*-**5b** 55.7% ee, and isobutyrate *R*-**17b** 72.2% ee (after hydrolysis); **s** = 10.7 and c = 44%. HPLC analysis: CHIRALCEL OD analytical column, 3% 2-propanol/hexanes, 1 mL/min flow rate. Retention times 13.2 min (*R*), according to (-) sign of opt. rotation, 16.3 min (*S*).[27]

Table 3-6, entry 7: Isobutyroylation of 5c with *ent*-20b. Following the general procedure **A**, racemic **5c** (17 mg, 0.1 mmol), isobutyric anhydride (21 μL, 0.1 mmol), and catalyst *ent*-**20b** (0.05 mL, 0.02 M in toluene, 0.001 mmol) in toluene were stirred at -40 °C for 4 h to afford unreacted alcohol *S*-**5c** 10.1% ee, and isobutyrate *R*-**17c** 25.2% ee (after hydrolysis); **s** = 1.8 and c = 29%. HPLC analysis: CHIRALCEL OD analytical column, 3% 2-propanol/hexanes, 1 mL/min flow rate. Retention times 11.8 min (*S*) according to (-) sign of opt. rotation, 18.4 min (*R*).[27]

Table 3-6, entry 8: Isobutyroylation of 5d with *ent*-20b. Following the general procedure **A**, racemic **5d** (17 mg, 0.1 mmol), isobutyric anhydride (21 μL, 0.1 mmol), and catalyst *ent*-**20b** (0.05 mL, 0.02 M in toluene, 0.001 mmol) in toluene were stirred at -40 °C for 4 h to afford unreacted alcohol *S*-**5d** 36.2% ee, and isobutyrate *R*-**17d** 74.0% ee (after hydrolysis); **s** = 9.5 and c = 33%. HPLC analysis: CHIRALCEL OB analytical column, 3% 2-propanol/hexanes, 1

mL/min flow rate. Retention times 13.4 min (*S*), according to (-) sign of opt. rotation, 21.4 min (*R*).[27]

***m*-Chlorobenzoylation of 5a with PhPBO 8d.** Following the general procedure **A**, racemic **5a** (22 mg, 0.12 mmol), *m*-chlorobenzoic anhydride (29 mg, 0.1 mmol), and catalyst **8d** (0.05 mL, 0.04 M in toluene, 0.002 mmol) in toluene were stirred at -40 °C for 6 h to afford unreacted alcohol *S*-**5a** 97.5% ee, and isobutyrate *R*-**24** 65.3% ee (after hydrolysis); **s** = 19.8 and c = 60%.

(*R*)-*N*-Benzoyl-*tert*-leucinal (22). Following the procedure developed by Shaw[21]: (*R*)-*tert*-Leucinol (214 mg, 1.82 mmol) and Et_3N (0.25 mL, 1.82 mmol) were dissolved in DCM (10 mL). The solution was cooled to 0 °C and treated with benzoyl chloride (0.23 mL, 2.01 mmol). The solution was stirred for 1 h, concentrated (aspirator) and the residue taken up in EtOAc. The solution was washed with 0.1 M HCl, then brine, dried over $MgSO_4$, filtered and concentrated (aspirator) yielding (*R*)-*N*-benzoyl-*tert*-leucinol as a white solid (309 mg, 77%). The material was used without additional purification.

Crude (*R*)-*N*-benzoyl-*tert*-leucinol (309 mg, 1.40 mmol) was taken up in DCM (1 mL) and DMSO (1 mL) and treated with Et_3N (0.7 mL, 5 mmol). The solution was cooled to 0 °C and a solution of SO_3•pyridine (1.11 g, 7.0 mmol, Aldrich) in DMSO (2 mL) was added dropwise over 10 min. After 1 h, the solution was poured into H_2O and extracted with Et_2O (2 x 10 mL). The combined organics were washed with 0.1 M HCl and brine, dried over $MgSO_4$, filtered and concentrated (aspirator). The residue was purified by flash chromatography (silica gel; 3 x 15 cm) with 40 % Et_2O/hexanes as the eluent yielding (*R*)-*N*-benzoyl-*tert*-leucinal as a white solid (**22**, 199 mg, 65%) was isolated. In order to avoid racemization, this material was used promptly upon purification.

Acetic acid 2-benzoylamino-1-(4-dimethylaminopyridin-3-yl)-3,3-dimethyl-butyl ester (20b, AcOLeDMAP). To a solution of *t*BuLi (2.9 mL, 1.45 M, 4.0 mmol in hexane) at –78 °C was added a solution of 3-bromo-4-dimethylaminopyridine **6C** (436 mg, 2.2 mmol) in THF (19 mL) dropwise. To the resulting solution was added dropwise a solution of (*R*)-*N*-benzoyl-*tert*-leucinal (**22**, 199 mg, 0.90 mmol) in THF (12.5 mL) at –78 °C. The solution was stirred at –78 °C for 30

min, then quenched with H_2O (5 mL). The solution was warmed to rt, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated (aspirator). The residue was taken up in DCM (10 mL) and treated with Et_3N (0.7 mL, 5 mmol) and Ac_2O (0.45 mL, 4.8 mmol). After stirring for 20 h at rt, the solution was poured into 2 M NaOH and extracted with DCM 3 x 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated (aspirator) yielding a yellow oil that was purified by column chromatography (silica gel; 5 x 15 cm) using 95:5 EtOAc/Et_3N to provide **12a** as a pale yellow solid (>98:2 dr). This material was recrystallized from Et_2O/hexanes to afford **23A** as a white powder (157 mg, 45%, diastereomerically pure). Spectral data matched the known compound.

A Representative Example of Competition Experiments: Table 3-3, entry 5. A solution 1-naphthyl methyl carbinol **5a** (17 mg, 0.1 mmol), *m*-chlorobenzoic anhydride (30 mg, 0.1 mmol), isobutyric anhydride (17 µL, 0.1 mmol, degassed), and ArPBO·HBF_4 (**8c**·HBF_4, 1.5 mg, 0.004 mmol) in toluene (0.7 mL) was treated with Et_3N (21 µL, 0.15 mmol). After stirring for 5 h, addition of *i*-$PrNH_2$ (0.1 mL) quenched the reaction, and the solvent was evaporated (N_2 stream). NMR assay of the crude reaction mixture revealed >18:1 of the *m*-chlorobenzoate/isobutyrate. These reactions were not worked up further.

General Procedure for Parallel Kinetic Resolution. A solution of **5a** (0.1 mmol), *m*-chlorobenzoic anhydride (23 mg, 0.1 mmol), isobutyric anhydride (17 µL, 0.1 mmol, degassed), and Et_3N (22 µL, 0.15 mmol) in toluene (0.8 mL) was cooled to -40 ^oC in a Cryocool. The catalysts were added as solutions: PhPBO **8c** (25 µL, 0.0022 mmol, 0.088M in DCM) and AcOLeDMAP **20b** (25 µL, 0.001 mmol, 0.04M in DCM). The reactions were stirred for 2-3 h and then quenched with *i*-$PrNH_2$ (0.1 mL). The mixture was concentrated (aspirator), and the ratio of products was determined by crude ^1H NMR spectroscopy. The products were purified by flash chromatography (2:1 Hex:Et_2O). Analytical TLC (2:1 Hex:Et_2O): *m*-chlorobenzoate: R_f = 0.44, isobutyrate: R_f = 0.32, alcohol: R_f = 0.12. Ester fractions were concentrated to afford **17a** and **24**.

Next, 5% NaOH/MeOH (1 mL) was added to saponify each ester prior to assay. The solution was warmed gently for 5 min and then left at room temperature for 2 h. Methanol was evaporated, and the residue was filtered through an 8 x 1.2 cm pad of silica gel in DCM. After solvent removal (aspirator), HPLC assay for each product was carried out on a chiral support.

Parallel Kinetic Resolutions:

Table 3.7, entry 1. Following the general procedure, racemic **5a** (17 mg, 0.1 mmol), PhPBO **8c** (0.0022 mmol), and AcOLeDMAP **20b** (0.001 mmol) were stirred for 3 h to afford *R*-**24**: 88% ee (after hydrolysis), *S*-**17a**: 75% ee (after hydrolysis) and recovered alcohol **5a**: 27% ee.

Table 3.7, entry 2. Following the general procedure, racemic **5a** (17 mg, 0.1 mmol), PhPBO **8c** (0.0026 mmol), and AcOLeDMAP **20b** (0.001 mmol) were stirred for 3 h to afford *R*-**24**: (14 mg, 44%) 87% ee (after hydrolysis), *S*-**17a**: (8 mg, 33%) 76% ee (after hydrolysis) and recovered alcohol **5a**: 8% ee.

Table 3.7, entry 3. Following the general procedure, racemic **5a** (17 mg, 0.1 mmol), PhPBO **8c** (0.0052 mmol), and AcOLeDMAP **20b** (0.002 mmol) were stirred for 2 h to afford *R*-**24**: 86% ee (after hydrolysis), *S*-**17a**: 75% ee (after hydrolysis) and recovered alcohol **5a**: 19% ee.

Preparation of mixed biphenyl cyclohexyl anhydride 25. A solution of 4-biphenyl carboxylic acid (999 mg, 5.0 mmol) in THF (15 mL) was cooled to 0 ^{o}C, and NaH (204 mg, 5.1 mmol) was added. After 30 min, the solution was allowed to warm to rt and stirred for an additional 1 h. The solution was re-cooled to 0 °C, and cyclohexyl carbonyl chloride (0.61 mL, 4.5 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C. The ice bath was removed and the mixture was stirred for an additional 40 min at rt. Activated carbon (~0.5g) and hexanes (10 mL) was added and the mixture was filtered through celite and concentrated to yield a white solid. The solid was taken up in hot hexanes, filtered (to remove the symmetrical biphenyl anhydride), and allowed to cool. Slow evaporation of the hexanes afforded **25** as a white crystalline solid (478 mg, 35%). IR (neat, cm^{-1}) 1783; 1725; 1607, 994; ^{1}H NMR (400 MHz,

$CDCl_3$, ppm) δ 8.10 (2H, d, *J*= 8.2 Hz) 7.69 (2H, d, *J*= 8.2 Hz) 7.62 (2H, d, *J*= 6.9 Hz) 7.50-7.39 (3H, m) 2.61 (1H, tt, *J*= 10.9, 3.5 Hz) 2.14-2.06 (2H, m) 1.88-1.80 (2H, m) 1.72-1.56 (3H, m) 1.42-1.23 (3H, m). ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ 171.5, 147.0, 139.6, 130.9, 129.0, 128.5, 127.6, 127.4, 127.3, 44.2, 28.5, 25.6, 25.2.

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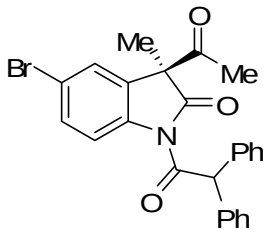
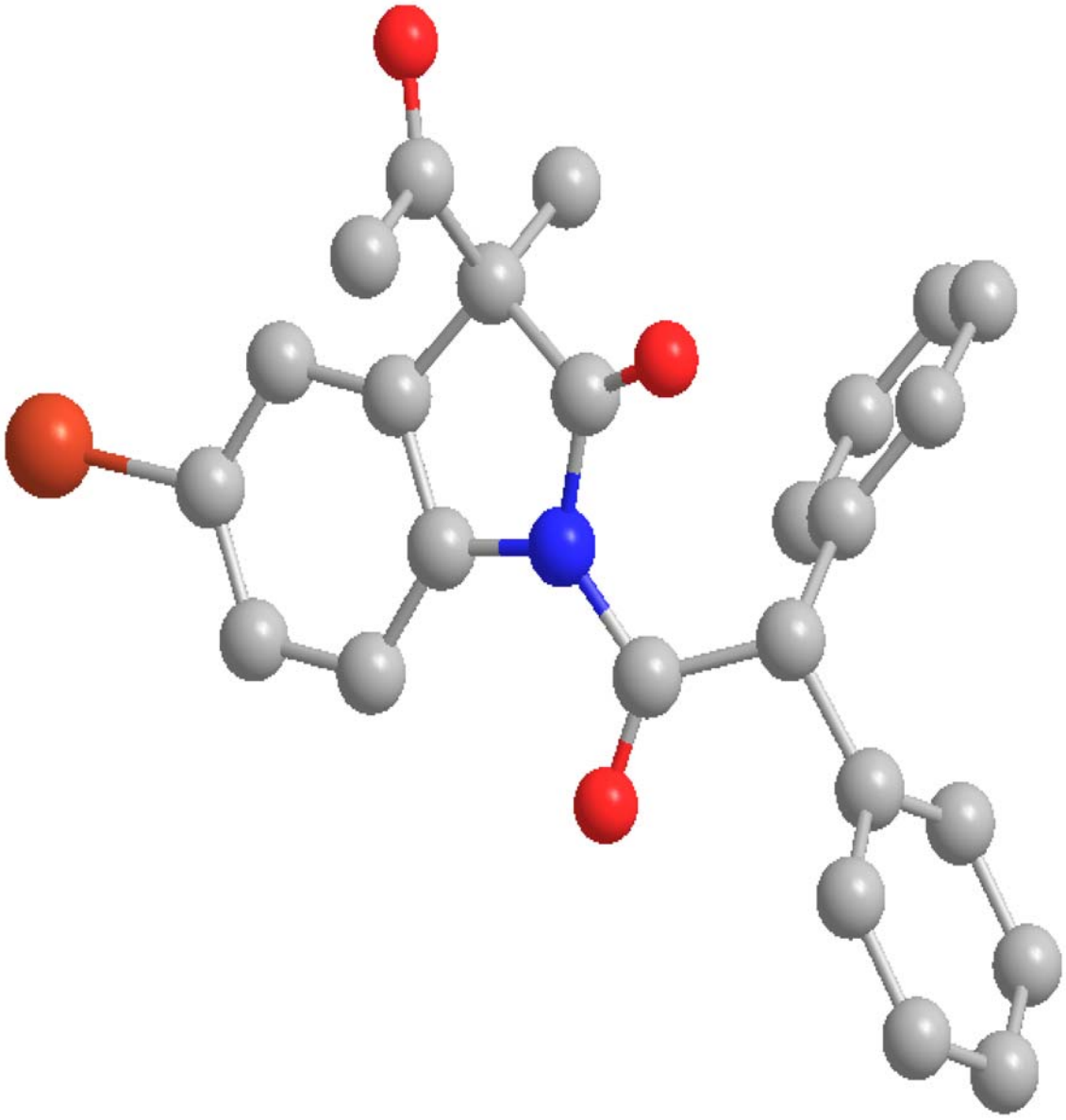
APPENDIX A:

X-ray Crystallography Data

Crystallographic analysis of 3-acetyl-5-bromo-1-diphenylacetyl-3-methyloxindole 23E.





Colorless needles of **23E** were grown from a hexane/diethyl ether solution of the compound at 22 deg. C. A crystal of dimensions 0.40 x 0.20 x 0.20 mm was mounted on a standard Bruker SMART 1K CCD-based X-ray diffractometer equipped with a LT-2 low temperature device and normal focus Mo-target X-ray tube (λ = 0.71073 A) operated at 2000 W power (50 kV, 40 mA). The X-ray intensities were measured at 123(2) K; the detector was placed at a distance 4.944 cm from the crystal. A total of 5190 frames were collected with a scan width of 0.5° in ω and 0.45 in phi with an exposure time of 20 s/frame. The integration of the data yielded a total of 44052 reflections to a maximum 2θ value of 56.84° of which 10446 were independent and 9314 were greater than $2\sigma(I)$. The final cell constants (Table 1) were based on the xyz centroids of 9872 reflections above $10\sigma(I)$. Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 6.12) software package, using the space group P1 with Z = 2 for the formula $C_{25}H_{20}NO_3Br$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. There are two crystallographically independent molecules in the crystal lattice. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0279 and wR2 = 0.0604 [based on I > 2sigma(I)], R1 = 0.0365 and wR2 = 0.0639 for all data.

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Crystal data and structure refinement for **23E**.

Identification code	**23E**
Empirical formula	$C_{25}H_{20}BrNO_3$
Formula weight	462.33
Temperature	123(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, P1
Unit cell dimensions	a = 7.2377(18) Å α = 103.179°
	b = 10.127(3) Å β = 96.629°
	c = 15.948(4) Å γ = 109.845°
Volume	1046.5(5) $Å^3$
Z, Calculated density	2, 1.467 Mg/m^3
Absorption coefficient	1.991 mm^{-1}
F(000)	472
Crystal size	0.40 x 0.20 x 0.20 mm
θ range for data collection	2.23 to 28.43°
Limiting indices	-9<=h<=9, -13<=k<=13, -21<=l<=21
Reflections collected / unique	44052 / 10446 [R(int) = 0.0391]
Completeness to θ = 28.43	99.4 %

Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10446 / 3 / 545
Goodness-of-fit on F^2	1.024
Final R indices [I>2σ(I)]	R1 = 0.0279, wR2 = 0.0604
R indices (all data)	R1 = 0.0365, wR2 = 0.0639
Absolute structure parameter	-0.013(4)
Largest diff. peak and hole	0.385 and -0.220 e.A^{-3}

Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters (A^2x10^3) for **23E**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br(1)	10410(1)	8412(1)	2495(1)	30(1)
Br(2)	7161(1)	9574(1)	5119(1)	31(1)
N(1)	1447(3)	4992(2)	1578(1)	19(1)
N(2)	-861(3)	7083(2)	6106(1)	20(1)
O(1)	-724(2)	4514(2)	254(1)	31(1)
O(2)	3721(3)	5266(2)	-943(1)	45(1)
O(3)	546(2)	4702(2)	2853(1)	29(1)
O(4)	-1505(3)	7841(2)	7498(1)	31(1)
O(5)	3998(3)	10569(2)	8483(1)	41(1)
O(6)	-3093(2)	5674(2)	4833(1)	27(1)
C(1)	7598(3)	7351(2)	2256(1)	23(1)
C(2)	6712(4)	6862(2)	2911(1)	22(1)
C(3)	4663(3)	6077(2)	2754(1)	20(1)
C(4)	3528(3)	5829(2)	1932(1)	18(1)
C(5)	937(3)	5031(2)	708(1)	22(1)
C(6)	2868(3)	5910(2)	450(1)	22(1)
C(7)	4423(3)	6357(2)	1282(1)	21(1)
C(8)	6470(3)	7109(2)	1433(1)	22(1)
C(9)	3365(3)	4897(3)	-298(1)	27(1)
C(10)	3410(5)	3512(3)	-155(2)	42(1)
C(11)	2598(4)	7196(3)	182(2)	31(1)
C(12)	119(3)	4264(2)	2067(1)	21(1)
C(13)	-1693(3)	2891(2)	1526(1)	20(1)
C(14)	-2938(3)	2214(2)	2136(1)	20(1)
C(15)	-3801(3)	3020(2)	2671(2)	27(1)
C(16)	-4883(3)	2460(3)	3256(2)	29(1)
C(17)	-5129(3)	1074(3)	3316(2)	26(1)
C(18)	-4339(4)	243(3)	2771(2)	25(1)
C(19)	-3259(3)	799(3)	2178(2)	23(1)
C(20)	-994(3)	1836(2)	935(1)	22(1)
C(21)	661(3)	1553(2)	1259(2)	26(1)
C(22)	1245(4)	539(3)	734(2)	35(1)
C(23)	187(5)	-201(3)	-120(2)	41(1)
C(24)	-1472(5)	68(3)	-450(2)	40(1)
C(25)	-2060(4)	1083(3)	73(2)	30(1)
C(26)	4601(3)	8724(2)	5371(2)	24(1)
C(27)	2945(3)	7896(2)	4691(1)	22(1)
C(28)	1045(3)	7288(2)	4864(1)	20(1)

C(29)	861(3)	7553(2)	5737(1)	18(1)
C(30)	-343(3)	7792(2)	7021(1)	22(1)
C(31)	1948(3)	8480(2)	7295(1)	22(1)
C(32)	2546(3)	8373(2)	6416(1)	21(1)
C(33)	4438(3)	8967(2)	6244(1)	23(1)
C(34)	2694(3)	10092(2)	7835(1)	25(1)
C(35)	1768(4)	11034(3)	7492(2)	36(1)
C(36)	2674(4)	7560(3)	7801(2)	32(1)
C(37)	-2732(3)	5977(2)	5622(1)	20(1)
C(38)	-4109(3)	5186(2)	6163(1)	20(1)
C(39)	-3008(3)	4598(2)	6759(1)	21(1)
C(40)	-1691(3)	3959(2)	6466(2)	26(1)
C(41)	-762(4)	3360(3)	7005(2)	34(1)
C(42)	-1186(4)	3394(3)	7834(2)	39(1)
C(43)	-2500(4)	4012(3)	8125(2)	37(1)
C(44)	-3403(3)	4619(3)	7593(2)	28(1)
C(45)	-6010(3)	4008(2)	5552(1)	20(1)
C(46)	-7379(3)	4430(3)	5098(2)	26(1)
C(47)	-9090(3)	3400(3)	4509(2)	32(1)
C(48)	-9477(3)	1928(3)	4374(2)	32(1)
C(49)	-8183(4)	1486(3)	4830(2)	28(1)
C(50)	-6442(3)	2524(2)	5423(2)	22(1)

Bond lengths [A] and angles [°] for **23E**.

Br(1)-C(1)	1.895(2)
Br(2)-C(26)	1.892(2)
N(1)-C(5)	1.407(3)
N(1)-C(4)	1.423(3)
N(1)-C(12)	1.424(3)
N(2)-C(30)	1.414(3)
N(2)-C(37)	1.421(3)
N(2)-C(29)	1.422(3)
O(1)-C(5)	1.201(3)
O(2)-C(9)	1.198(3)
O(3)-C(12)	1.194(3)
O(4)-C(30)	1.202(3)
O(5)-C(34)	1.196(3)
O(6)-C(37)	1.200(3)
C(1)-C(8)	1.386(3)
C(1)-C(2)	1.387(3)
C(2)-C(3)	1.385(3)
C(3)-C(4)	1.385(3)
C(4)-C(7)	1.397(3)
C(5)-C(6)	1.539(3)
C(6)-C(7)	1.506(3)
C(6)-C(11)	1.524(3)
C(6)-C(9)	1.548(3)
C(7)-C(8)	1.379(3)
C(9)-C(10)	1.482(4)
C(12)-C(13)	1.534(3)
C(13)-C(20)	1.517(3)
C(13)-C(14)	1.522(3)

C(14)-C(15)	1.391(3)
C(14)-C(19)	1.391(3)
C(15)-C(16)	1.384(3)
C(16)-C(17)	1.380(3)
C(17)-C(18)	1.378(3)
C(18)-C(19)	1.392(3)
C(20)-C(21)	1.393(3)
C(20)-C(25)	1.396(3)
C(21)-C(22)	1.385(3)
C(22)-C(23)	1.381(4)
C(23)-C(24)	1.391(4)
C(24)-C(25)	1.386(4)
C(26)-C(33)	1.384(3)
C(26)-C(27)	1.385(3)
C(27)-C(28)	1.392(3)
C(28)-C(29)	1.388(3)
C(29)-C(32)	1.395(3)
C(30)-C(31)	1.528(3)
C(31)-C(32)	1.506(3)
C(31)-C(34)	1.533(3)
C(31)-C(36)	1.540(3)
C(32)-C(33)	1.384(3)
C(34)-C(35)	1.499(3)
C(37)-C(38)	1.533(3)
C(38)-C(39)	1.516(3)
C(38)-C(45)	1.521(3)
C(39)-C(40)	1.389(3)
C(39)-C(44)	1.390(3)
C(40)-C(41)	1.393(3)
C(41)-C(42)	1.388(4)
C(42)-C(43)	1.373(4)
C(43)-C(44)	1.381(3)
C(45)-C(50)	1.386(3)
C(45)-C(46)	1.398(3)
C(46)-C(47)	1.383(3)
C(47)-C(48)	1.379(4)
C(48)-C(49)	1.373(4)
C(49)-C(50)	1.400(3)

C(5)-N(1)-C(4)	110.17(17)
C(5)-N(1)-C(12)	126.68(17)
C(4)-N(1)-C(12)	123.15(16)
C(30)-N(2)-C(37)	126.85(17)
C(30)-N(2)-C(29)	109.21(17)
C(37)-N(2)-C(29)	123.73(17)
C(8)-C(1)-C(2)	121.6(2)
C(8)-C(1)-Br(1)	118.93(17)
C(2)-C(1)-Br(1)	119.45(16)
C(3)-C(2)-C(1)	120.7(2)
C(4)-C(3)-C(2)	117.9(2)
C(3)-C(4)-C(7)	121.02(19)
C(3)-C(4)-N(1)	129.63(19)
C(7)-C(4)-N(1)	109.24(17)
O(1)-C(5)-N(1)	126.1(2)
O(1)-C(5)-C(6)	125.75(19)
N(1)-C(5)-C(6)	108.15(17)

C(7)-C(6)-C(11)	113.92(18)
C(7)-C(6)-C(5)	102.14(17)
C(11)-C(6)-C(5)	109.19(18)
C(7)-C(6)-C(9)	109.33(18)
C(11)-C(6)-C(9)	111.82(18)
C(5)-C(6)-C(9)	109.99(17)
C(8)-C(7)-C(4)	121.01(19)
C(8)-C(7)-C(6)	128.72(19)
C(4)-C(7)-C(6)	110.21(18)
C(7)-C(8)-C(1)	117.7(2)
O(2)-C(9)-C(10)	123.6(2)
O(2)-C(9)-C(6)	119.7(2)
C(10)-C(9)-C(6)	116.61(19)
O(3)-C(12)-N(1)	118.75(19)
O(3)-C(12)-C(13)	125.16(19)
N(1)-C(12)-C(13)	115.93(17)
C(20)-C(13)-C(14)	113.35(17)
C(20)-C(13)-C(12)	110.00(17)
C(14)-C(13)-C(12)	109.94(16)
C(15)-C(14)-C(19)	118.2(2)
C(15)-C(14)-C(13)	119.70(19)
C(19)-C(14)-C(13)	122.12(19)
C(16)-C(15)-C(14)	121.3(2)
C(17)-C(16)-C(15)	120.1(2)
C(18)-C(17)-C(16)	119.4(2)
C(17)-C(18)-C(19)	120.7(2)
C(14)-C(19)-C(18)	120.3(2)
C(21)-C(20)-C(25)	119.1(2)
C(21)-C(20)-C(13)	120.56(19)
C(25)-C(20)-C(13)	120.31(19)
C(22)-C(21)-C(20)	120.7(2)
C(23)-C(22)-C(21)	120.1(2)
C(22)-C(23)-C(24)	119.8(2)
C(25)-C(24)-C(23)	120.3(2)
C(24)-C(25)-C(20)	120.1(2)
C(33)-C(26)-C(27)	121.6(2)
C(33)-C(26)-Br(2)	118.27(17)
C(27)-C(26)-Br(2)	120.16(17)
C(26)-C(27)-C(28)	120.9(2)
C(29)-C(28)-C(27)	117.9(2)
C(28)-C(29)-C(32)	120.6(2)
C(28)-C(29)-N(2)	130.2(2)
C(32)-C(29)-N(2)	109.14(18)
O(4)-C(30)-N(2)	125.9(2)
O(4)-C(30)-C(31)	126.21(19)
N(2)-C(30)-C(31)	107.90(17)
C(32)-C(31)-C(30)	101.74(17)
C(32)-C(31)-C(34)	109.79(17)
C(30)-C(31)-C(34)	111.83(18)
C(32)-C(31)-C(36)	112.30(19)
C(30)-C(31)-C(36)	108.81(18)
C(34)-C(31)-C(36)	111.95(18)
C(33)-C(32)-C(29)	121.5(2)
C(33)-C(32)-C(31)	128.39(19)
C(29)-C(32)-C(31)	110.11(19)
C(32)-C(33)-C(26)	117.5(2)

O(5)-C(34)-C(35)	122.3(2)
O(5)-C(34)-C(31)	120.8(2)
C(35)-C(34)-C(31)	116.87(19)
O(6)-C(37)-N(2)	119.26(19)
O(6)-C(37)-C(38)	124.50(19)
N(2)-C(37)-C(38)	116.14(17)
C(39)-C(38)-C(45)	112.98(17)
C(39)-C(38)-C(37)	111.15(17)
C(45)-C(38)-C(37)	109.85(16)
C(40)-C(39)-C(44)	119.2(2)
C(40)-C(39)-C(38)	120.96(19)
C(44)-C(39)-C(38)	119.70(19)
C(39)-C(40)-C(41)	120.4(2)
C(42)-C(41)-C(40)	119.2(2)
C(43)-C(42)-C(41)	120.6(2)
C(42)-C(43)-C(44)	120.1(2)
C(43)-C(44)-C(39)	120.4(2)
C(50)-C(45)-C(46)	118.4(2)
C(50)-C(45)-C(38)	122.65(19)
C(46)-C(45)-C(38)	118.96(19)
C(47)-C(46)-C(45)	121.1(2)
C(48)-C(47)-C(46)	119.8(2)
C(49)-C(48)-C(47)	120.2(2)
C(48)-C(49)-C(50)	120.3(2)
C(45)-C(50)-C(49)	120.2(2)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (A^2 x 10^3) for **23E**. The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$h^2 a^{*2}$ U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Br(1)	23(1)	31(1)	31(1)	8(1)	2(1)	5(1)
Br(2)	24(1)	34(1)	30(1)	9(1)	11(1)	4(1)
N(1)	21(1)	20(1)	15(1)	5(1)	2(1)	7(1)
N(2)	20(1)	19(1)	18(1)	4(1)	5(1)	5(1)
O(1)	27(1)	38(1)	23(1)	14(1)	-1(1)	7(1)
O(2)	57(1)	60(1)	26(1)	15(1)	21(1)	27(1)
O(3)	32(1)	30(1)	17(1)	6(1)	5(1)	2(1)
O(4)	32(1)	26(1)	26(1)	0(1)	14(1)	2(1)
O(5)	46(1)	35(1)	29(1)	-5(1)	-9(1)	14(1)
O(6)	28(1)	28(1)	19(1)	7(1)	3(1)	2(1)
C(1)	22(1)	19(1)	25(1)	4(1)	2(1)	7(1)
C(2)	28(1)	20(1)	18(1)	3(1)	-1(1)	10(1)
C(3)	28(1)	18(1)	16(1)	5(1)	5(1)	11(1)
C(4)	23(1)	15(1)	18(1)	5(1)	4(1)	9(1)
C(5)	27(1)	22(1)	18(1)	7(1)	3(1)	10(1)
C(6)	25(1)	22(1)	17(1)	6(1)	4(1)	8(1)
C(7)	29(1)	17(1)	16(1)	3(1)	4(1)	10(1)

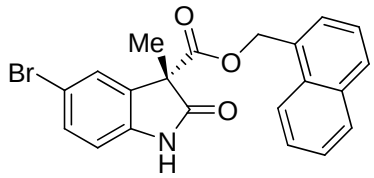
C(8)	28(1)	17(1)	21(1)	5(1)	9(1)	8(1)
C(9)	24(1)	34(1)	17(1)	3(1)	2(1)	7(1)
C(10)	61(2)	31(1)	32(1)	0(1)	16(1)	20(1)
C(11)	36(1)	36(1)	27(1)	17(1)	7(1)	16(1)
C(12)	24(1)	21(1)	18(1)	8(1)	5(1)	9(1)
C(13)	21(1)	20(1)	19(1)	5(1)	2(1)	8(1)
C(14)	18(1)	19(1)	20(1)	3(1)	1(1)	6(1)
C(15)	25(1)	22(1)	35(1)	6(1)	7(1)	9(1)
C(16)	22(1)	27(1)	34(1)	2(1)	9(1)	8(1)
C(17)	18(1)	28(1)	27(1)	6(1)	5(1)	3(1)
C(18)	22(1)	21(1)	32(1)	9(1)	8(1)	5(1)
C(19)	21(1)	20(1)	28(1)	3(1)	7(1)	9(1)
C(20)	23(1)	20(1)	21(1)	6(1)	5(1)	6(1)
C(21)	27(1)	23(1)	27(1)	6(1)	6(1)	9(1)
C(22)	40(1)	30(1)	45(2)	17(1)	17(1)	19(1)
C(23)	63(2)	28(1)	42(2)	7(1)	27(1)	24(1)
C(24)	56(2)	32(1)	26(1)	0(1)	10(1)	12(1)
C(25)	33(1)	29(1)	23(1)	6(1)	4(1)	8(1)
C(26)	23(1)	22(1)	28(1)	10(1)	10(1)	7(1)
C(27)	27(1)	25(1)	17(1)	7(1)	7(1)	12(1)
C(28)	21(1)	22(1)	16(1)	6(1)	2(1)	9(1)
C(29)	22(1)	16(1)	20(1)	7(1)	7(1)	8(1)
C(30)	27(1)	18(1)	18(1)	3(1)	6(1)	6(1)
C(31)	25(1)	21(1)	18(1)	4(1)	5(1)	5(1)
C(32)	25(1)	18(1)	17(1)	3(1)	3(1)	7(1)
C(33)	22(1)	21(1)	22(1)	5(1)	1(1)	6(1)
C(34)	24(1)	26(1)	21(1)	3(1)	6(1)	6(1)
C(35)	42(2)	26(1)	33(1)	2(1)	-2(1)	12(1)
C(36)	42(1)	30(1)	22(1)	10(1)	4(1)	12(1)
C(37)	21(1)	19(1)	21(1)	6(1)	4(1)	7(1)
C(38)	21(1)	20(1)	19(1)	6(1)	6(1)	8(1)
C(39)	19(1)	20(1)	20(1)	5(1)	2(1)	3(1)
C(40)	24(1)	28(1)	27(1)	9(1)	6(1)	10(1)
C(41)	28(1)	31(1)	43(1)	13(1)	2(1)	14(1)
C(42)	39(1)	39(1)	36(1)	17(1)	-7(1)	12(1)
C(43)	42(1)	44(2)	22(1)	15(1)	3(1)	11(1)
C(44)	26(1)	33(1)	21(1)	7(1)	6(1)	9(1)
C(45)	17(1)	25(1)	19(1)	8(1)	8(1)	7(1)
C(46)	25(1)	30(1)	30(1)	16(1)	8(1)	12(1)
C(47)	18(1)	52(2)	32(1)	25(1)	6(1)	10(1)
C(48)	20(1)	44(1)	22(1)	9(1)	5(1)	-1(1)
C(49)	22(1)	24(1)	29(1)	5(1)	9(1)	-2(1)
C(50)	19(1)	24(1)	22(1)	7(1)	6(1)	7(1)

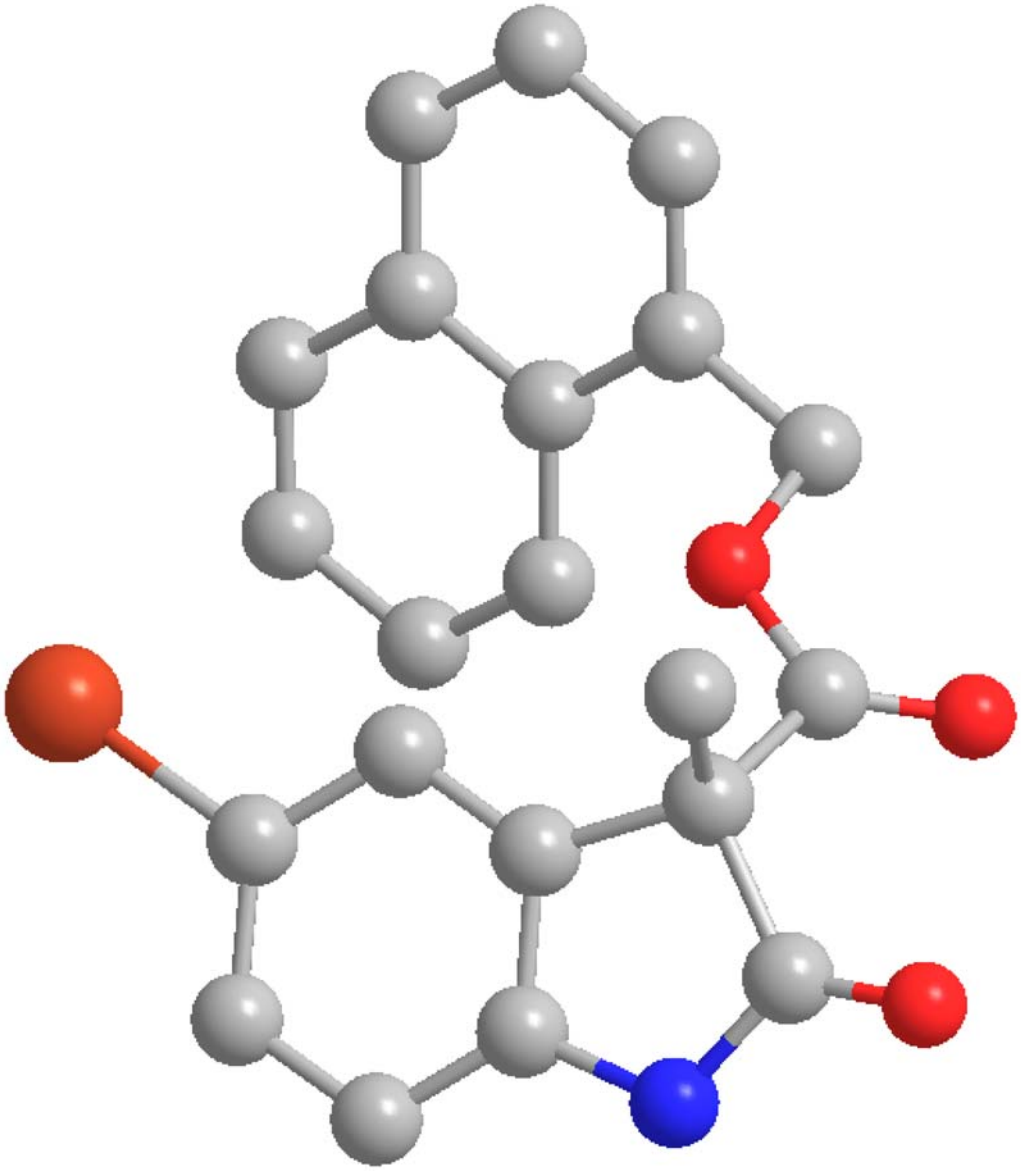
Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **23E**.

	x	y	z	U(eq)
H(2A)	7521	7068	3474	27
H(3A)	4054	5719	3196	24
H(8A)	7086	7450	988	26

H(10A)	2034	2789	-280	62
H(10B)	4051	3695	458	62
H(10C)	4175	3136	-549	62
H(11A)	2297	7815	672	46
H(11B)	1486	6825	-331	46
H(11C)	3837	7773	32	46
H(13A)	-2552	3202	1139	24
H(15A)	-3644	3974	2633	33
H(16A)	-5457	3029	3617	35
H(17A)	-5838	697	3729	32
H(18A)	-4534	-720	2801	30
H(19A)	-2738	209	1801	28
H(21A)	1397	2061	1845	31
H(22A)	2373	353	962	42
H(23A)	592	-892	-482	50
H(24A)	-2206	-446	-1036	49
H(25A)	-3191	1266	-157	35
H(27A)	3109	7742	4099	27
H(28A)	-90	6711	4399	24
H(33A)	5583	9520	6708	28
H(35A)	521	10942	7701	54
H(35B)	1470	10718	6846	54
H(35C)	2707	12058	7704	54
H(36A)	2189	6544	7432	47
H(36B)	2150	7590	8342	47
H(36C)	4146	7961	7952	47
H(38A)	-4513	5923	6548	24
H(40A)	-1423	3930	5894	31
H(41A)	150	2933	6806	40
H(42A)	-560	2985	8205	46
H(43A)	-2788	4023	8692	44
H(44A)	-4301	5055	7799	33
H(46A)	-7129	5442	5195	32
H(47A)	-9996	3705	4198	39
H(48A)	-10643	1219	3964	38
H(49A)	-8470	471	4744	33
H(50A)	-5553	2212	5738	26

Crystallographic analysis of 5-Bromo-3-methyl-3-(1-naphthyl)methoxycarbonyloxindole e13A.





Colorless blocks of **23** were grown from benzene/hexanes by slow diffusion at 25 °C. A crystal of dimensions 0.20 x 0.17 x 0.14 mm was mounted on a Bruker SMART APEX CCD-based X-ray diffractometer equipped with a low temperature device and fine focus Mo-target X-ray tube (λ = 0.71073 A) operated at 1500 W power (50 kV, 30 mA). The X-ray intensities were measured at 85(1) K; the detector was placed at a distance 5.055 cm from the crystal. A total of 3625 frames were collected with a scan width of 0.5° in ω and 0.45° in phi with an exposure time of 15 s/frame. The integration of the data yielded a total of 54434 reflections to a maximum 2θ value of 56.74° of which 4323 were independent and 4294 were greater than 2σ(I). The final cell constants (Table 1) were based on the xyz centroids of 9373 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection; the data were processed with SADABS and corrected for absorption. The structure was solved and refined with the Bruker SHELXTL (version 2008/3) software package, using the space group P2(1)2(1)2(1) with Z = 4 for the formula $C_{21}H_{16}NO_3Br$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of idealized or refined positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0217 and wR2 = 0.0543 [based on I > 2sigma(I)], R1 = 0.0218 and wR2 = 0.0544 for all data. Additional details are presented in Table 12 and are given as Supporting Information in a CIF file.

Sheldrick, G.M. SHELXTL, v. 2008/3; Bruker Analytical X-ray, Madison, WI, 2008.

Sheldrick, G.M. SADABS, v. 2008/1. Program for Empirical Absorption Correction of Area Detector Data, University of Gottingen: Gottingen, Germany, 2008.

Saint Plus, v. 7.54a, Bruker Analytical X-ray, Madison, WI, 2008.

Crystal data and structure refinement for **e13A**.

Identification code	**e13A**
Empirical formula	$C_{21}H_{16}BrNO_3$
Formula weight	410.26
Temperature	85(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 5.6298(4) Å alpha = 90 deg.
	b = 8.2145(6) Å beta = 90 deg.
	c = 37.372(3) Å gamma = 90 deg.
Volume	1728.3(2) $Å^3$
Z, Calculated density	4, 1.577 Mg/m^3

Absorption coefficient	2.400 mm^{-1}
F(000)	832
Crystal size	0.20 x 0.17 x 0.14 mm
Theta range for data collection	2.18 to 28.37 deg.
Limiting indices	-7<=h<=7, -10<=k<=10, -49<=l<=49
Reflections collected / unique	54434 / 4323 [R(int) = 0.0385]
Completeness to theta = 28.37	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7153 and 0.6325
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4323 / 0 / 240
Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R1 = 0.0217, wR2 = 0.0543
R indices (all data)	R1 = 0.0218, wR2 = 0.0544
Absolute structure parameter	0.006(6)
Largest diff. peak and hole	0.453 and -0.257 $e.A^{-3}$

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **e13A**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br(1)	4712(1)	7680(1)	1181(1)	16(1)
C(1)	2076(3)	7554(2)	1498(1)	13(1)
C(2)	1183(4)	8967(2)	1648(1)	16(1)
C(3)	-759(4)	8866(2)	1881(1)	15(1)
C(4)	-1655(3)	7340(2)	1955(1)	13(1)
C(5)	-3867(3)	5307(2)	2207(1)	12(1)
C(6)	-2066(3)	4477(2)	1954(1)	11(1)
C(7)	-725(3)	5923(2)	1805(1)	11(1)
C(8)	1158(3)	6013(2)	1570(1)	12(1)
C(9)	-477(3)	3344(2)	2181(1)	14(1)
C(10)	-3275(3)	3438(2)	1668(1)	12(1)
C(11)	-2557(3)	2135(2)	1108(1)	17(1)
C(12)	-604(3)	2153(2)	835(1)	16(1)
C(13)	684(4)	764(2)	772(1)	20(1)
C(14)	2620(4)	758(3)	531(1)	22(1)
C(15)	3254(3)	2158(3)	358(1)	21(1)
C(16)	1957(4)	3615(3)	409(1)	17(1)
C(17)	2545(4)	5060(3)	222(1)	21(1)
C(18)	1226(4)	6444(3)	265(1)	23(1)
C(19)	-750(4)	6448(2)	497(1)	21(1)
C(20)	-1349(4)	5073(2)	684(1)	18(1)
C(21)	-26(3)	3617(2)	647(1)	15(1)
O(1)	-5264(3)	4637(2)	2408(1)	16(1)
O(2)	-5264(2)	2929(2)	1676(1)	20(1)
O(3)	-1713(2)	3125(2)	1407(1)	18(1)
N(1)	-3533(3)	6940(2)	2185(1)	14(1)

Bond lengths [A] and angles [deg] for **e13A**.

Br(1)-C(1)	1.9028(16)
C(1)-C(2)	1.384(3)
C(1)-C(8)	1.393(2)
C(2)-C(3)	1.400(3)
C(3)-C(4)	1.379(2)
C(4)-C(7)	1.393(2)
C(4)-N(1)	1.402(2)
C(5)-O(1)	1.220(2)
C(5)-N(1)	1.357(2)
C(5)-C(6)	1.544(2)
C(6)-C(7)	1.513(2)
C(6)-C(10)	1.528(2)
C(6)-C(9)	1.546(2)
C(7)-C(8)	1.381(3)
C(10)-O(2)	1.195(2)
C(10)-O(3)	1.339(2)
C(11)-O(3)	1.462(2)
C(11)-C(12)	1.498(2)
C(12)-C(13)	1.372(3)
C(12)-C(21)	1.431(2)
C(13)-C(14)	1.416(3)
C(14)-C(15)	1.366(3)
C(15)-C(16)	1.415(3)
C(16)-C(17)	1.417(3)
C(16)-C(21)	1.427(3)
C(17)-C(18)	1.367(3)
C(18)-C(19)	1.411(3)
C(19)-C(20)	1.370(3)
C(20)-C(21)	1.416(3)

C(2)-C(1)-C(8)	123.32(16)
C(2)-C(1)-Br(1)	119.39(14)
C(8)-C(1)-Br(1)	117.28(13)
C(1)-C(2)-C(3)	119.11(17)
C(4)-C(3)-C(2)	117.59(16)
C(3)-C(4)-C(7)	122.88(15)
C(3)-C(4)-N(1)	127.66(17)
C(7)-C(4)-N(1)	109.45(16)
O(1)-C(5)-N(1)	124.95(17)
O(1)-C(5)-C(6)	126.96(16)
N(1)-C(5)-C(6)	107.97(15)
C(7)-C(6)-C(10)	113.81(14)
C(7)-C(6)-C(5)	101.88(14)
C(10)-C(6)-C(5)	112.44(14)
C(7)-C(6)-C(9)	112.70(14)
C(10)-C(6)-C(9)	107.79(14)
C(5)-C(6)-C(9)	108.08(14)
C(8)-C(7)-C(4)	119.94(16)
C(8)-C(7)-C(6)	131.30(16)
C(4)-C(7)-C(6)	108.74(15)
C(7)-C(8)-C(1)	117.14(16)
O(2)-C(10)-O(3)	124.51(17)

O(2)-C(10)-C(6)	126.52(17)
O(3)-C(10)-C(6)	108.93(15)
O(3)-C(11)-C(12)	106.01(14)
C(13)-C(12)-C(21)	119.56(17)
C(13)-C(12)-C(11)	119.75(17)
C(21)-C(12)-C(11)	120.67(16)
C(12)-C(13)-C(14)	121.32(18)
C(15)-C(14)-C(13)	119.98(19)
C(14)-C(15)-C(16)	120.87(18)
C(15)-C(16)-C(17)	121.44(18)
C(15)-C(16)-C(21)	119.26(18)
C(17)-C(16)-C(21)	119.28(18)
C(18)-C(17)-C(16)	120.86(19)
C(17)-C(18)-C(19)	120.10(19)
C(20)-C(19)-C(18)	120.39(19)
C(19)-C(20)-C(21)	121.12(18)
C(20)-C(21)-C(16)	118.25(17)
C(20)-C(21)-C(12)	122.79(17)
C(16)-C(21)-C(12)	118.95(16)
C(10)-O(3)-C(11)	116.79(14)
C(5)-N(1)-C(4)	111.92(15)

Symmetry transformations used to generate equivalent atoms:

Anisotropic displacement parameters (A^2 x 10^3) for **23**.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Br(1)	14(1)	16(1)	18(1)	2(1)	5(1)	-2(1)
C(1)	13(1)	16(1)	11(1)	3(1)	2(1)	-2(1)
C(2)	20(1)	13(1)	14(1)	1(1)	-1(1)	-4(1)
C(3)	19(1)	12(1)	13(1)	-2(1)	3(1)	0(1)
C(4)	14(1)	16(1)	10(1)	1(1)	1(1)	-1(1)
C(5)	12(1)	14(1)	9(1)	0(1)	0(1)	1(1)
C(6)	11(1)	12(1)	10(1)	0(1)	1(1)	-2(1)
C(7)	13(1)	11(1)	10(1)	0(1)	-2(1)	-2(1)
C(8)	12(1)	14(1)	12(1)	0(1)	-1(1)	1(1)
C(9)	14(1)	15(1)	14(1)	2(1)	-1(1)	1(1)
C(10)	13(1)	12(1)	12(1)	2(1)	-1(1)	1(1)
C(11)	21(1)	18(1)	12(1)	-5(1)	0(1)	-6(1)
C(12)	20(1)	17(1)	12(1)	-3(1)	-2(1)	-2(1)
C(13)	28(1)	17(1)	14(1)	-3(1)	-3(1)	0(1)
C(14)	25(1)	26(1)	16(1)	-7(1)	-3(1)	7(1)
C(15)	20(1)	31(1)	11(1)	-4(1)	-1(1)	5(1)
C(16)	16(1)	25(1)	10(1)	-2(1)	-2(1)	1(1)
C(17)	19(1)	30(1)	14(1)	1(1)	0(1)	-5(1)
C(18)	30(1)	23(1)	15(1)	3(1)	-1(1)	-6(1)
C(19)	28(1)	16(1)	20(1)	-1(1)	-2(1)	0(1)

C(20)	18(1)	20(1)	16(1)	-2(1)	1(1)	1(1)
C(21)	16(1)	18(1)	11(1)	-2(1)	-1(1)	0(1)
O(1)	15(1)	17(1)	14(1)	1(1)	4(1)	-2(1)
O(2)	14(1)	24(1)	22(1)	-7(1)	2(1)	-4(1)
O(3)	18(1)	22(1)	13(1)	-7(1)	3(1)	-7(1)
N(1)	15(1)	13(1)	12(1)	-1(1)	4(1)	0(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **23**.

	x	y	z	U(eq)
H(2A)	1880	9991	1595	19
H(3A)	-1436	9815	1985	18
H(8A)	1800	5065	1461	15
H(9A)	703	2819	2027	21
H(9B)	-1462	2509	2296	21
H(9C)	336	3983	2366	21
H(11A)	-4032	2601	1006	20
H(11B)	-2885	1008	1188	20
H(13A)	268	-212	893	24
H(14A)	3479	-219	489	27
H(15A)	4582	2153	201	25
H(17A)	3872	5068	65	25
H(18A)	1640	7405	138	27
H(19A)	-1670	7410	524	26
H(20A)	-2675	5097	841	21
H(1A)	-4150(40)	7600(30)	2324(6)	19(6)

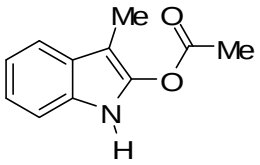
Hydrogen bonds for **e13A** [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1A)...O(1)#1	0.83(2)	1.98(2)	2.7716(19)	160(2)

Symmetry transformations used to generate equivalent atoms:
#1 -x-1,y+1/2,-z+1/2

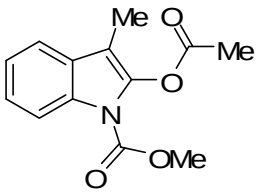
APPENDIX B:

NMR Spectra


Me
O
Me
O
N
H

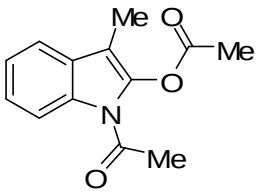
9
8
7
6
5
4
3
2
1
ppm

Me
O
Me
O
N
H
168.565
139.587
131.281
127.178
121.655
119.817
118.484
110.748
95.717
77.317
77.002
76.679
20.913
7.003
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
Me
O
N
O
OMe

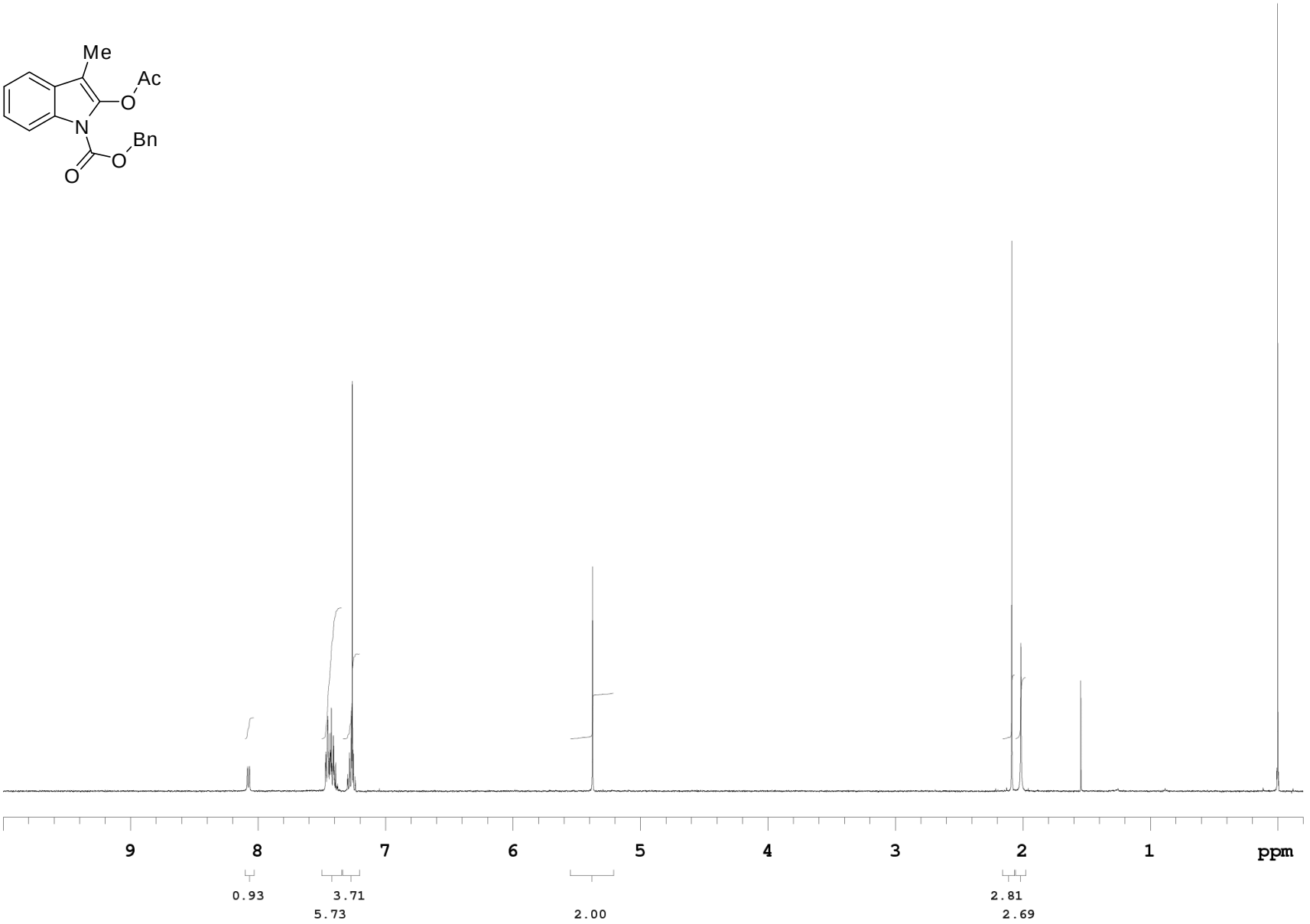
9
8
7
6
5
4
3
2
1
ppm

Me
O
Me
O
N
O
OMe
168.908
150.785
137.454
132.055
128.231
124.305
123.140
118.606
115.303
105.223
77.337
77.022
76.707
53.603
20.391
6.913
220
200
180
160
140
120
100
80
60
40
20
0
ppm

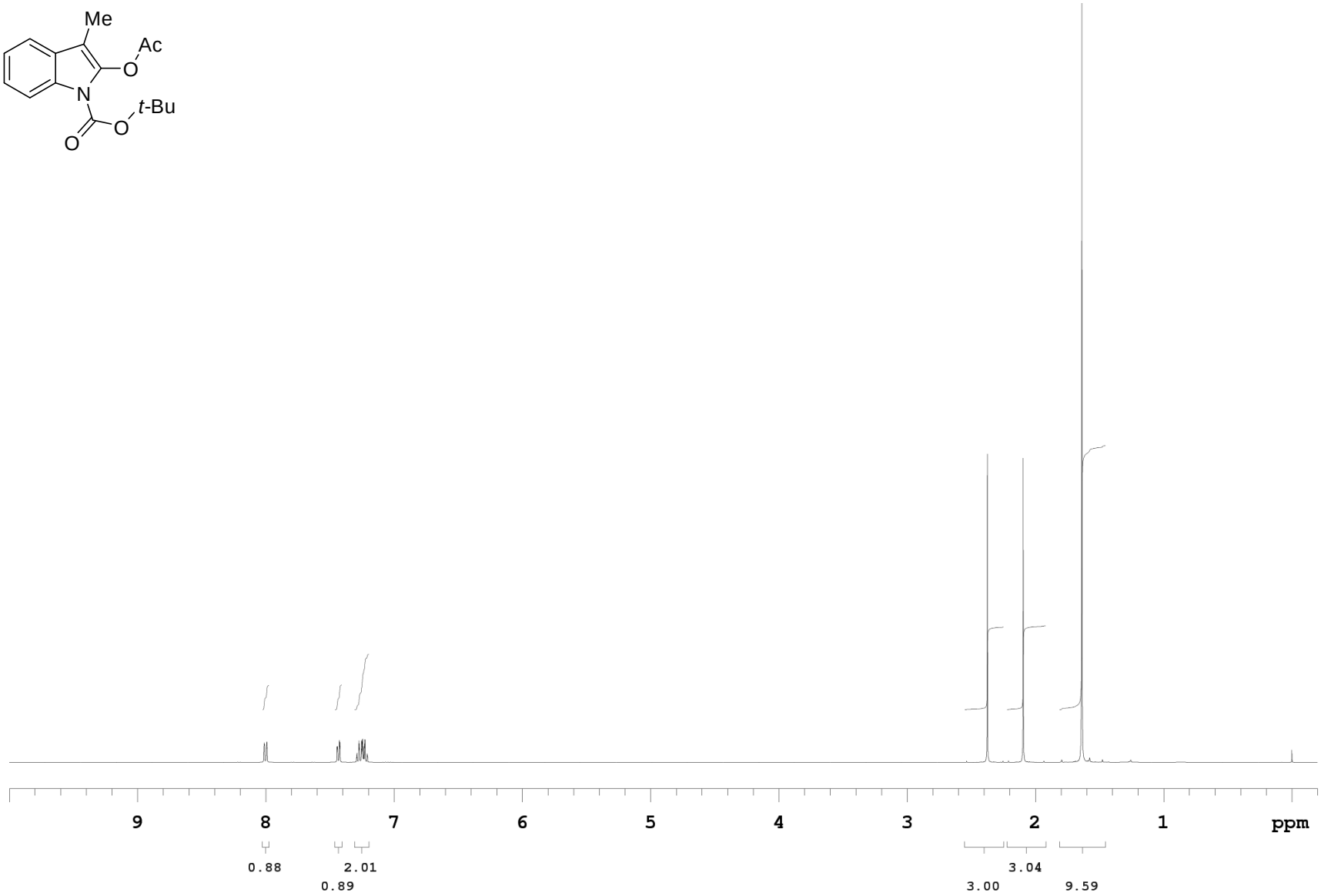

Me
O
Me
O
N
O
Me

9
8
7
6
5
4
3
2
1
ppm

Me
O
Me
O
N
O
Me
167.885
167.724
136.958
132.563
128.300
124.872
123.627
118.419
116.162
105.490
77.332
77.010
76.695
25.939
20.658
7.355
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
Ac
O
N
Bn
O
O
9
8
7
6
5
4
3
2
1
ppm
0.93
3.71
5.73
2.00
2.81
2.69

Me
Ac
O
N
Bn
O
O
168.794
150.142
137.287
134.666
132.363
128.907
128.876
128.815
128.273
124.401
123.164
118.549
115.403
105.230
77.349
77.032
76.715
68.907
19.961
6.936
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
Ac
O
N
t-Bu
O
O
9
8
7
6
5
4
3
2
1
ppm
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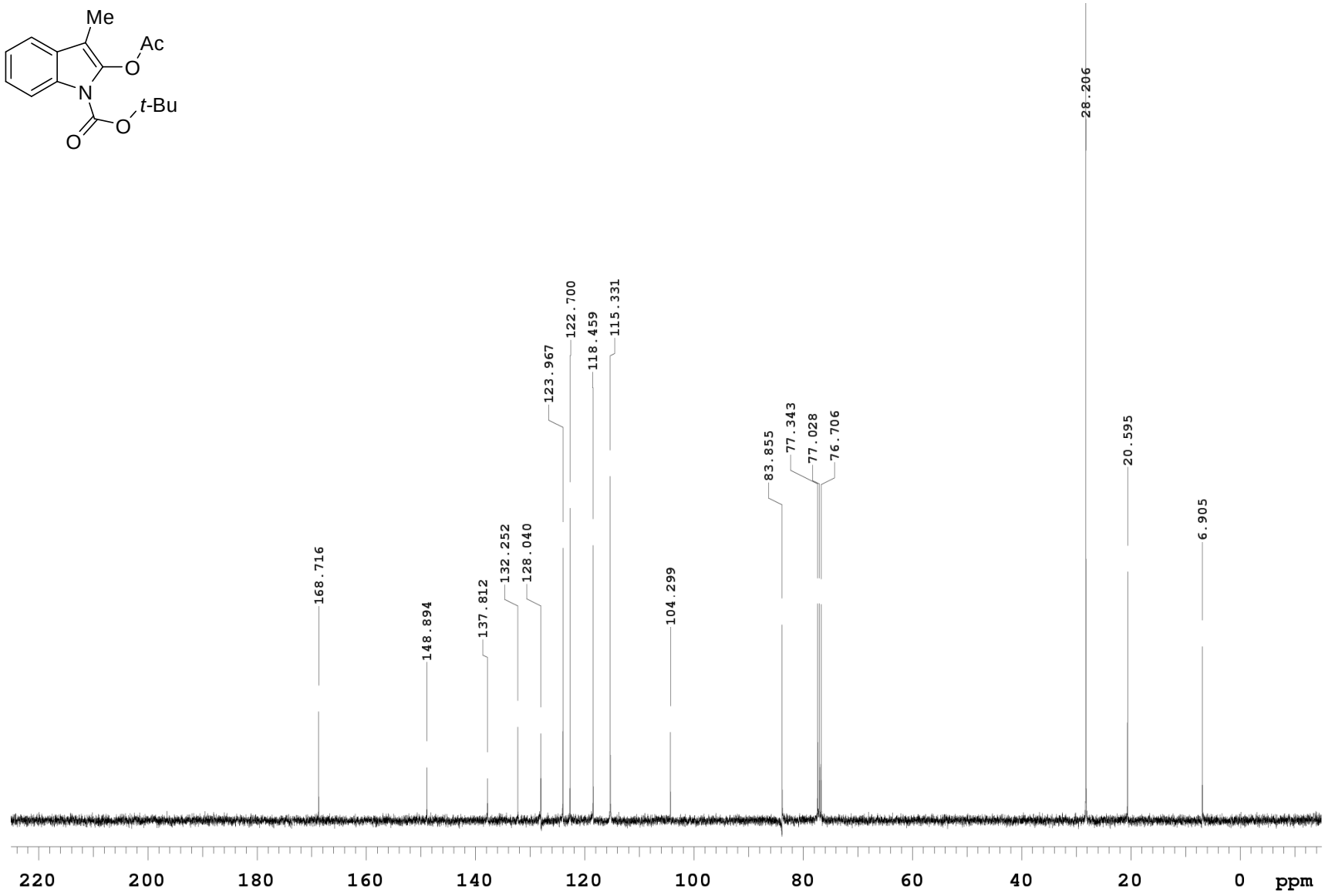
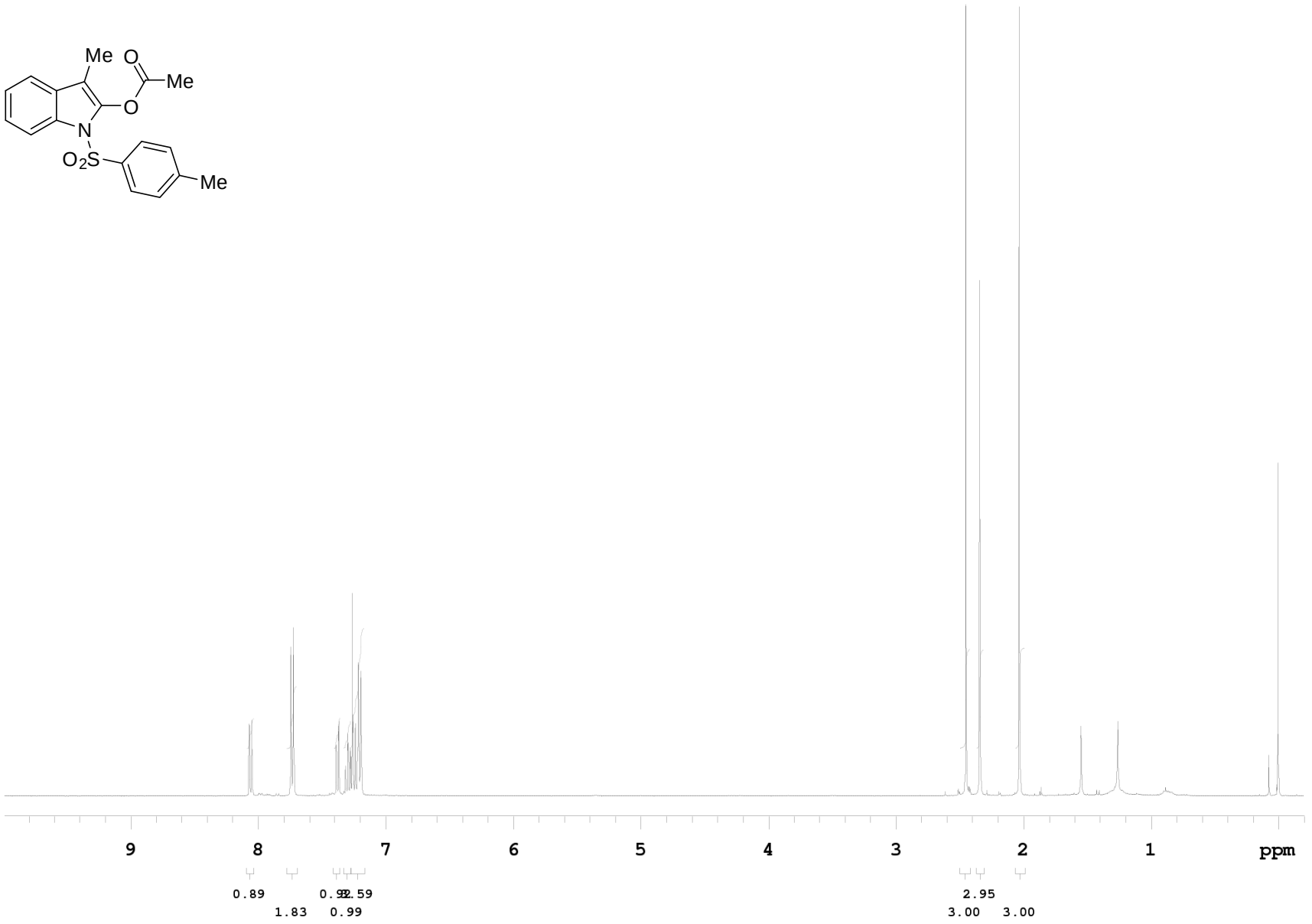
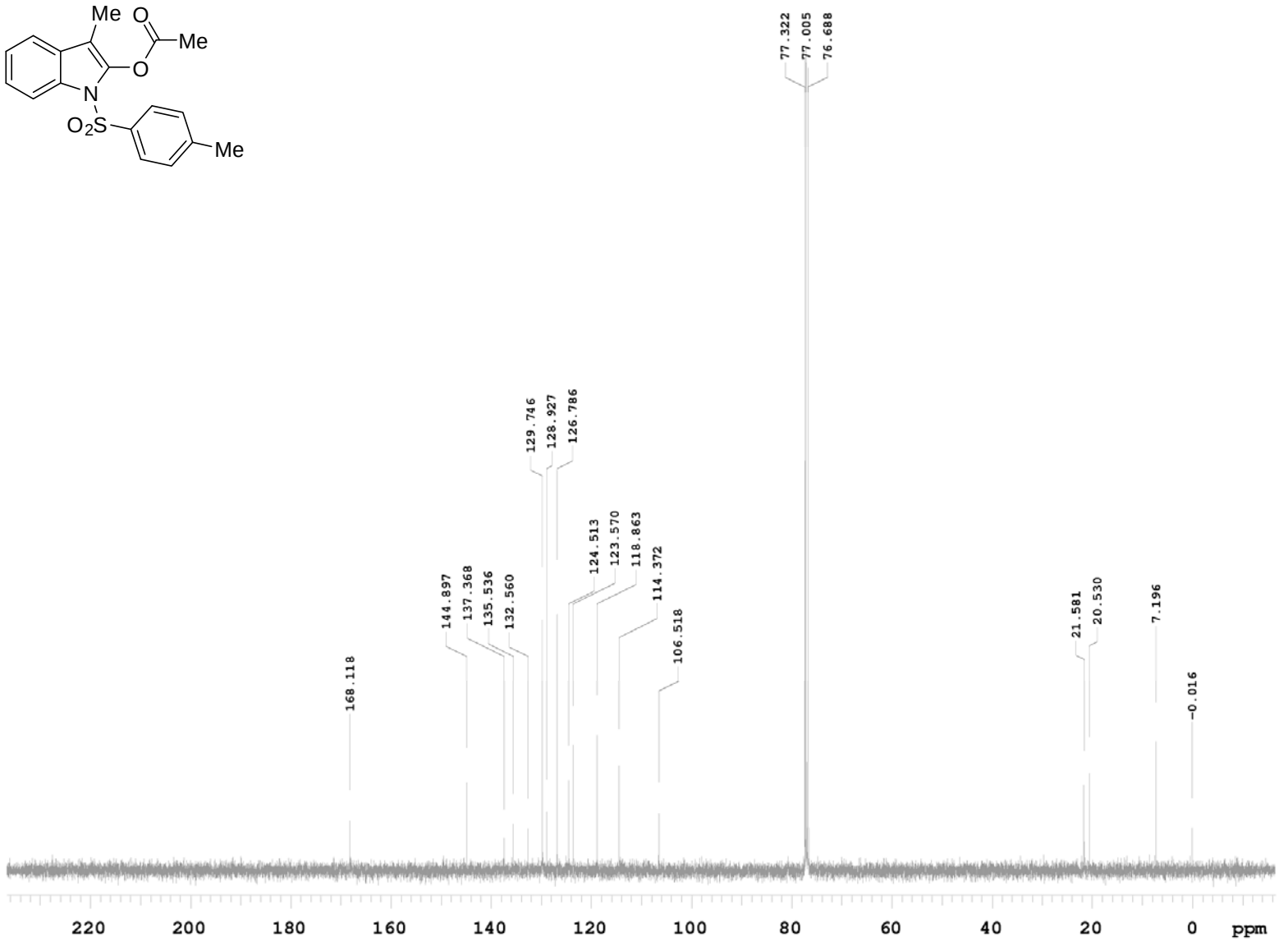
0.89
2.01
3.00
3.04
9.59


Me
Ac
O
N
t-Bu
O
O
168.716
148.894
137.812
132.252
128.040
123.967
122.700
118.459
115.331
104.299
83.855
77.343
77.028
76.706
28.206
20.595
6.905
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
Me
O
N
O2S
Me
9
8
7
6
5
4
3
2
1
ppm
0.89
1.83
0.99
2.59
2.95
3.00
3.00


Me
O
Me
O
N
O2S
Me
77.322
77.005
76.688
129.746
128.927
126.786
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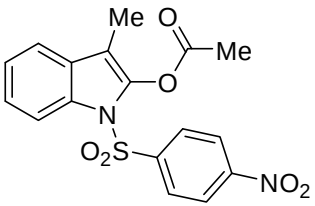
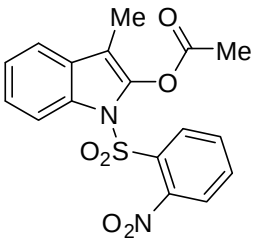
123.570
118.863
114.372
106.518
144.897
137.368
135.536
132.560
168.118
21.581
20.530
7.196
0.016
220
200
180
160
140
120
100
80
60
40
20
0
ppm

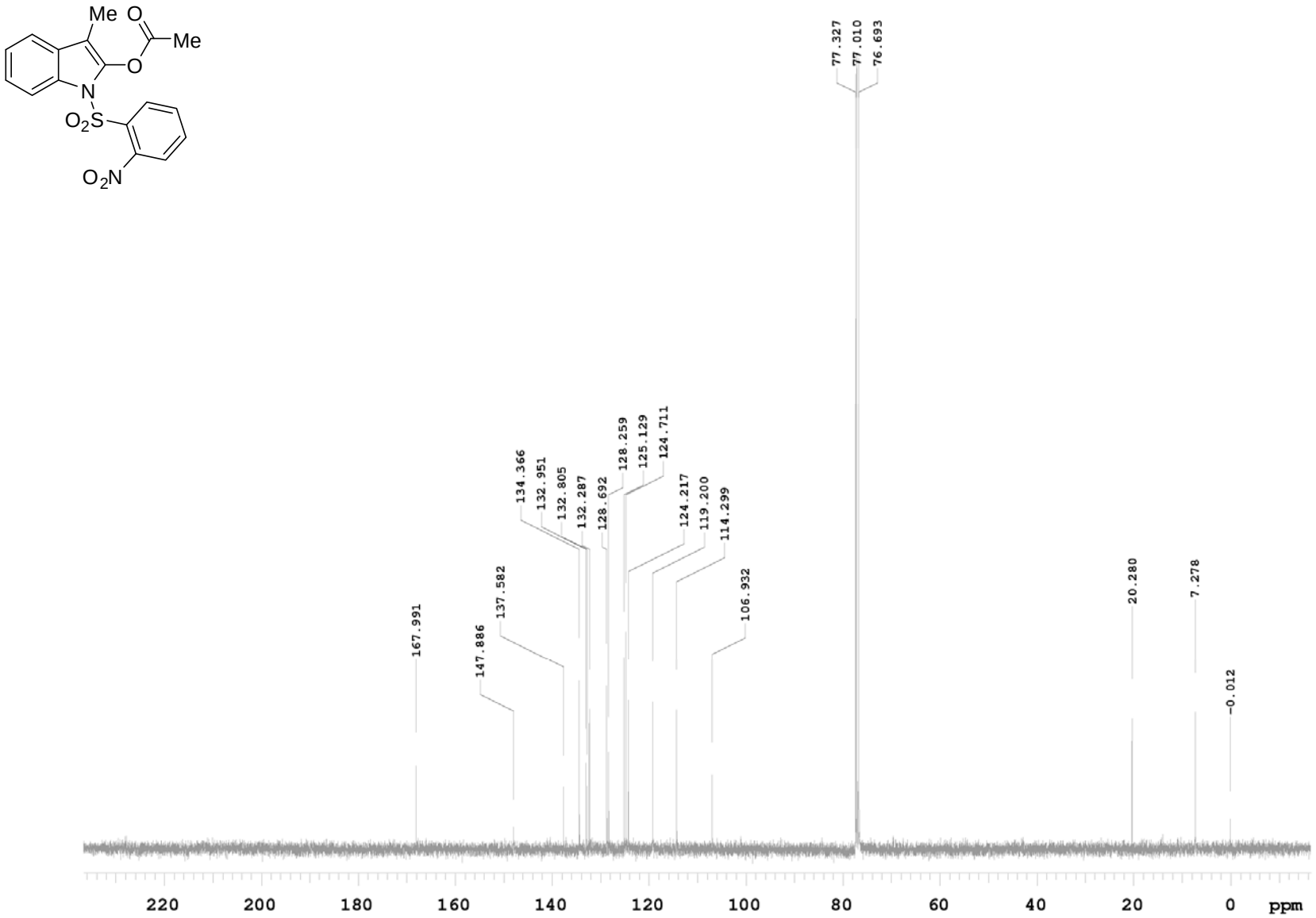

Me
O
Me
O
N
O2S
NO2

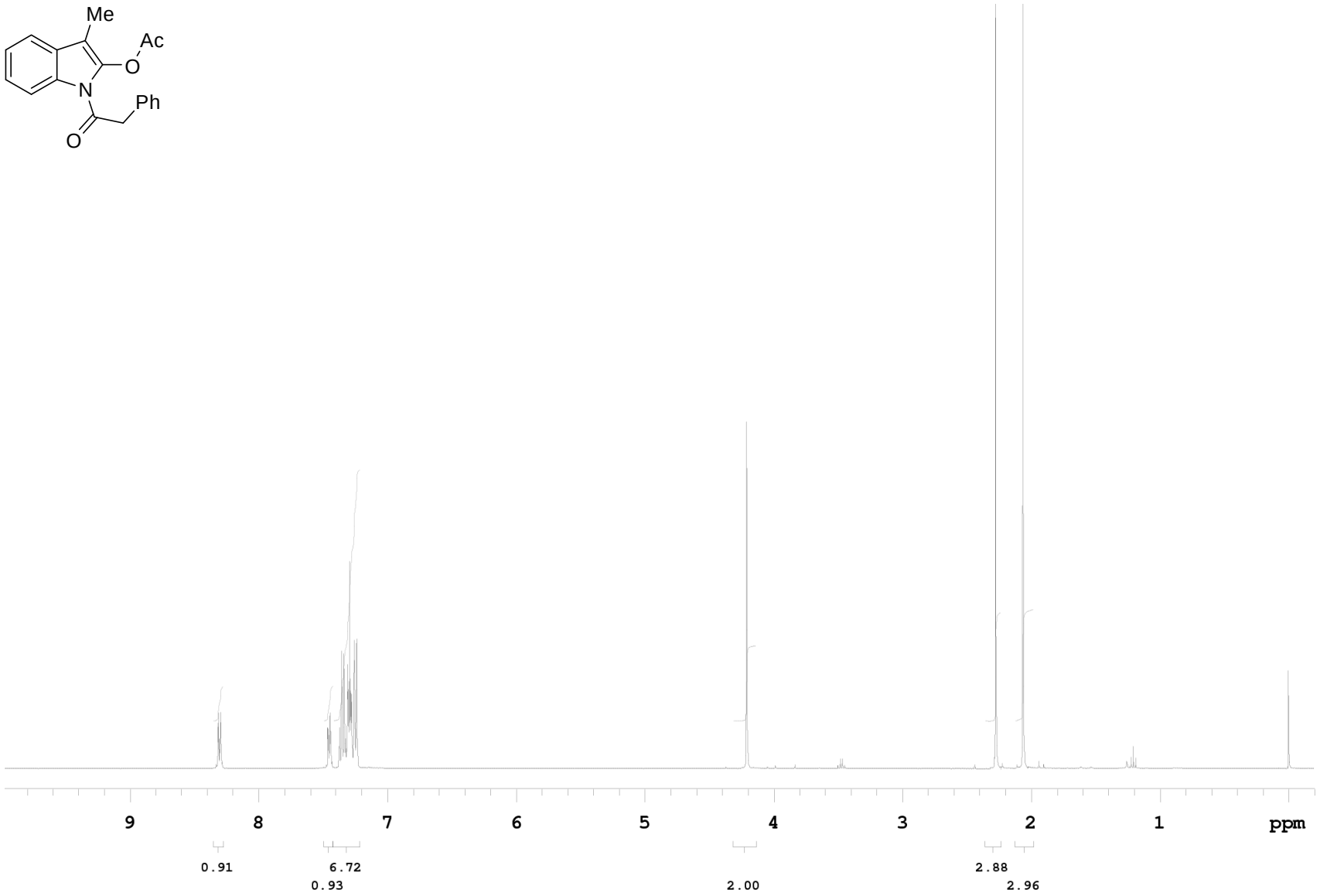
9
8
7
6
5
4
3
2
1
ppm

Me
O
Me
O
N
O2S
NO2
168.041
150.622
143.311
137.070
132.368
129.188
128.126
125.160
124.456
124.391
119.344
114.297
108.114
77.327
77.004
76.689
20.484
7.262
220
200
180
160
140
120
100
80
60
40
20
0
ppm

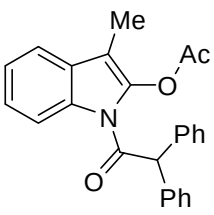

Me
O
Me
O
N
O2S
O2N

9
8
7
6
5
4
3
2
1
ppm
1.00
0.99
0.96
0.96
1.92
2.01
3.00
3.13


Me
O
Me
O
N
O2S
O2N
77.327
77.010
76.693
134.366
132.951
132.805
132.287
128.692
128.259
125.129
124.711
124.217
119.200
114.299
106.932
167.991
147.886
137.582
20.280
7.278
-0.012
220
200
180
160
140
120
100
80
60
40
20
0
ppm

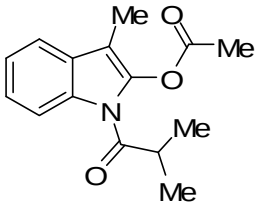

Me
Ac
O
N
Ph
O
9
8
7
6
5
4
3
2
1
ppm
0.91
6.72
0.93
2.00
2.88
2.96

Me
Ac
O
N
Ph
O
129.291
128.727
77.330
77.013
76.696
128.410
127.258
124.993
123.741
118.438
116.328
44.053
20.546
7.521
133.566
132.770
105.846
169.039
167.462
136.843
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
Ac
O
N
Ph
O
Ph

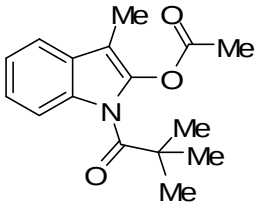
9
8
7
6
5
4
3
2
1
ppm

Me
Ac
O
N
Ph
O
Ph
170.512
166.989
139.271
136.692
133.088
129.155
128.715
128.437
127.426
125.038
123.822
118.431
116.336
106.169
77.330
77.007
76.692
58.548
20.077
7.661
0.001
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
Me
O
N
Me
O
Me

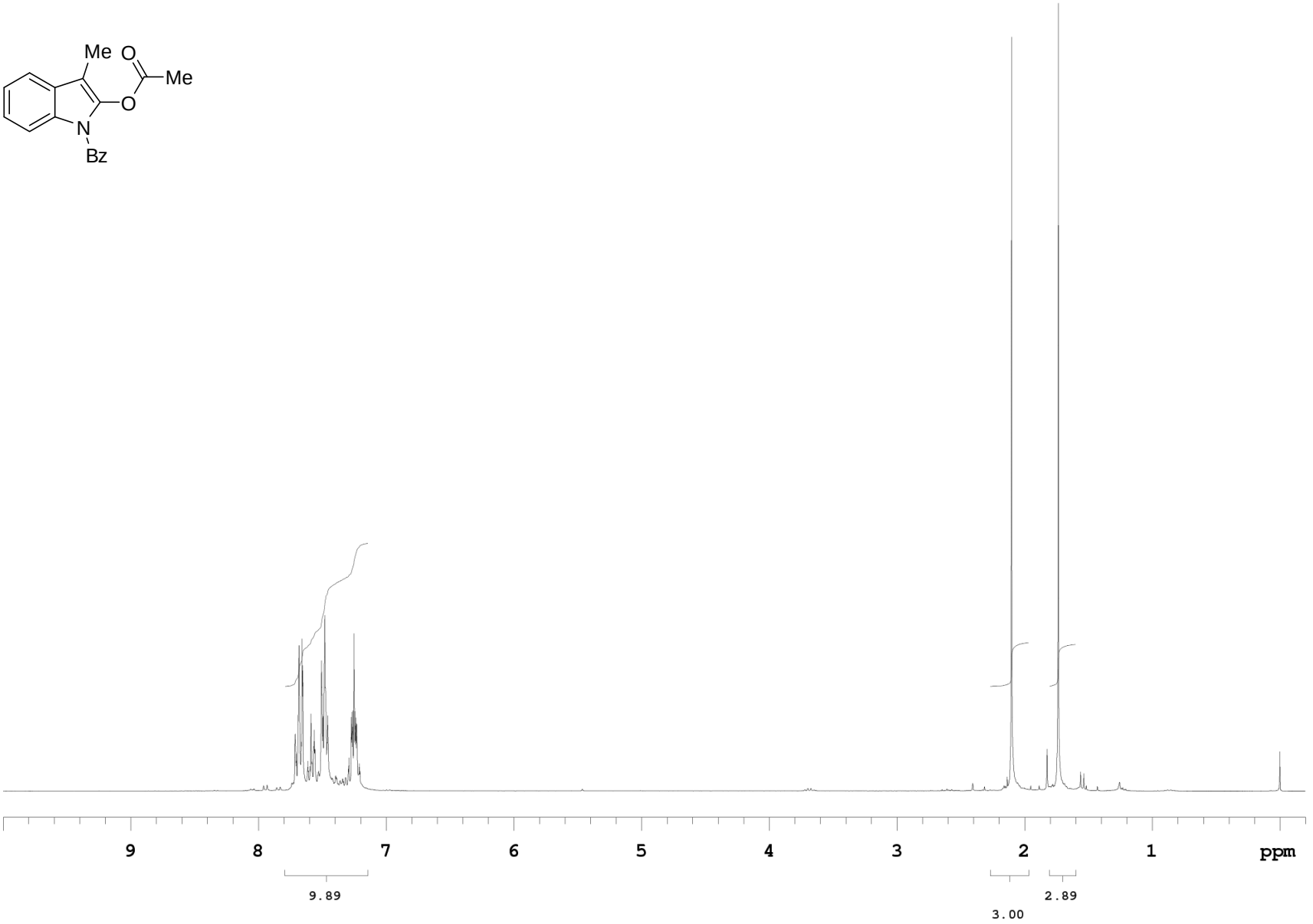
9
8
7
6
5
4
3
2
1
ppm

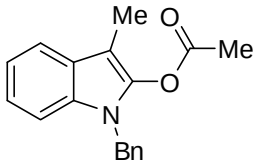
Me
O
Me
O
N
Me
O
Me
176.042
167.479
137.029
132.707
128.363
124.723
123.367
118.423
115.954
105.421
77.337
77.014
76.699
35.261
20.604
19.498
7.514
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
Me
O
N
Me
Me
O
Me

9
8
7
6
5
4
3
2
1
ppm

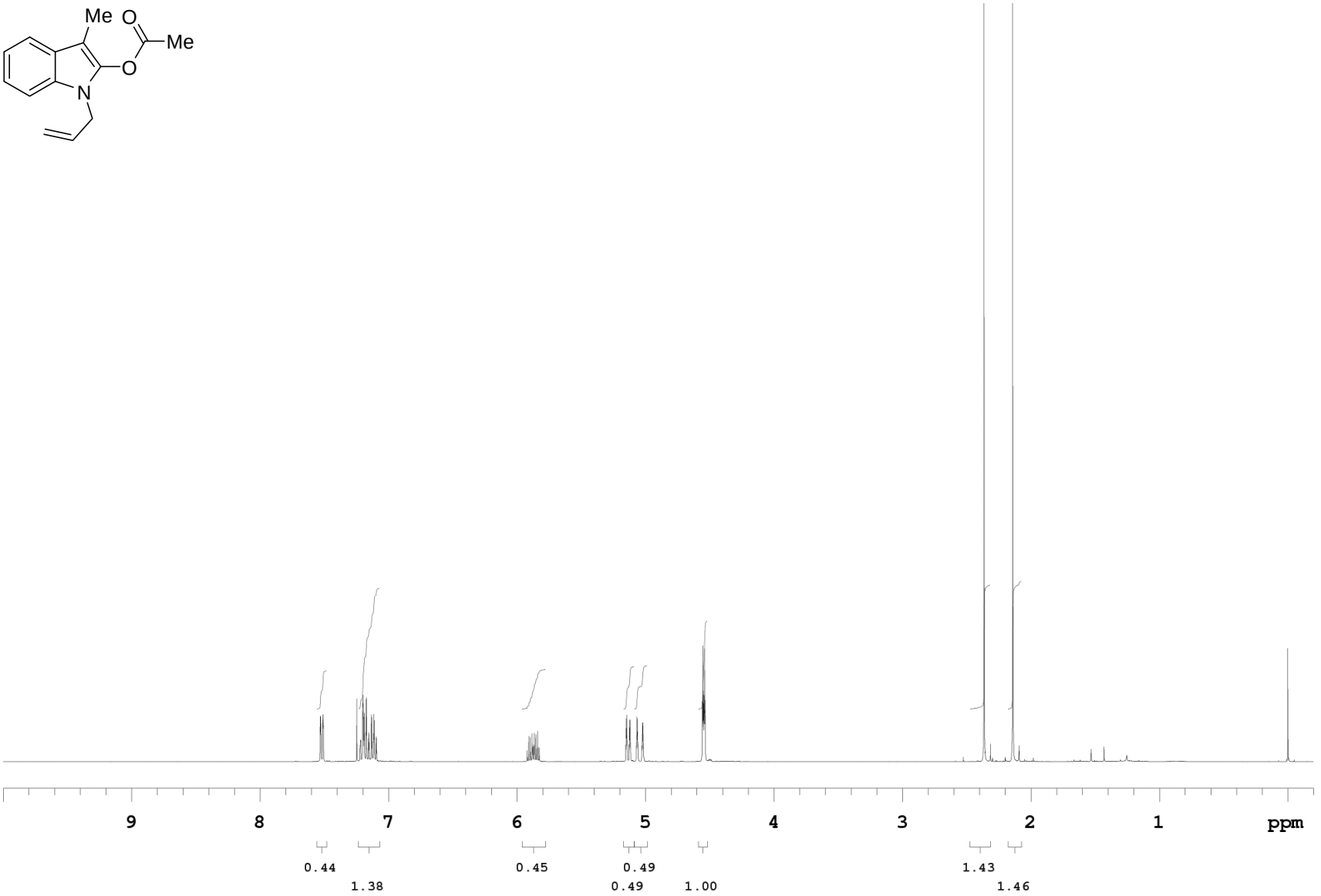
Me
O
Me
O
N
Me
Me
O
Me
181.205
167.185
136.983
132.537
127.790
123.578
121.945
118.612
113.279
102.804
77.328
77.005
76.690
43.295
27.825
20.734
7.673
220
200
180
160
140
120
100
80
60
40
20
0
ppm

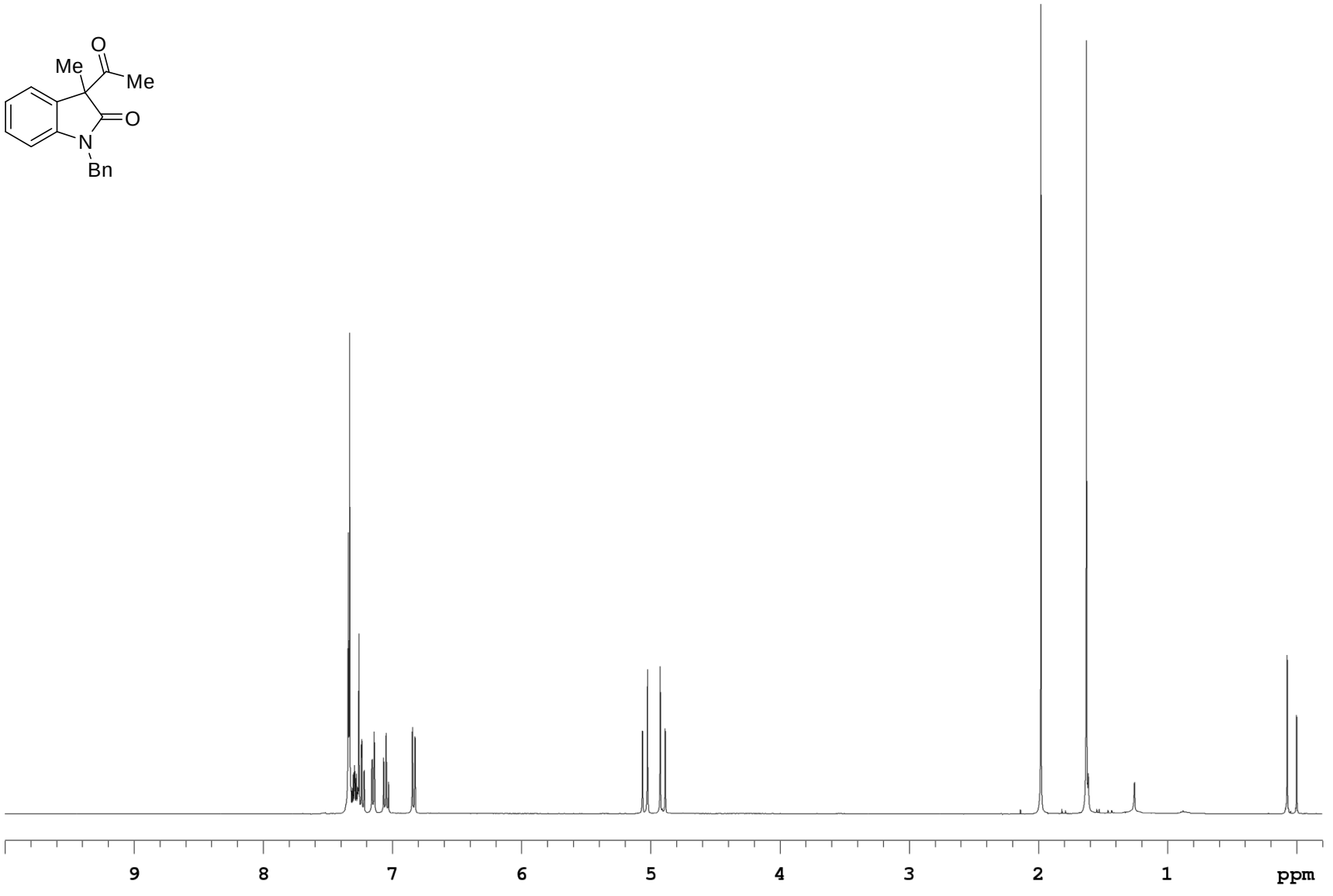

Me
O
Me
O
N
Bz
9
8
7
6
5
4
3
2
1
ppm
9.89
3.00
2.89


Me
O
Me
O
N
Bn

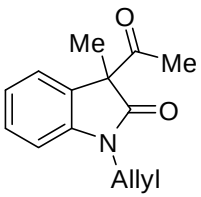
9
8
7
6
5
4
3
2
1
ppm

Me
O
Me
O
N
Bn
128.695
127.450
126.849
126.505
121.502
119.553
118.718
109.320
77.331
77.009
76.694
167.789
138.899
137.287
132.416
97.226
45.870
20.232
7.560
220
200
180
160
140
120
100
80
60
40
20
0
ppm

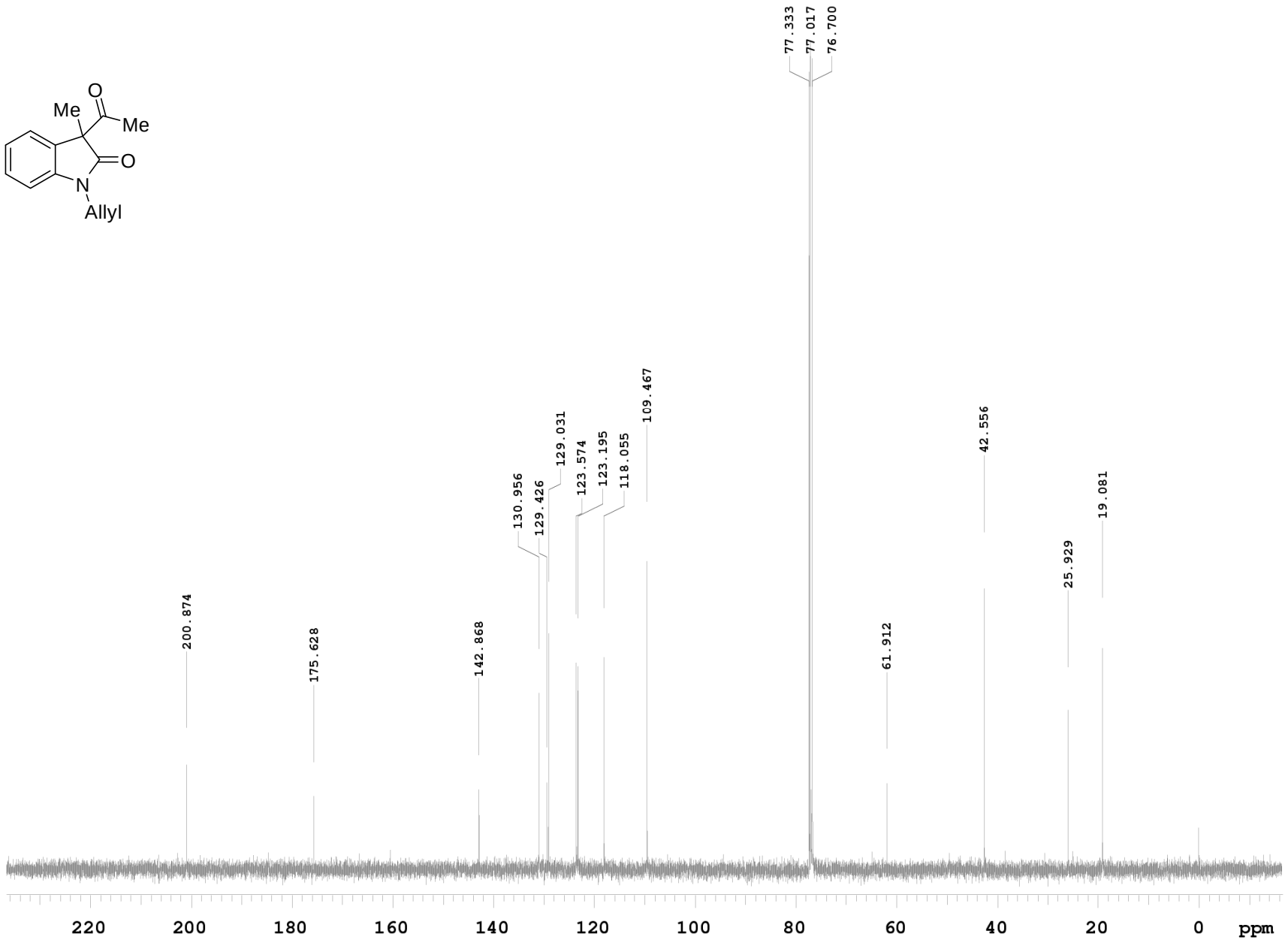

Me
O
Me
O
N
9
8
7
6
5
4
3
2
1
ppm
0.44
1.38
0.45
0.49
0.49
1.00
1.43
1.46

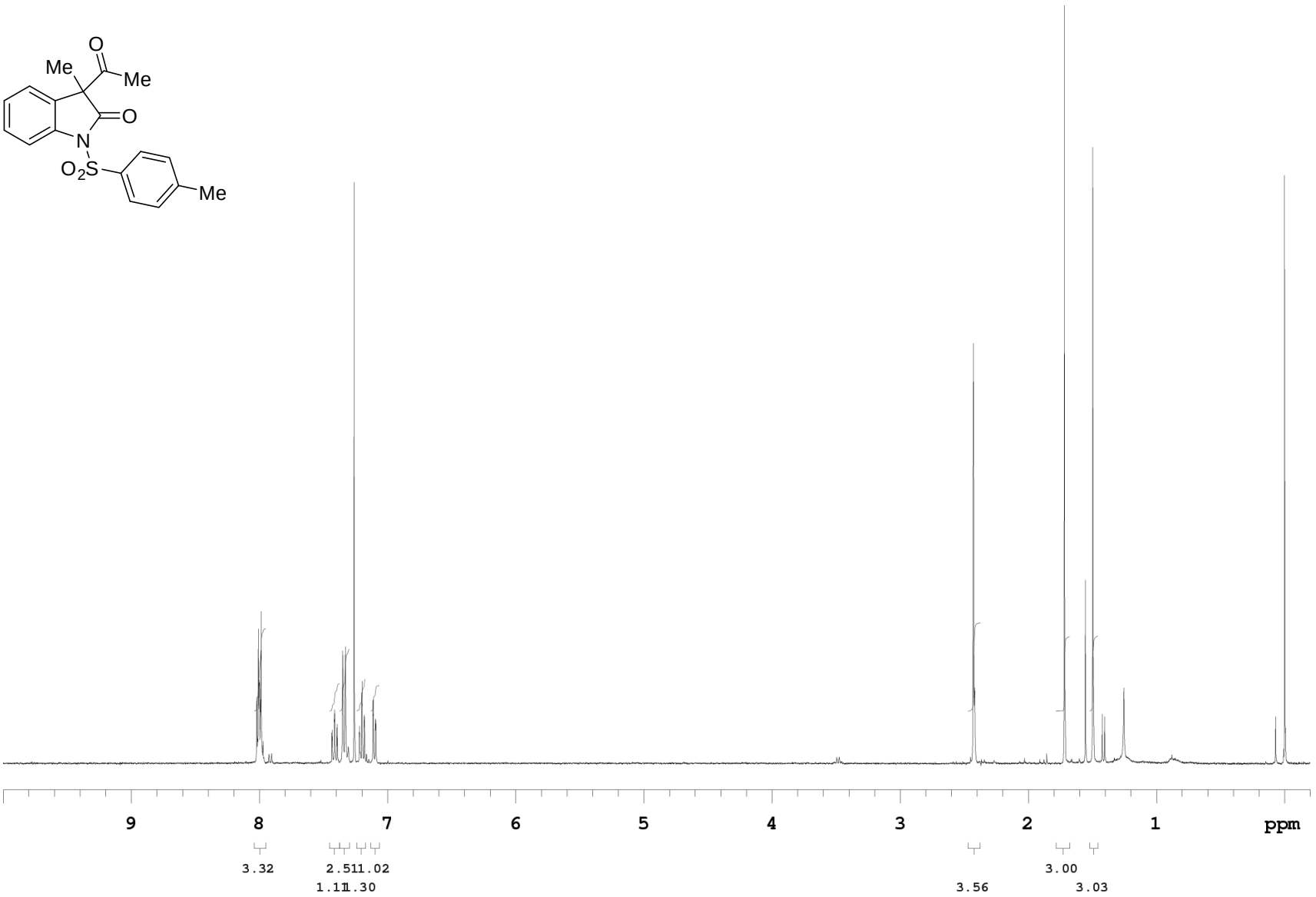

O
Me
Me
O
N
Bn
9
8
7
6
5
4
3
2
1
ppm

Me
O
Me
O
N
Bn
200.888
176.004
142.836
135.570
129.446
129.043
128.911
127.886
127.431
123.564
123.241
109.587
77.335
77.020
76.705
61.945
44.101
26.103
19.188
220
200
180
160
140
120
100
80
60
40
20
0
ppm

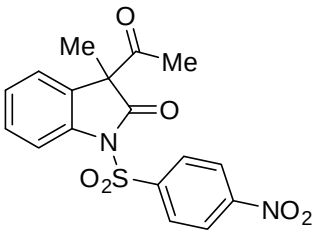

O
Me
Me
O
N
Allyl

9
8
7
6
5
4
3
2
1
ppm
1.13
1.27
1.07
1.01
1.06
2.22
1.10
1.29
3.00
3.49


Me
O
Me
O
N
Allyl
77.333
77.017
76.700
200.874
175.628
142.868
130.956
129.426
129.031
123.574
123.195
118.055
109.467
61.912
42.556
25.929
19.081
220
200
180
160
140
120
100
80
60
40
20
0
ppm

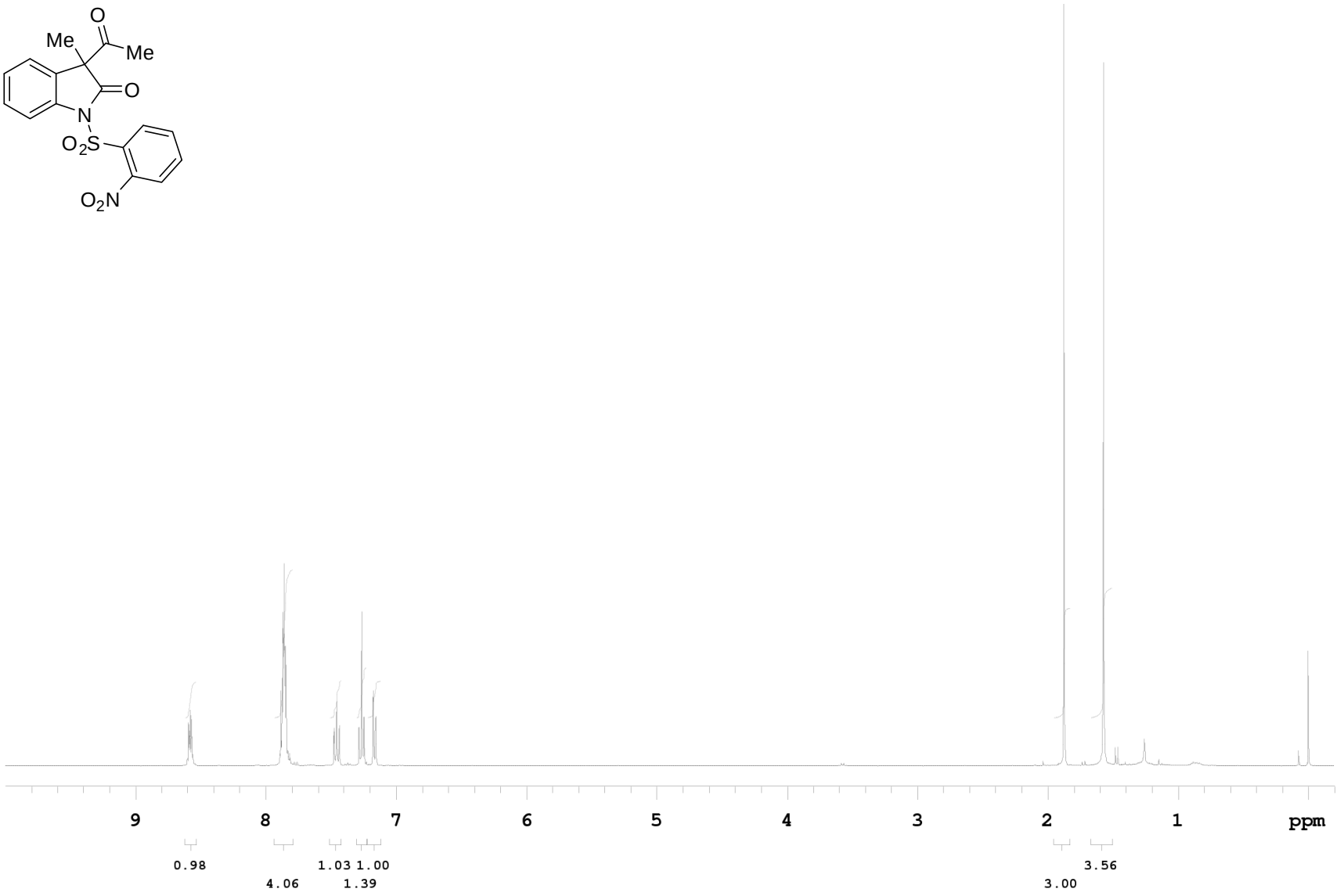

O
Me
Me
O
N
O2S
Me
9
8
7
6
5
4
3
2
1
ppm
3.32
2.51
1.11
1.02
1.30
3.56
3.00
3.03

Me
O
Me
O
N
O2S
Me
77.322
77.205
77.000
76.685
129.851
129.814
128.276
127.968
127.910
125.500
123.749
114.226
146.068
139.102
134.707
198.787
174.138
62.115
25.871
21.747
19.520
-0.016
220
200
180
160
140
120
100
80
60
40
20
0
ppm

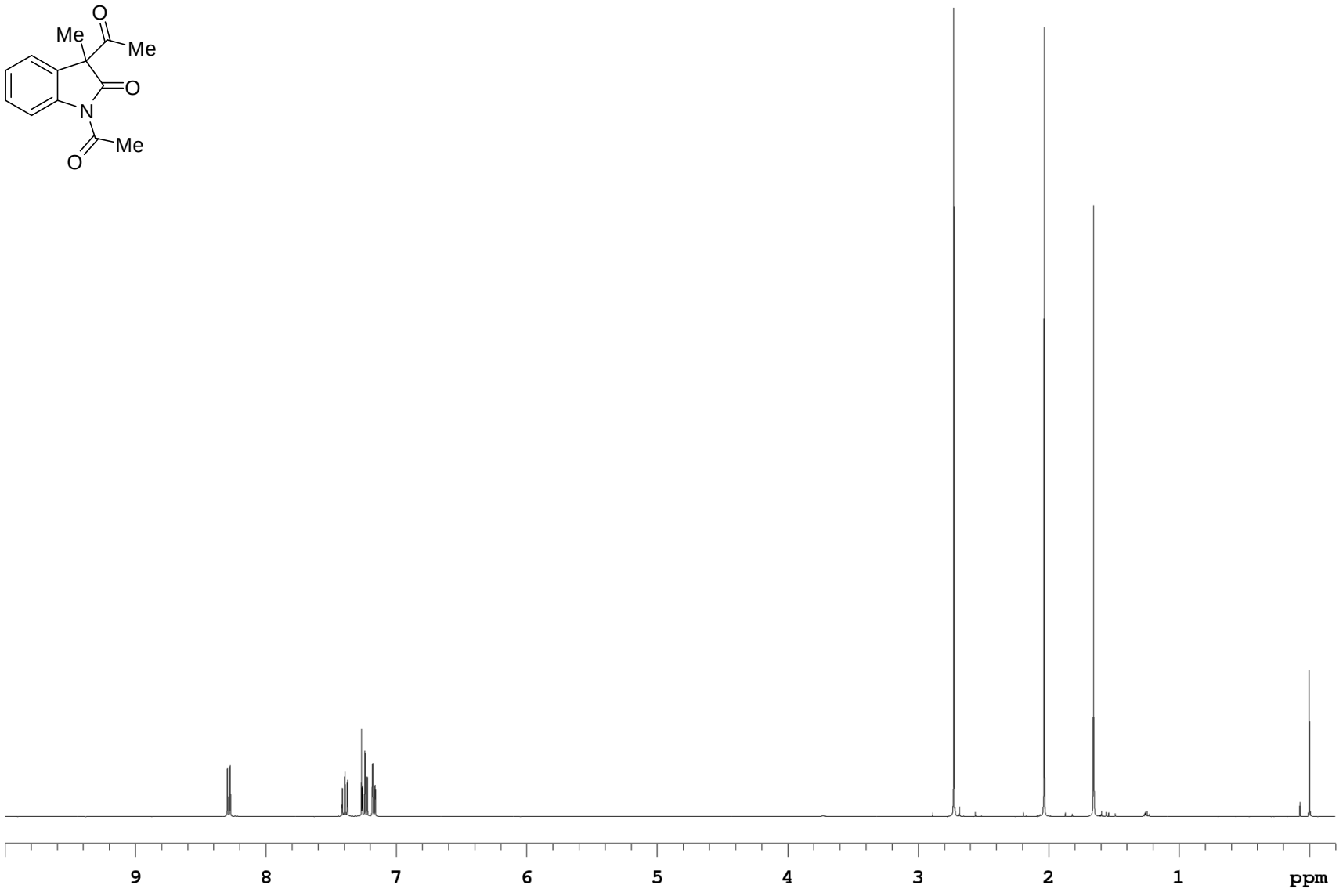

O
Me
Me
O
N
O2S
NO2

9
8
7
6
5
4
3
2
1
ppm

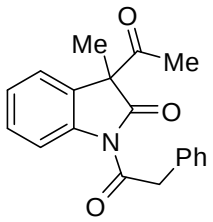
Me
O
Me
O
N
O2S
NO2
198.297
174.198
151.204
142.832
138.356
130.057
129.500
128.247
126.123
124.446
124.109
114.037
77.323
77.001
76.686
62.080
25.982
19.726
0.015
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
Me
Me
O
N
O2S
O2N
9
8
7
6
5
4
3
2
1
ppm
0.98
4.06
1.03
1.39
1.00
3.00
3.56

Me
O
Me
O
N
O2S
O2N
77.327
77.010
76.693
135.726
134.892
132.271
130.872
129.921
127.749
125.739
124.765
123.482
115.087
198.525
174.307
147.971
139.329
62.037
26.054
19.429
220
200
180
160
140
120
100
80
60
40
20
0
ppm

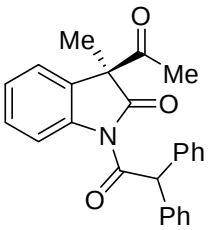

Me
O
Me
O
N
O
Me
9
8
7
6
5
4
3
2
1
ppm

Me
O
Me
O
N
O
Me
199.445
176.620
170.701
140.024
129.520
128.487
125.828
123.081
117.030
77.336
77.021
76.698
62.590
26.690
26.082
20.017
220
200
180
160
140
120
100
80
60
40
20
0
ppm

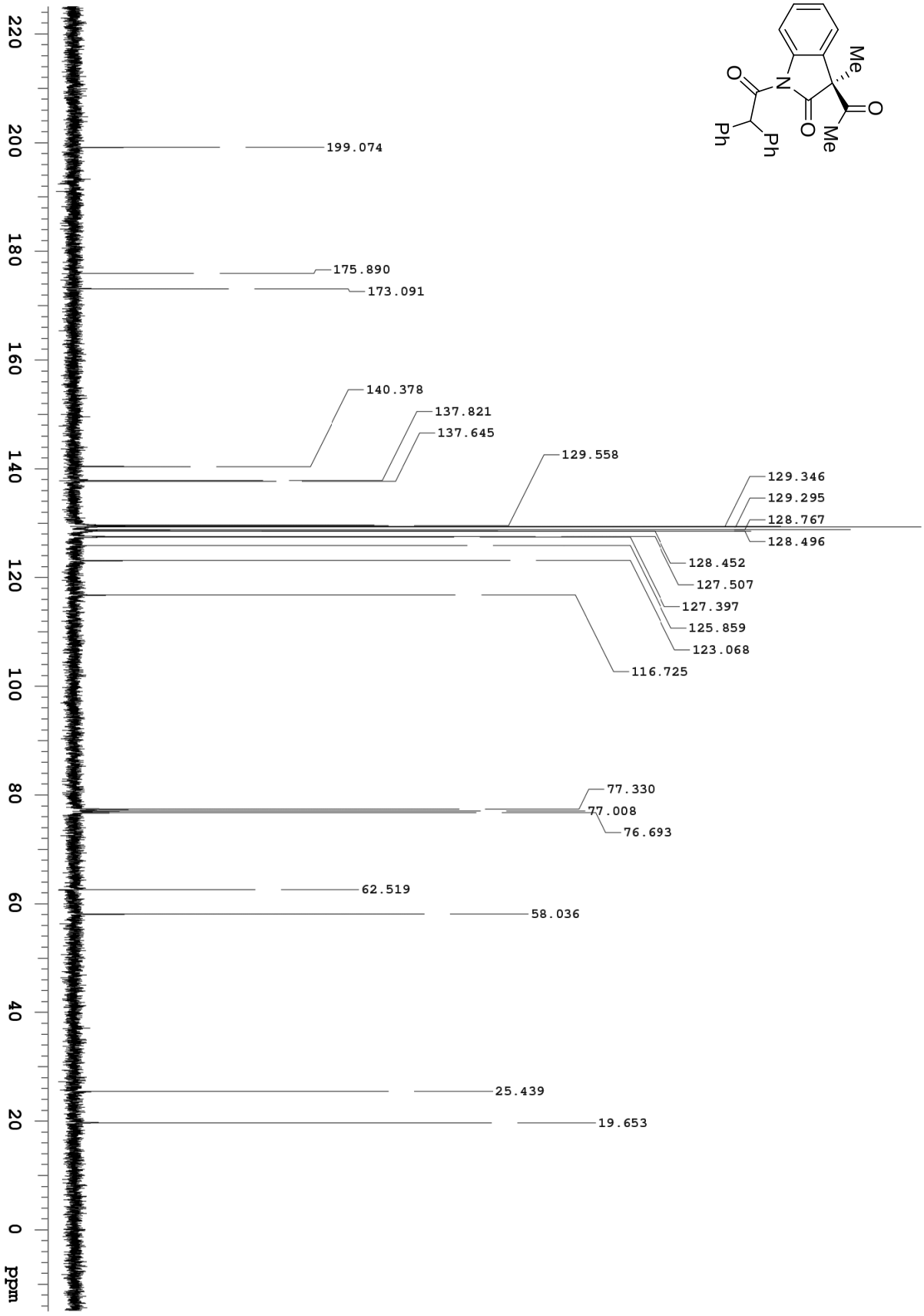

O
Me
Me
O
N
Ph
O

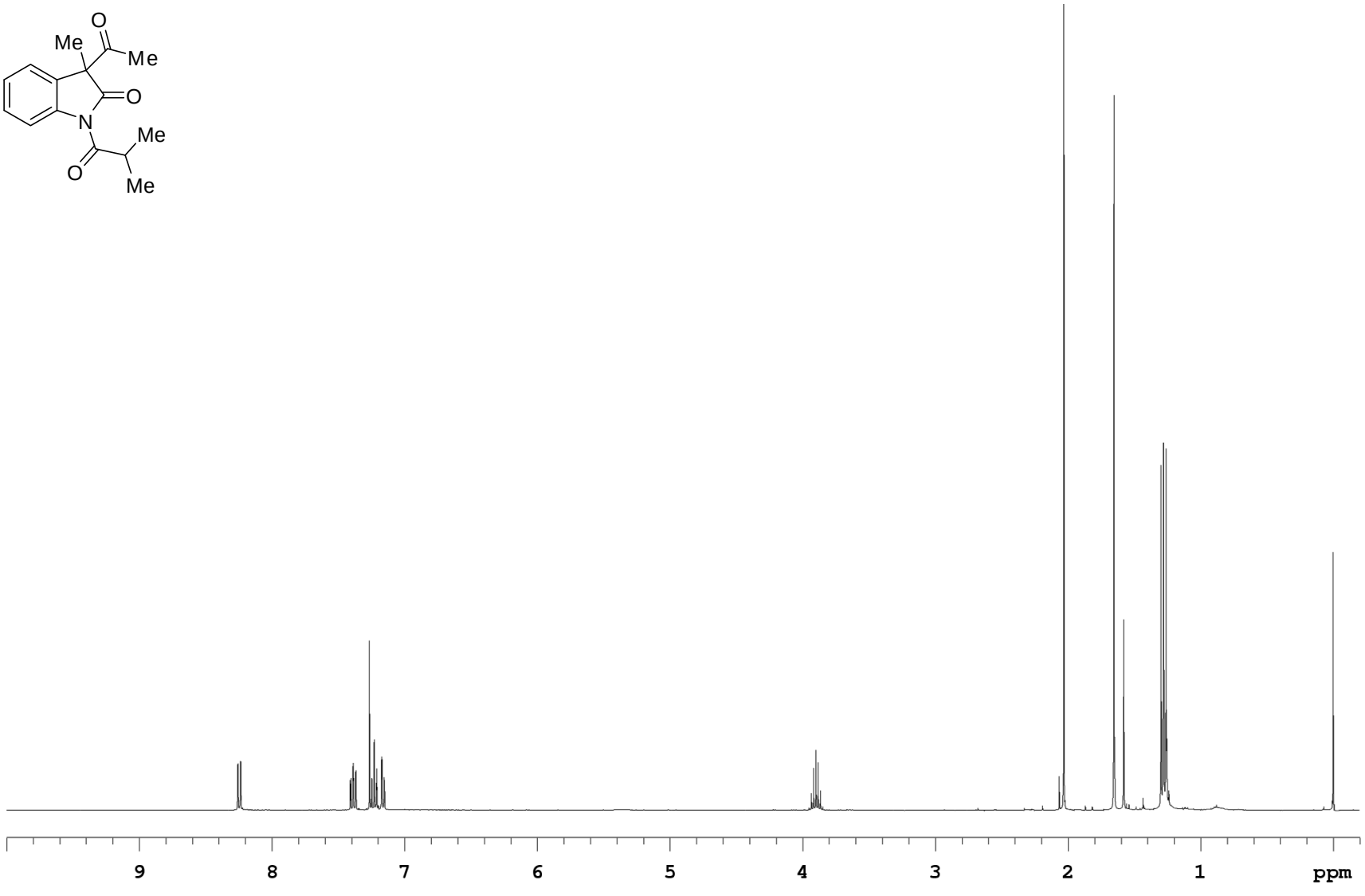
9
8
7
6
5
4
3
2
1
ppm

Me
O
Me
O
N
Ph
O
77.327
77.003
76.686
128.608
129.605
129.520
128.523
127.294
125.848
123.058
116.897
140.164
133.370
199.275
176.263
171.780
62.555
44.607
25.838
19.855
220
200
180
160
140
120
100
80
60
40
20
0
ppm

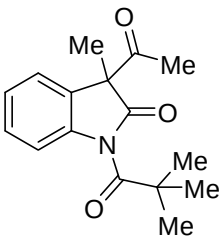

O
Me
Me
O
N
Ph
O
Ph

9
8
7
6
5
4
3
2
1
ppm


199.074
175.890
173.091
140.378
137.821
137.645
129.558
129.346
129.295
128.767
128.496
128.452
127.507
127.397
125.859
123.068
116.725
77.330
77.008
76.693
62.519
58.036
25.439
19.653
220
200
180
160
140
120
100
80
60
40
20
0
ppm
Me
O
N
O
O
Me
O
Ph
Ph

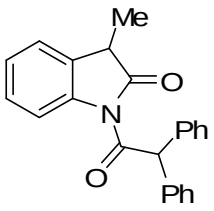

O
Me
Me
O
N
Me
O
Me
9
8
7
6
5
4
3
2
1
ppm

O
Me
Me
O
N
Me
O
Me
77.325
77.010
76.688
129.487
128.608
125.656
123.041
117.085
199.559
178.389
176.162
140.540
62.792
35.257
26.086
20.028
18.914
18.768
220
200
180
160
140
120
100
80
60
40
20
0
ppm

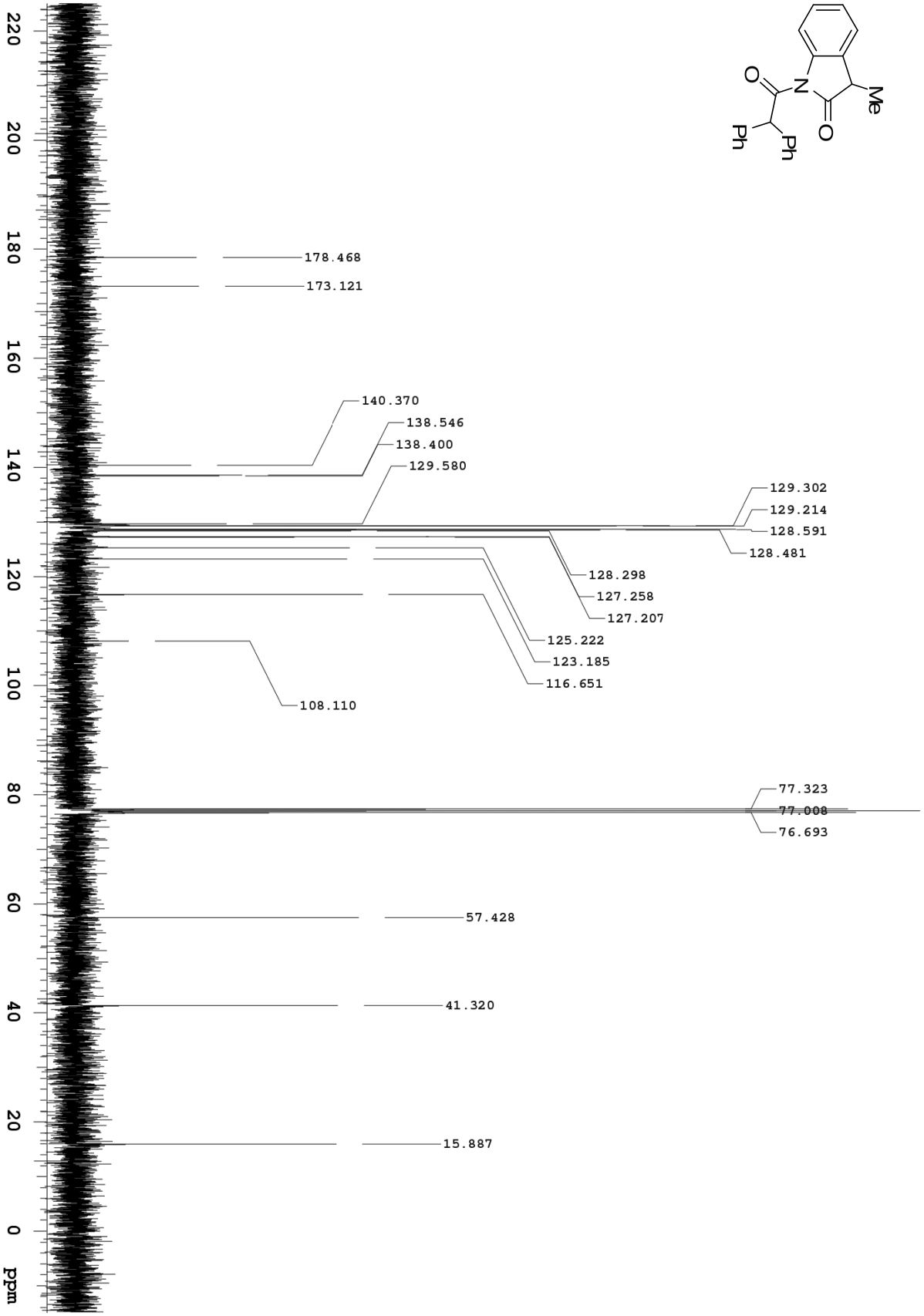

O
Me
Me
O
N
Me
Me
O
Me

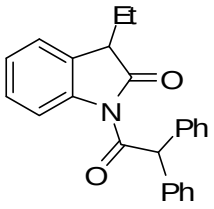
9
8
7
6
5
4
3
2
1
ppm

O
Me
Me
O
N
Me
Me
O
Me
199.830
182.315
175.115
140.987
129.348
129.260
124.938
123.429
114.595
77.325
77.010
76.688
62.550
43.578
26.730
26.203
19.764
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
N
Ph
O
Ph

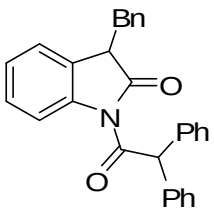
9
8
7
6
5
4
3
2
1
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm
178.468
173.121
140.370
138.546
138.400
129.580
129.302
129.214
128.591
128.481
128.298
127.258
127.207
125.222
123.185
116.651
108.110
77.323
77.008
76.693
57.428
41.320
15.887
O
N
O
Me
Ph
Ph


Et
O
N
Ph
O
Ph

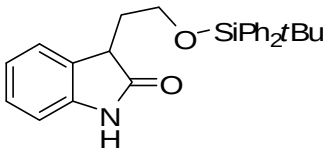
9
8
7
6
5
4
3
2
1
ppm

Et
O
N
Ph
O
Ph
177.788
173.107
141.075
138.445
138.372
129.289
129.252
128.512
128.490
128.227
127.868
127.216
127.186
125.091
123.355
116.470
77.317
77.002
76.680
57.569
47.196
24.401
9.296
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Bn
O
N
Ph
O
Ph

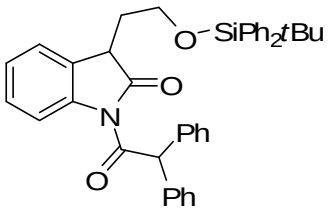
246
9
8
7
6
5
4
3
2
1
ppm

Bn
O
N
Ph
O
Ph
129.258
129.236
129.214
128.533
128.474
128.350
128.328
127.346
127.222
127.156
126.819
124.812
124.006
116.556
176.996
172.886
140.685
138.480
138.297
136.532
77.323
77.008
76.693
57.377
47.715
37.394
220
200
180
160
140
120
100
80
60
40
20
0
ppm

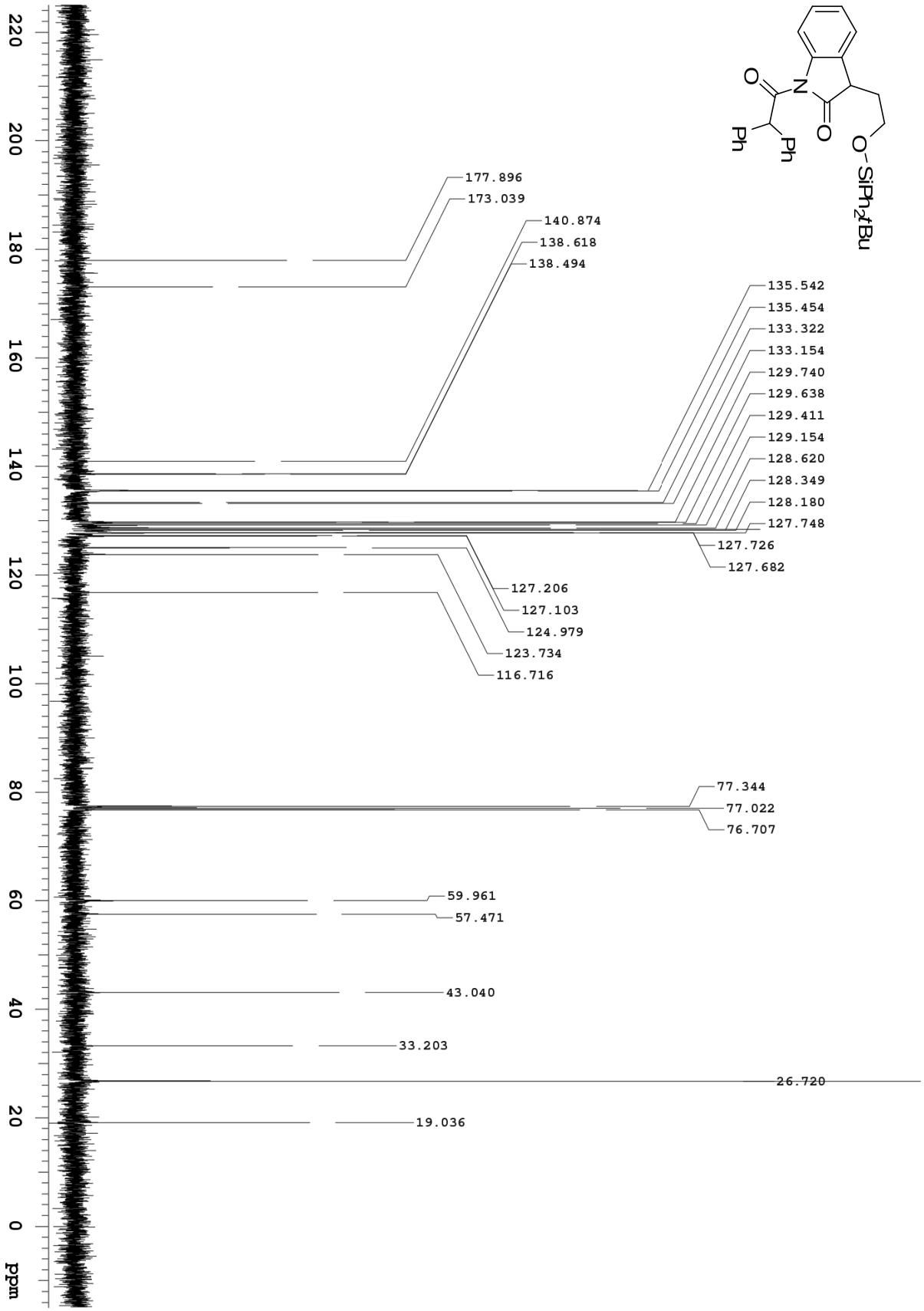

O
SiPh2tBu
O
N
H

9
8
7
6
5
4
3
2
1
ppm

O
SiPh2tBu
O
N
H
135.602
135.492
133.485
133.441
129.639
129.536
129.265
127.764
127.676
127.617
124.445
122.057
109.685
77.323
77.008
76.686
60.431
42.873
32.743
26.721
19.074
-0.008
180.636
141.652
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
SiPh2tBu
O
N
Ph
O
Ph

250
9
8
7
6
5
4
3
2
1
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm
177.896
173.039
140.874
138.618
138.494
135.542
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127.206
127.103
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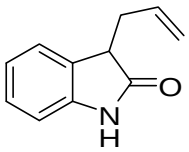
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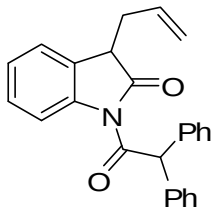
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O
Ph

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123.640
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77.062
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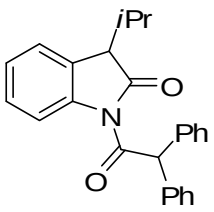
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iPr
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Ph
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127.205
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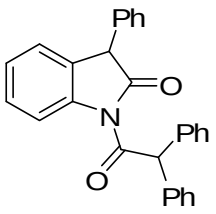
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O
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127.267
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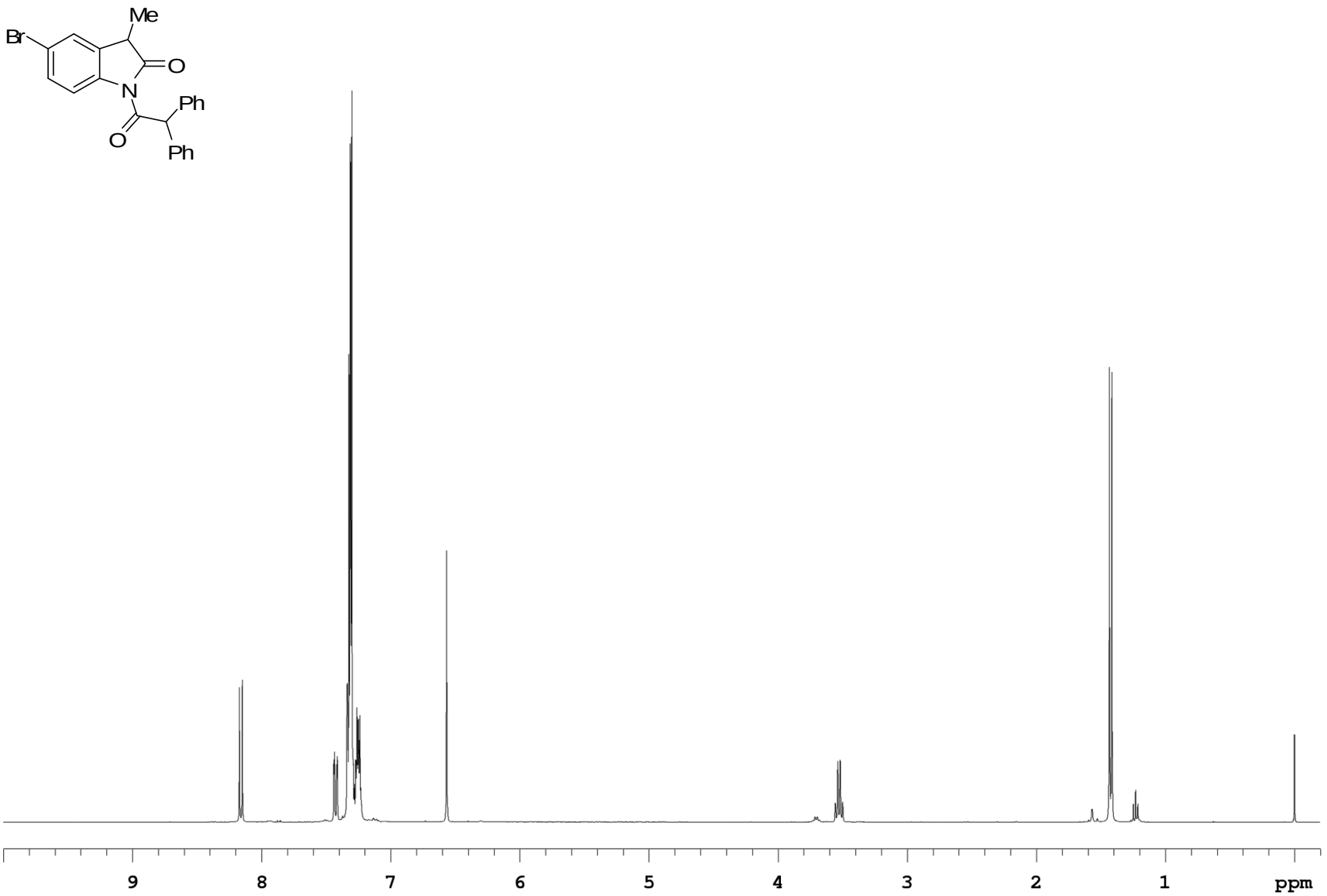
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Ph
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1
ppm

Me
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N
Ph
O
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131.279
129.250
129.177
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128.532
127.367
127.316
126.430
118.321
118.240
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77.029
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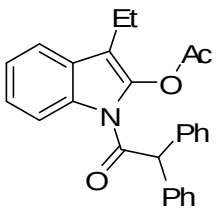
Et
Ac
O
N
Ph
O
Ph

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4
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1
ppm

Et
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N
Ph
O
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116.307
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77.001
76.686
58.549
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0
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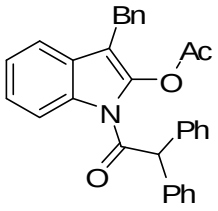
Bn
Ac
O
N
Ph
O
Ph

9
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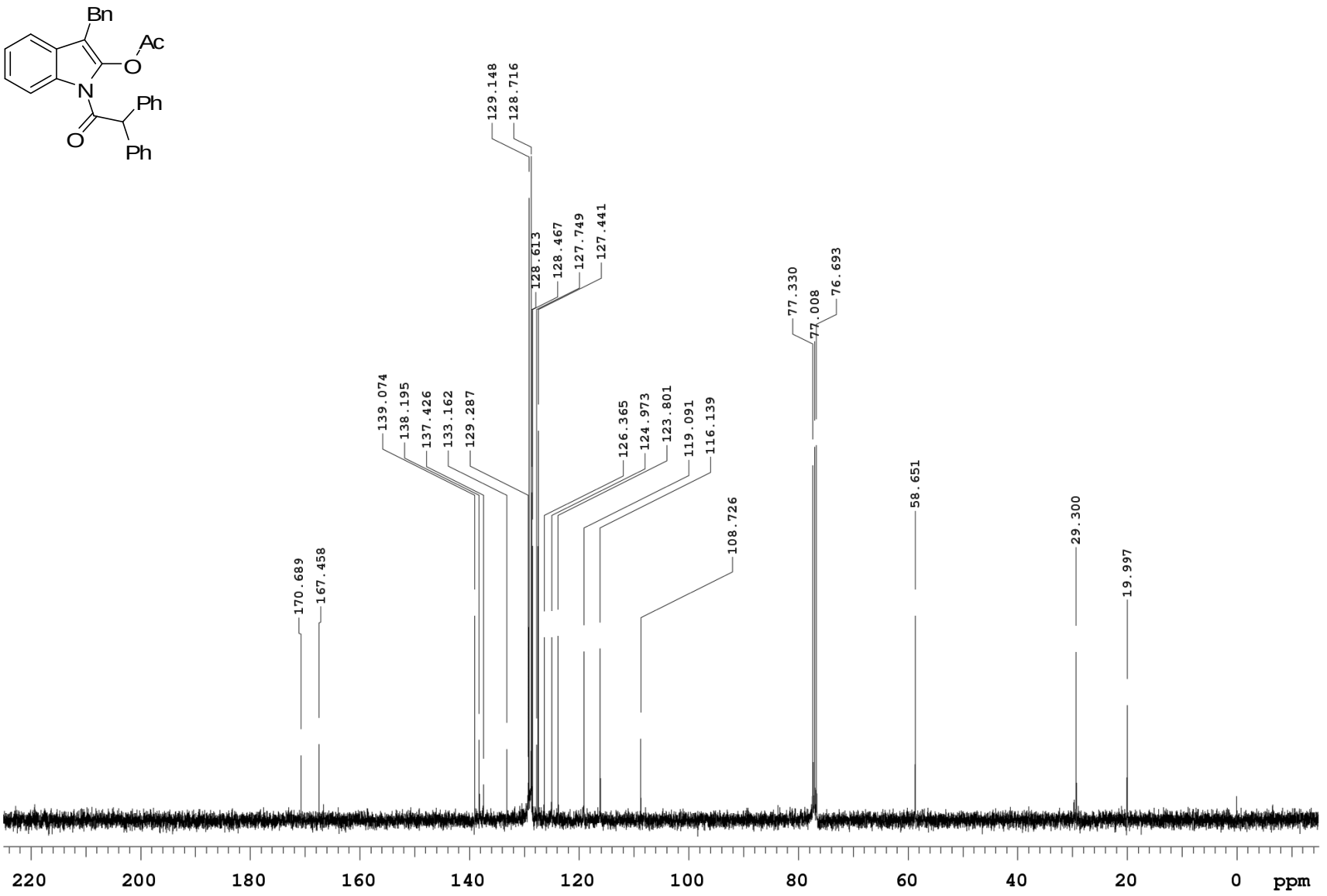
7
6
5
4
3
2
1
ppm


Bn
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Ph
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128.613
128.467
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127.441
126.365
124.973
123.801
119.091
116.139
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77.330
77.008
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120
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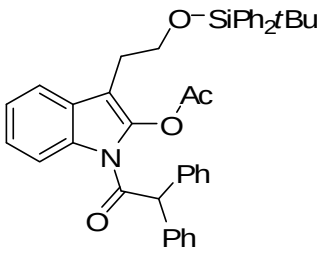
60
40
20
0
ppm


O⁻ SiPh2tBu
Ac
O
N
Ph
O
Ph

9
8
7
6
5
4
3
2
1
ppm

O⁻SiPh2tBu
Ac
O
N
Ph
O
Ph
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133.587
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127.734
127.654
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123.698
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116.051
107.085
139.213
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76.693
62.285
58.563
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19.154
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120
100
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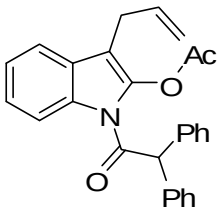
60
40
20
0
ppm


Ac
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N
Ph
O
Ph

268
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4
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1
ppm

Ac
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Ph
O
Ph
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58.611
27.662
20.095
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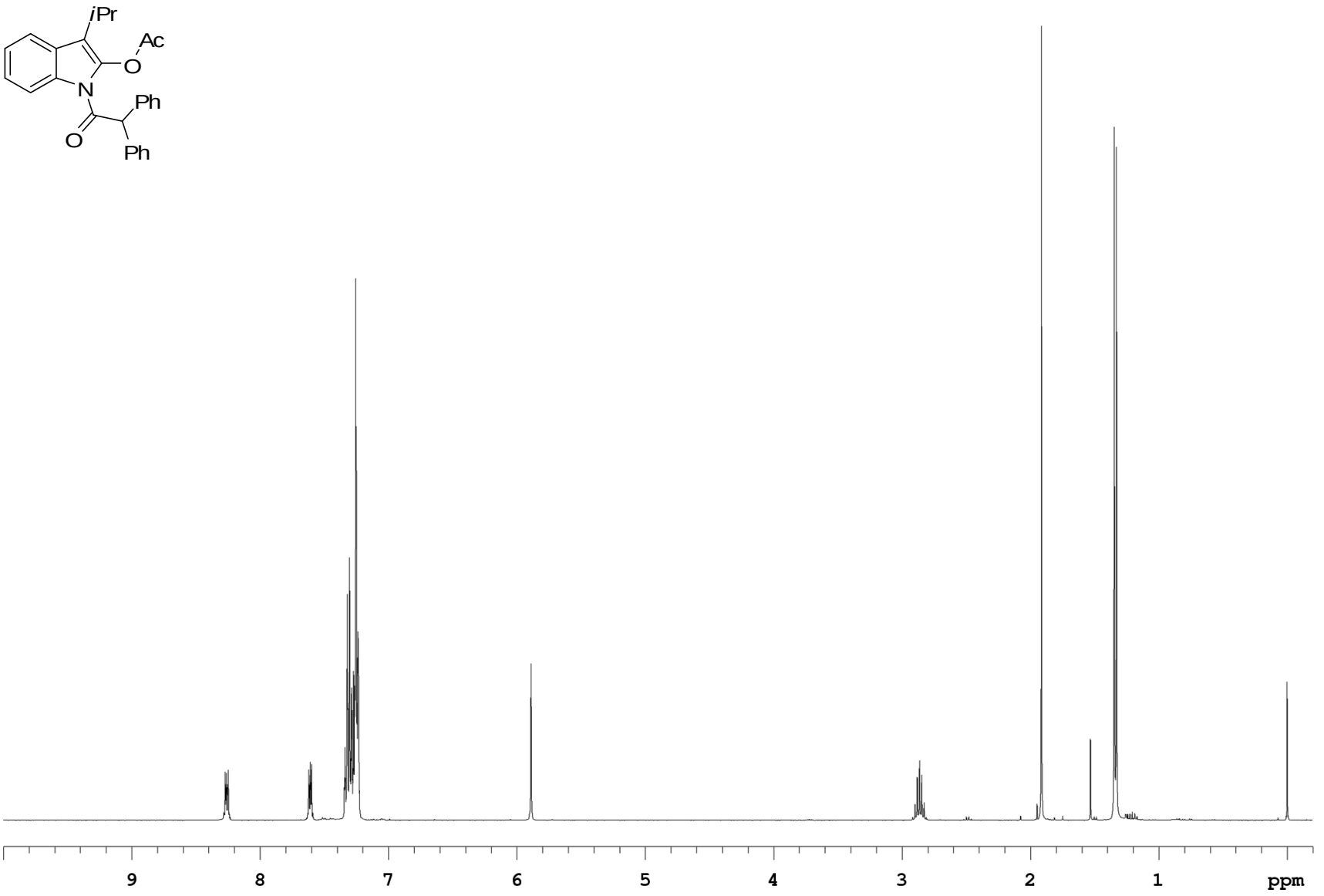
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Ph
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iPr
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Ph
O
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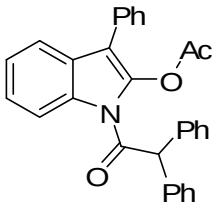
Ph
Ac
O
N
Ph
O
Ph

9
8
7
6
5
4
3
2
1
ppm

Ph
Ac
O
N
Ph
O
Ph
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127.493
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77.323
77.008
76.693
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-0.001
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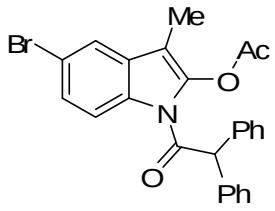
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O
N
Ph
O
Ph

274
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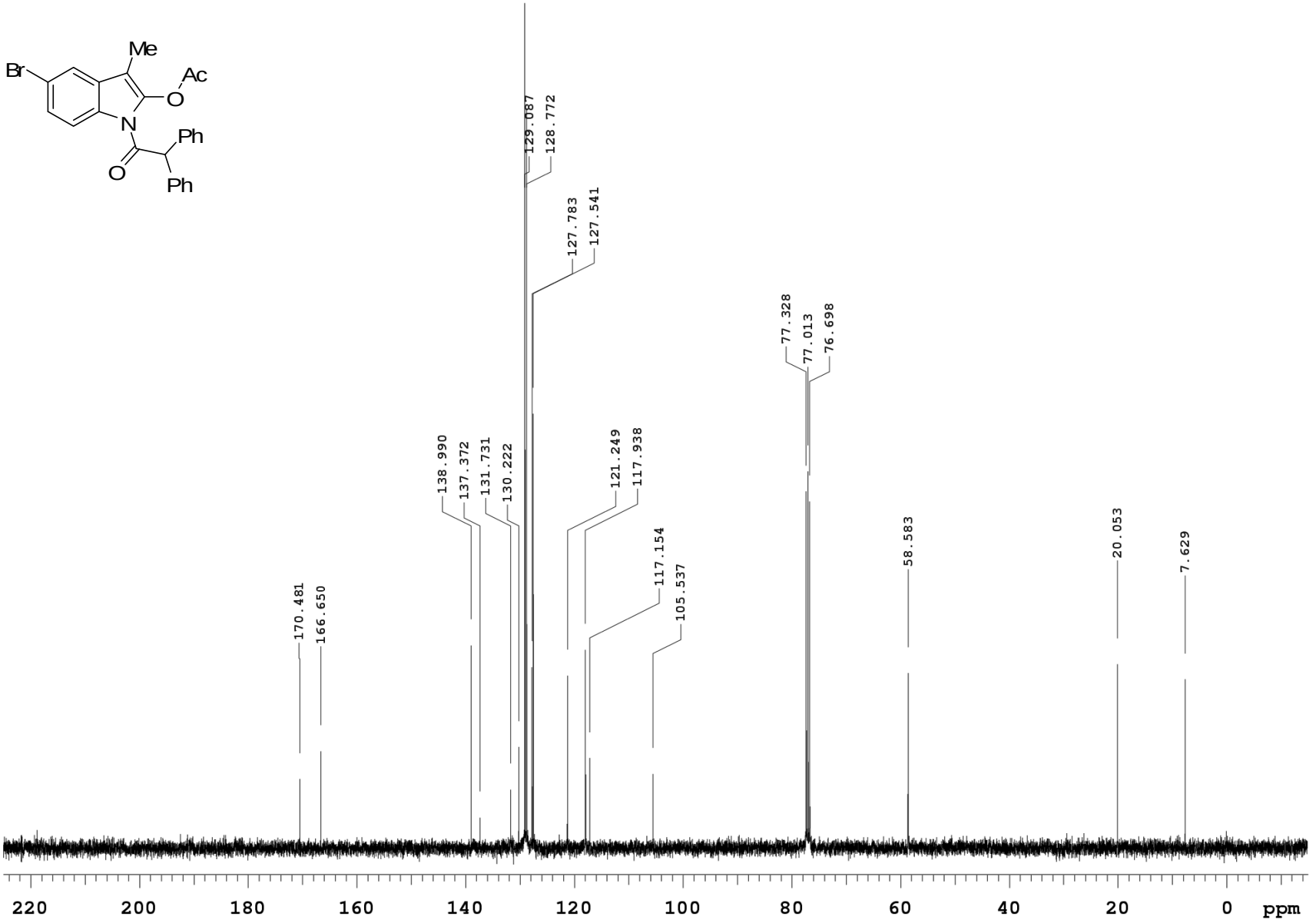
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121.249
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77.013
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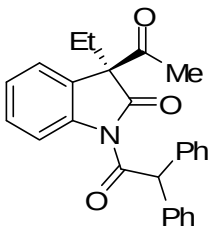
Et
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Me
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Ph

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ppm

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Me
O
N
Ph
O
Ph
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127.480
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126.396
125.825
123.312
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77.347
77.025
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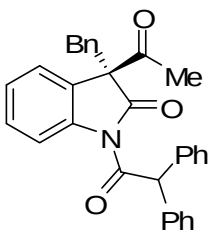
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Bn
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Ph
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278
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ppm

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Ph
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Ph
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126.955
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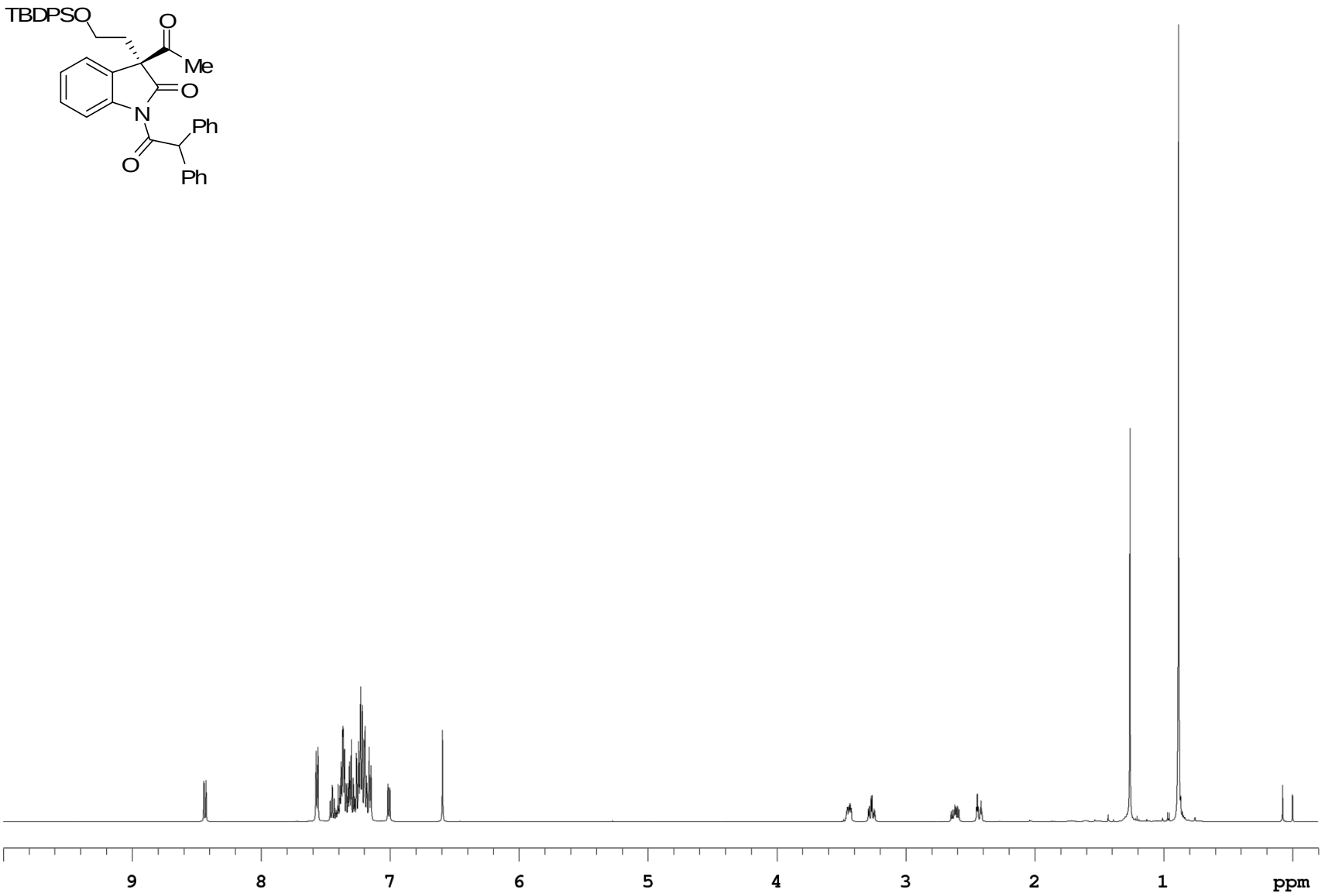
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4
3
2
1
ppm

TBDPSO
O
Me
O
N
Ph
O
Ph
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132.751
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129.535
129.499
129.367
128.861
128.231
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127.609
127.491
127.213
125.580
125.492
123.844
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77.344
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76.707
65.565
59.837
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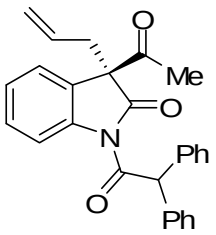
O
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Ph
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Ph

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8
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5
4
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1
ppm

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N
Ph
O
Ph
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128.534
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126.073
125.795
123.421
120.183
116.660
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76.694
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26.224
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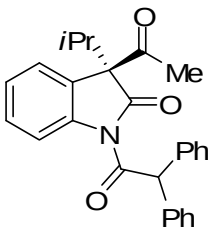
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Ph

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8
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4
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2
1
ppm

iPr
O
Me
O
N
Ph
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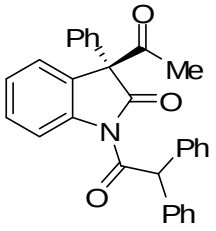
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Ph
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4
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2
1
ppm

Ph
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Me
O
N
Ph
O
Ph
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129.340
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128.856
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127.303
125.685
125.663
125.604
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77.200
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76.680
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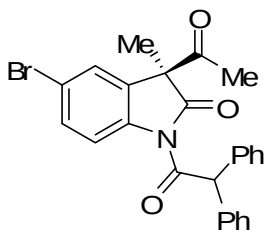
Me
O
Me
Br
O
N
Ph
O
Ph

9
8
7
6
5
4
3
2
1
ppm

Br
Me
O
Me
O
N
O
Ph
Ph
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172.965
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137.409
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129.322
129.256
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128.545
127.630
127.512
126.355
118.913
118.276
77.350
77.035
76.713
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19.855
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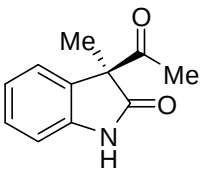
Me
O
Me
O
N
H

9
8
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6
5
4
3
2
1
ppm

Me
O
Me
O
N
H
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178.472
140.967
130.111
129.203
123.768
123.277
110.480
77.334
77.019
76.704
62.647
25.956
18.872
0.012
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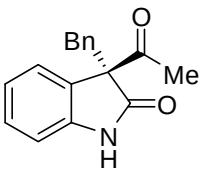
200
180
160
140
120
100
80
60
40
20
0
ppm


Bn
O
Me
O
N
H

9
8
7
6
5
4
3
2
1
ppm

Bn
O
Me
O
N
H
200.462
176.033
141.188
134.954
129.900
129.270
127.746
127.321
126.662
124.692
122.941
109.932
77.320
76.998
76.683
68.369
38.717
26.770
220
200
180
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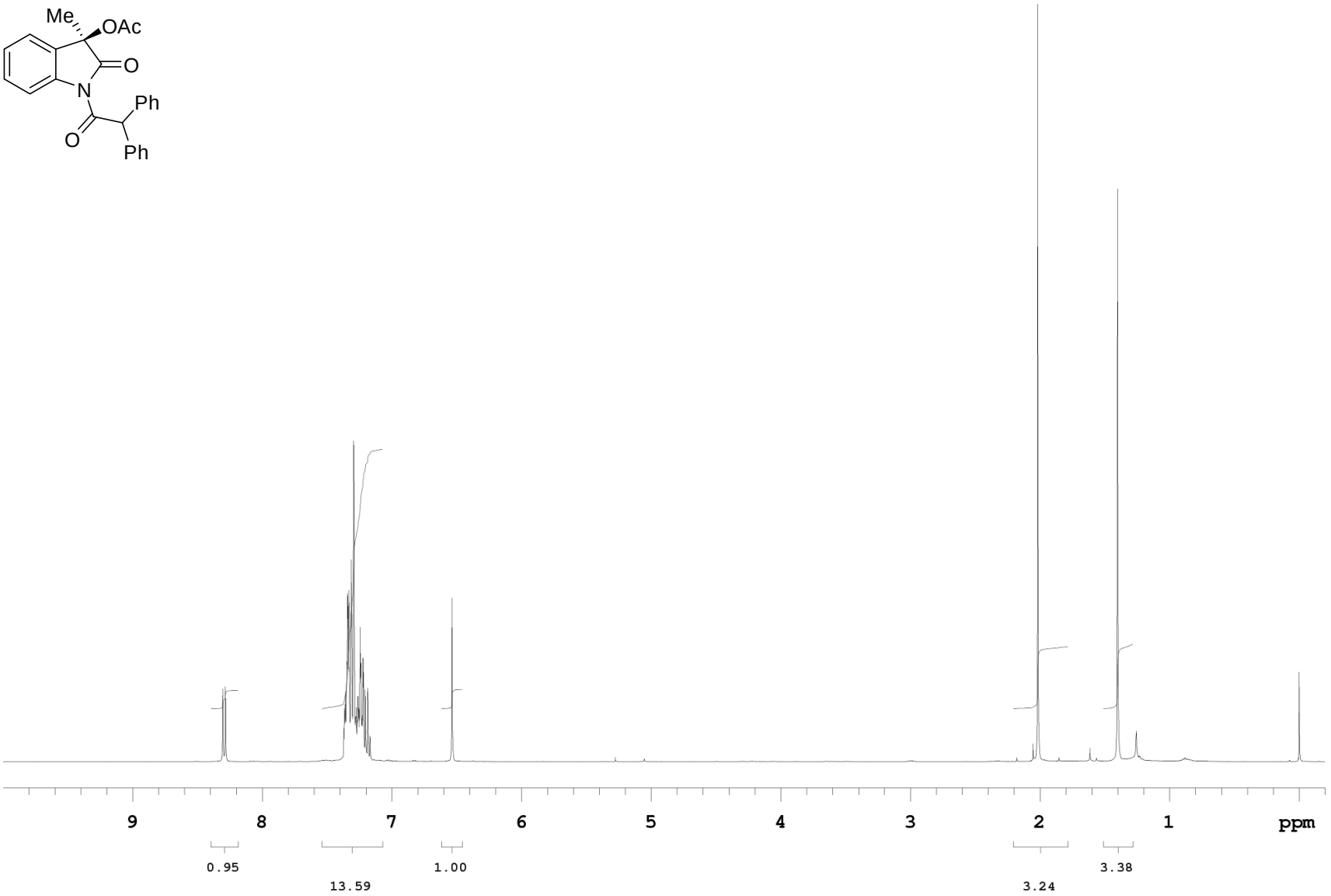
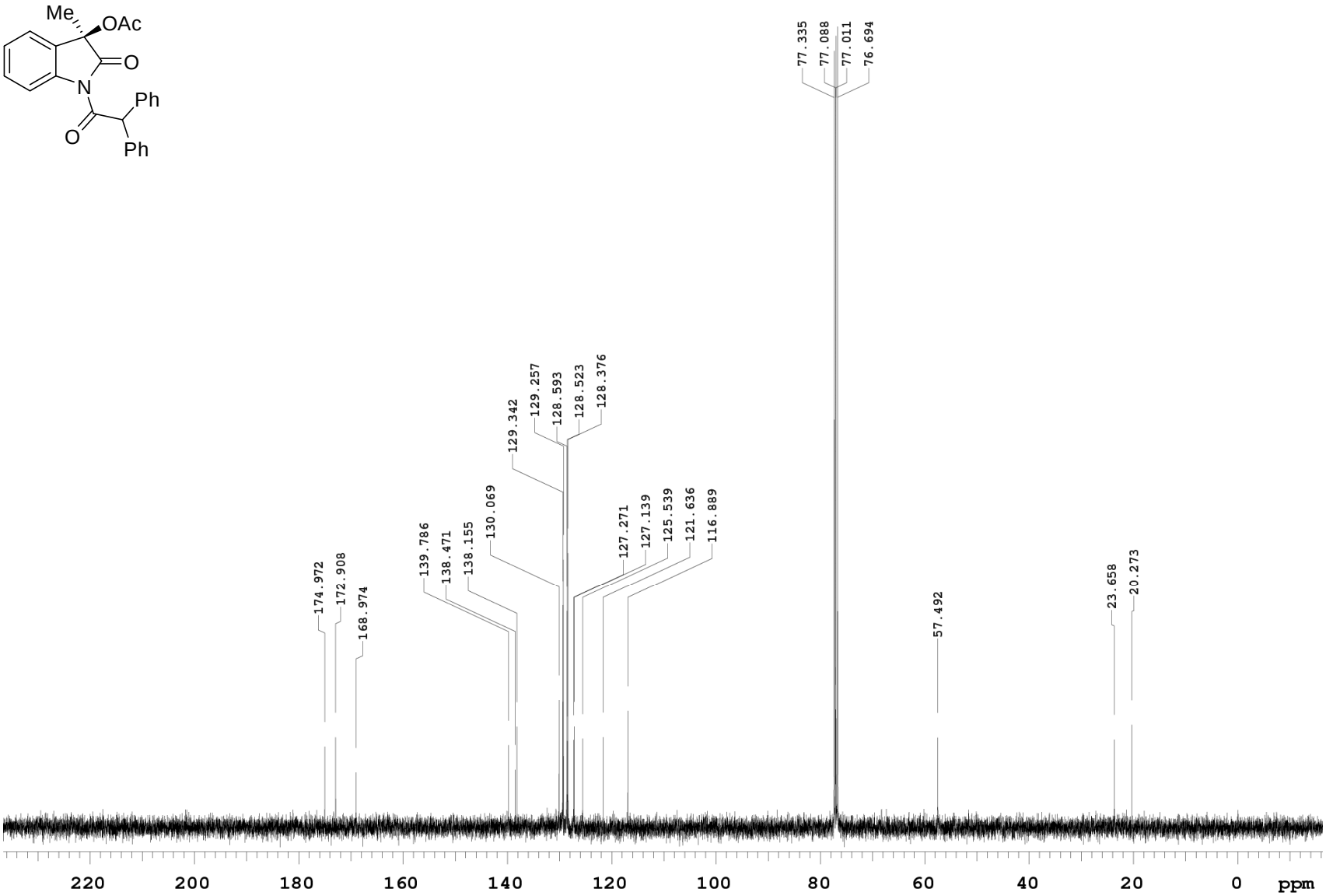
140
120
100
80
60
40
20
0
ppm


Me
OAc
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.95
13.59
1.00
3.24
3.38


Me
OAc
O
N
Ph
O
Ph
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77.088
77.011
76.694
174.972
172.908
168.974
139.786
138.471
138.155
130.069
129.342
129.257
128.593
128.523
128.376
127.271
127.139
125.539
121.636
116.889
57.492
23.658
20.273
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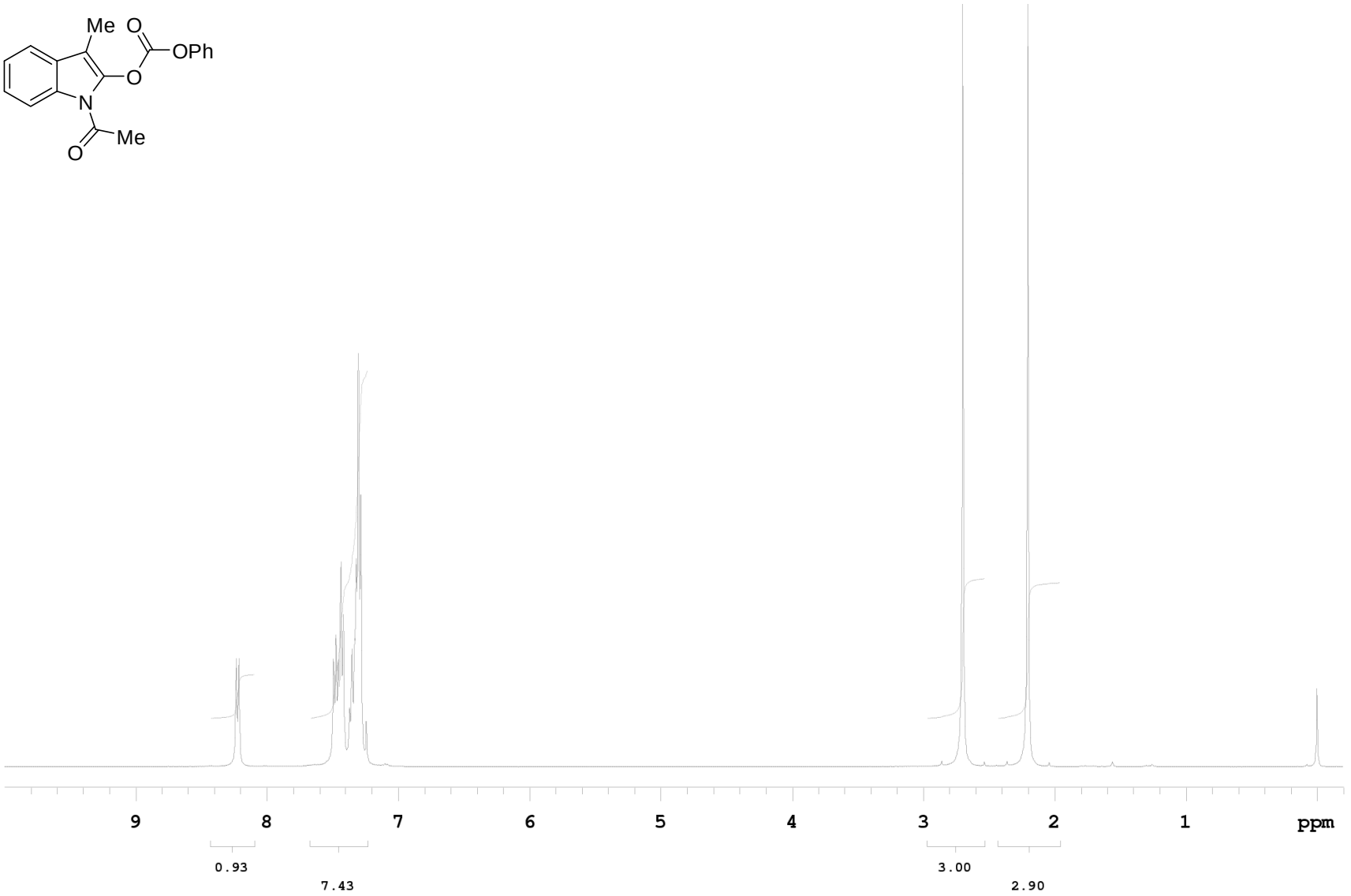
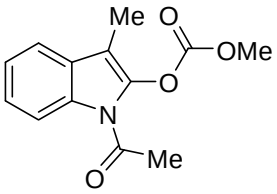
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
OPh
O
N
O
Me
9
8
7
6
5
4
3
2
1
ppm
0.93
7.43
3.00
2.90

Me
O
OPh
O
N
O
Me
167.961
150.847
150.584
137.181
132.280
129.783
128.021
126.807
125.222
123.715
120.569
118.783
115.946
105.805
77.335
77.018
76.701
26.132
7.201
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
OMe
O
N
Me
O

9
8
7
6
5
4
3
2
1
ppm

Me
O
OMe
O
N
O
Me
168.023
152.633
137.199
132.306
128.043
125.149
123.684
118.601
116.154
105.525
77.338
77.016
76.701
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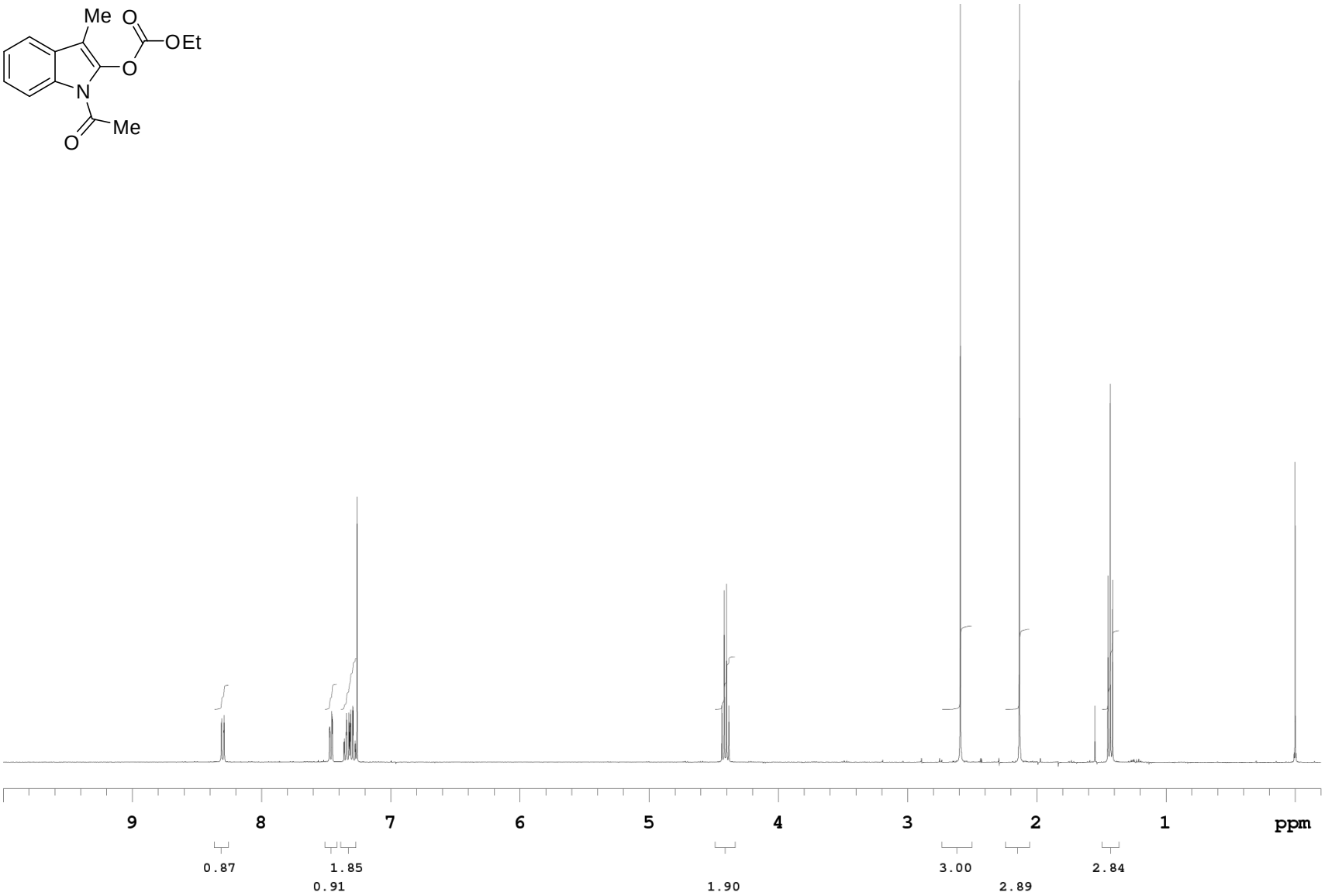
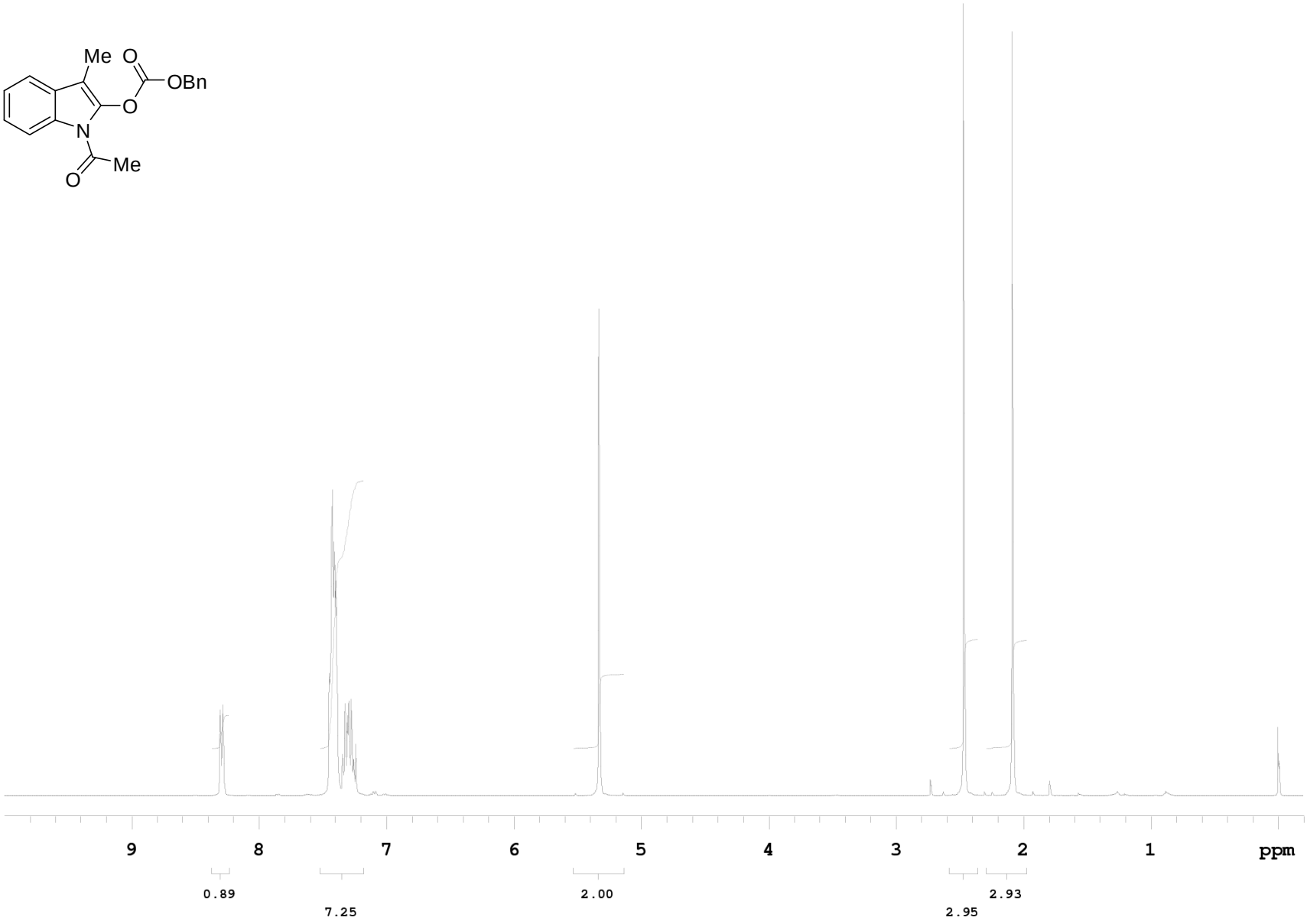
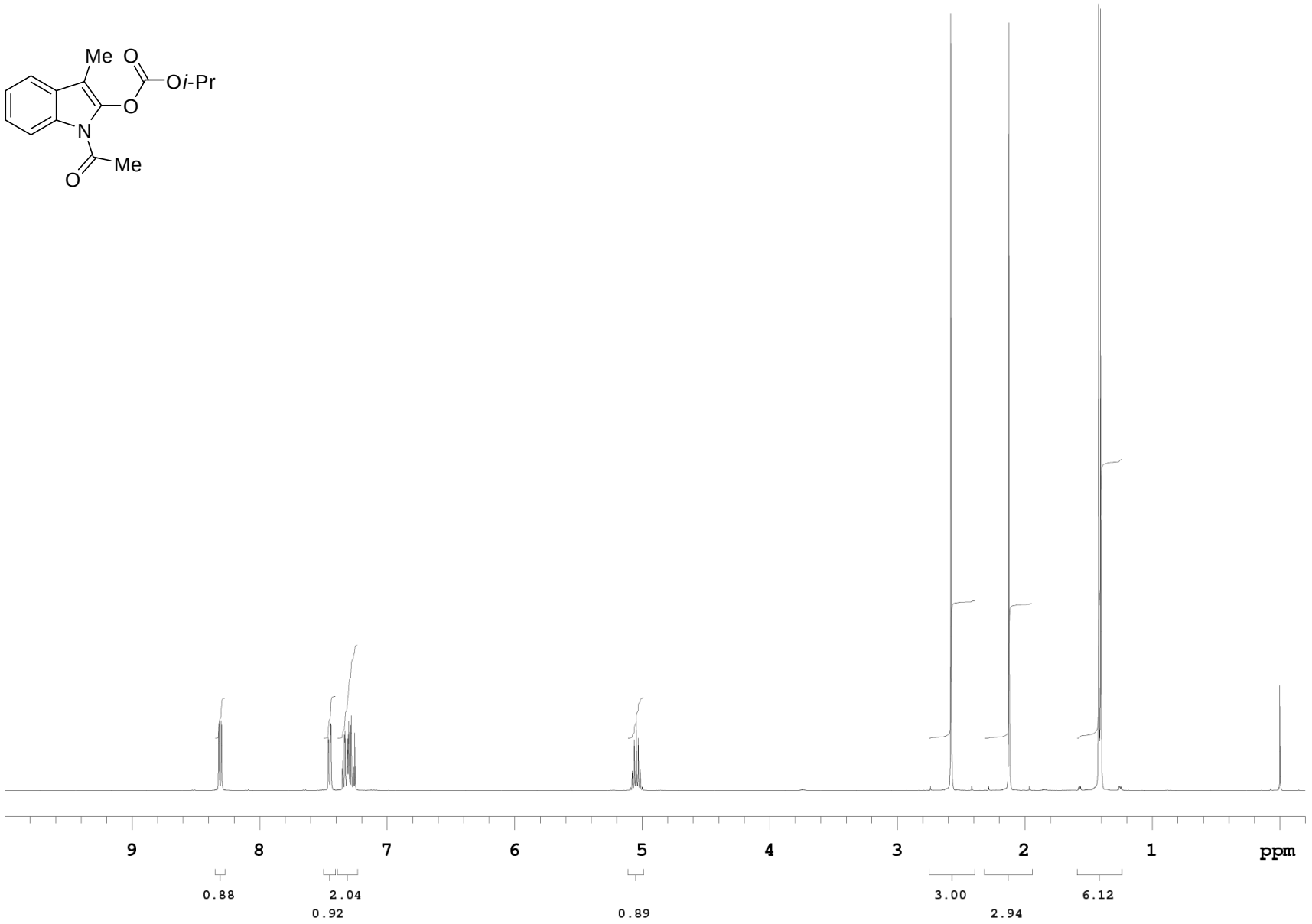
25.887
7.142
220
200
180
160
140
120
100
80
60
40
20
0
ppm

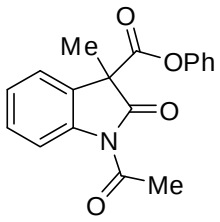

Me
O
OEt
O
N
O
Me
9
8
7
6
5
4
3
2
1
ppm
0.87
1.85
0.91
1.90
3.00
2.89
2.84


Me
O
OBn
O
N
O
Me
9
8
7
6
5
4
3
2
1
ppm
0.89
7.25
2.00
2.95
2.93

Me
O
OBn
O
N
O
Me
167.981
152.019
137.131
134.070
132.354
129.185
128.806
128.659
128.002
125.150
123.673
118.533
116.260
105.485
77.332
77.015
76.691
71.628
25.704
7.129
220
200
180
160
140
120
100
80
60
40
20
0
ppm

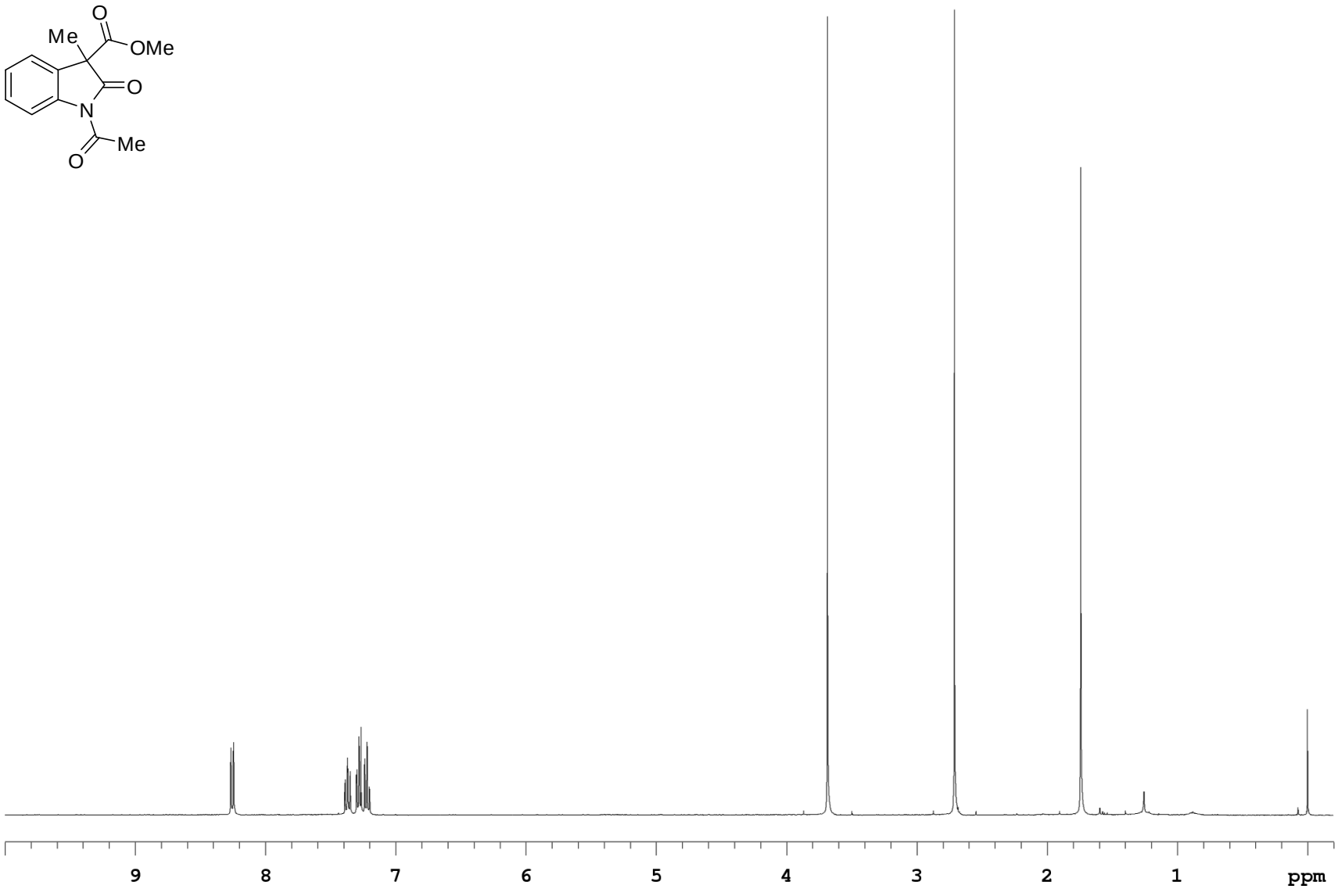

Me
O
O
Oi-Pr
O
N
O
Me
9
8
7
6
5
4
3
2
1
ppm
0.88
2.04
0.92
0.89
3.00
2.94
6.12

Me
O
O
Oi-Pr
O
N
O
Me
77.329
77.012
76.695
168.040
151.420
137.282
132.374
128.107
125.053
123.639
118.483
116.257
105.388
74.855
25.762
21.611
7.148
220
200
180
160
140
120
100
80
60
40
20
0
ppm

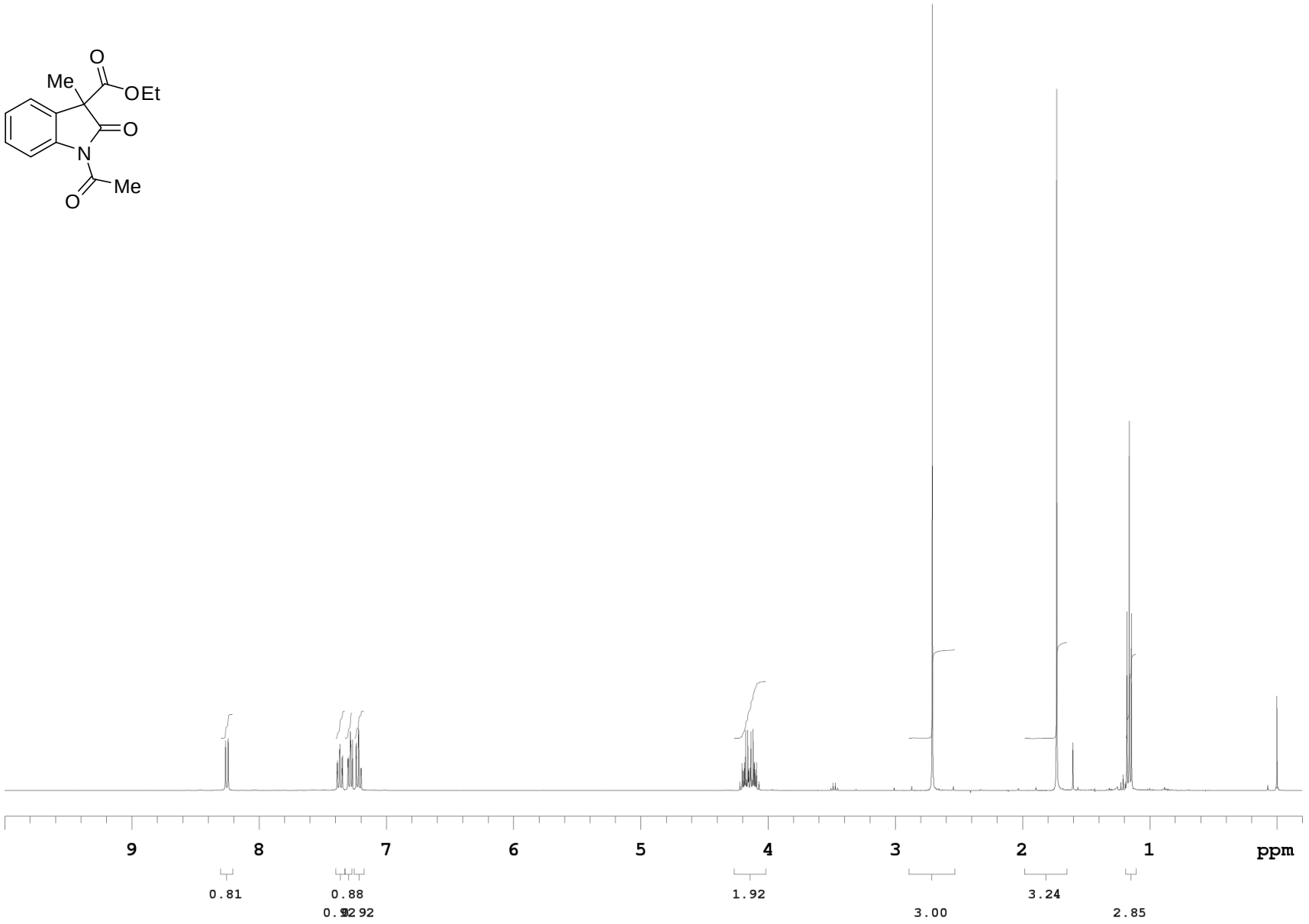

O
Me
OPh
O
N
O
Me

9
8
7
6
5
4
3
2
1
ppm

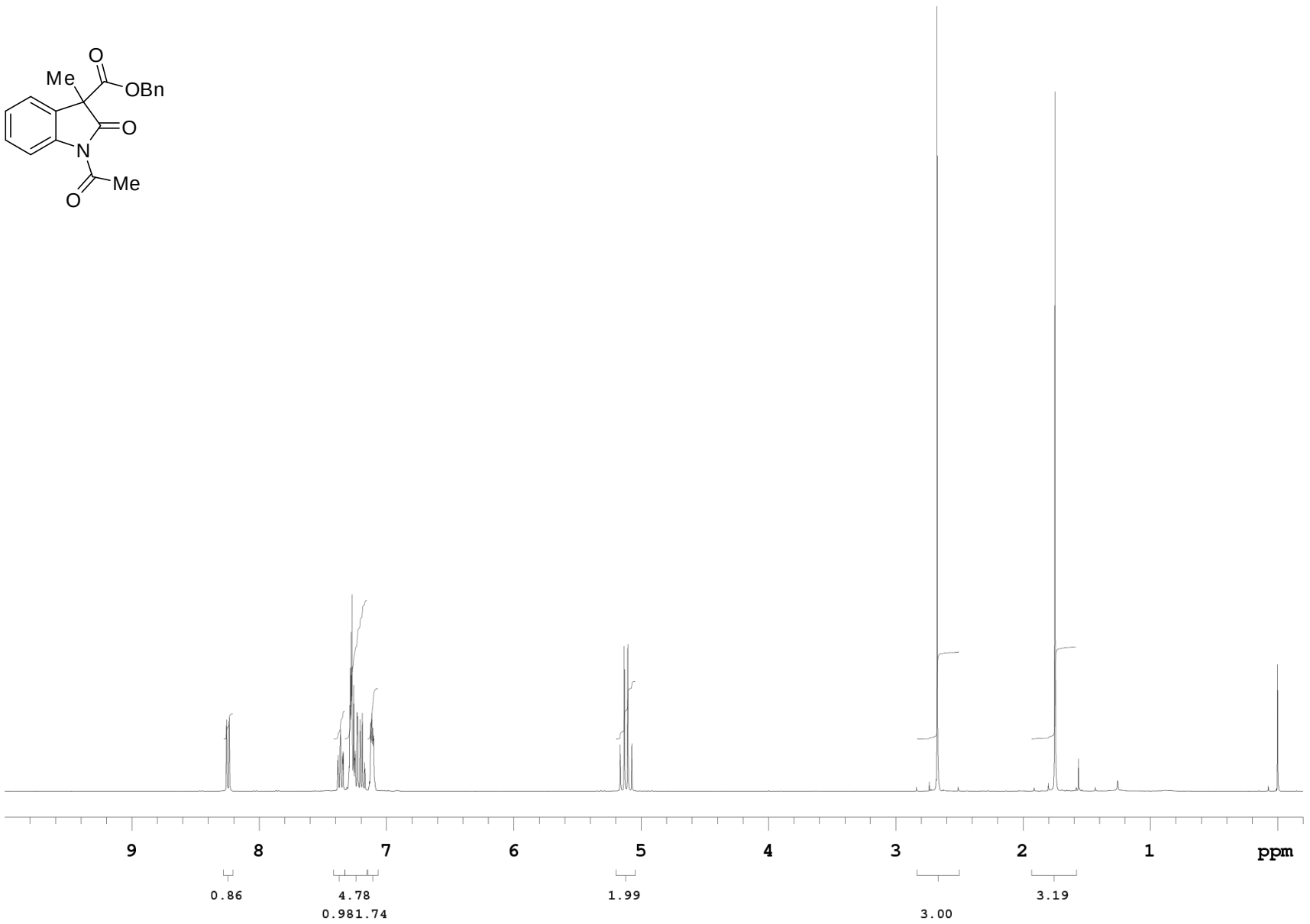
Me
OPh
O
O
N
O
Me
198.419
175.140
172.965
139.255
137.563
137.409
132.552
130.355
129.322
129.256
128.846
128.545
127.630
127.512
126.355
118.913
118.276
77.350
77.035
76.713
62.246
58.085
25.576
19.855
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
OMe
O
N
Me
O
9
8
7
6
5
4
3
2
1
ppm

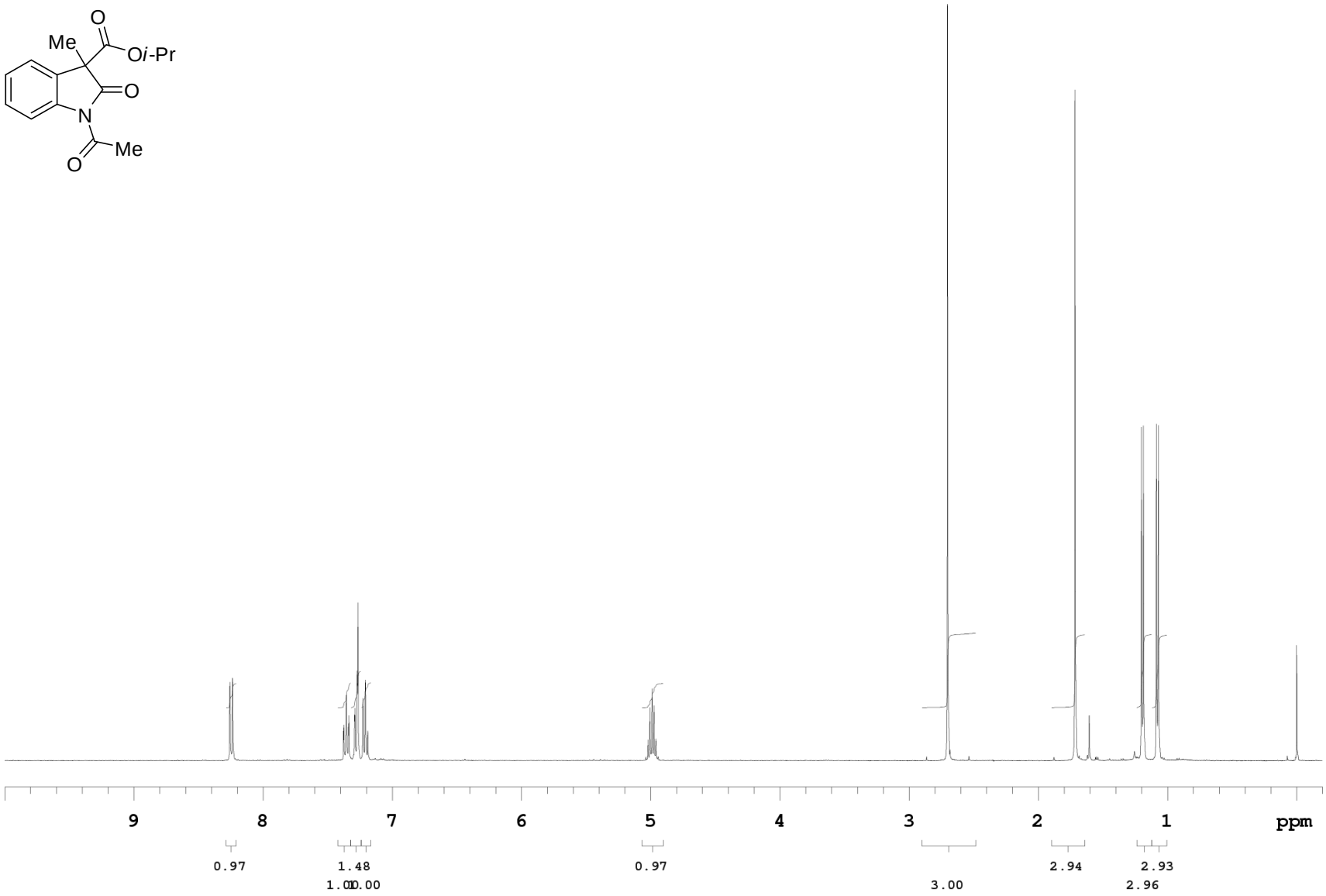
Me
OMe
O
O
N
O
Me
175.732
170.802
169.447
139.868
129.423
128.925
125.555
122.706
116.882
77.327
77.012
76.697
55.630
53.330
26.644
20.814
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
Me
OEt
O
N
O
Me
9
8
7
6
5
4
3
2
1
ppm
0.81
0.88
1.92
3.00
3.24
2.85

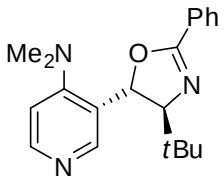
Me
OEt
O
O
N
O
Me
77.334
77.018
76.701
175.853
170.821
168.911
139.878
129.334
129.094
125.508
122.624
116.842
62.331
55.776
26.603
20.658
13.825
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
Me
OBn
O
N
O
Me
9
8
7
6
5
4
3
2
1
ppm
0.86
4.78
0.981.74
1.99
3.00
3.19

Me
OBn
O
O
N
O
Me
175.655
170.754
168.651
139.934
135.026
129.437
128.803
128.510
128.278
127.381
125.487
122.720
116.891
77.345
77.028
76.711
67.567
55.863
26.575
20.468
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
Me
O*i*-Pr
O
N
O
Me
9
8
7
6
5
4
3
2
1
ppm
0.97
1.48
1.00
0.97
3.00
2.94
2.93
2.96

Me
O
O*i*-Pr
O
N
O
Me
175.950
170.852
168.398
139.867
129.260
129.194
125.458
122.513
116.800
77.332
77.017
76.702
70.095
55.950
26.577
21.361
21.229
20.475
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Ph
Me2N
O
N
tBu
N

8
7
6
5
4
3
2
1
ppm

Me2N
O
Ph
N
tBu
N
162.278
158.836
151.113
150.114
131.266
129.036
128.381
128.267
127.872
112.843
84.761
77.265
77.013
76.756
76.723
44.137
34.795
25.864
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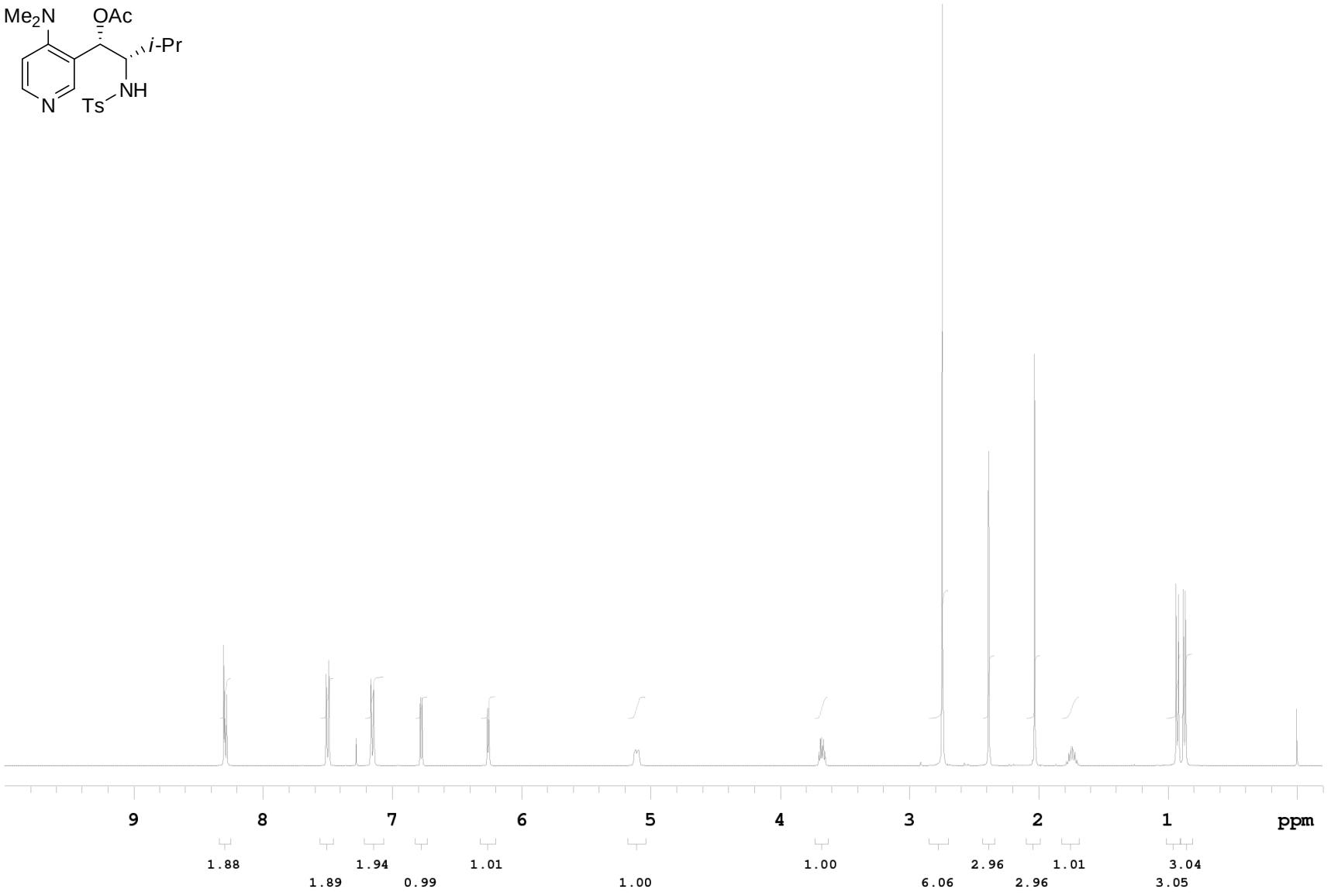
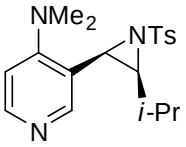
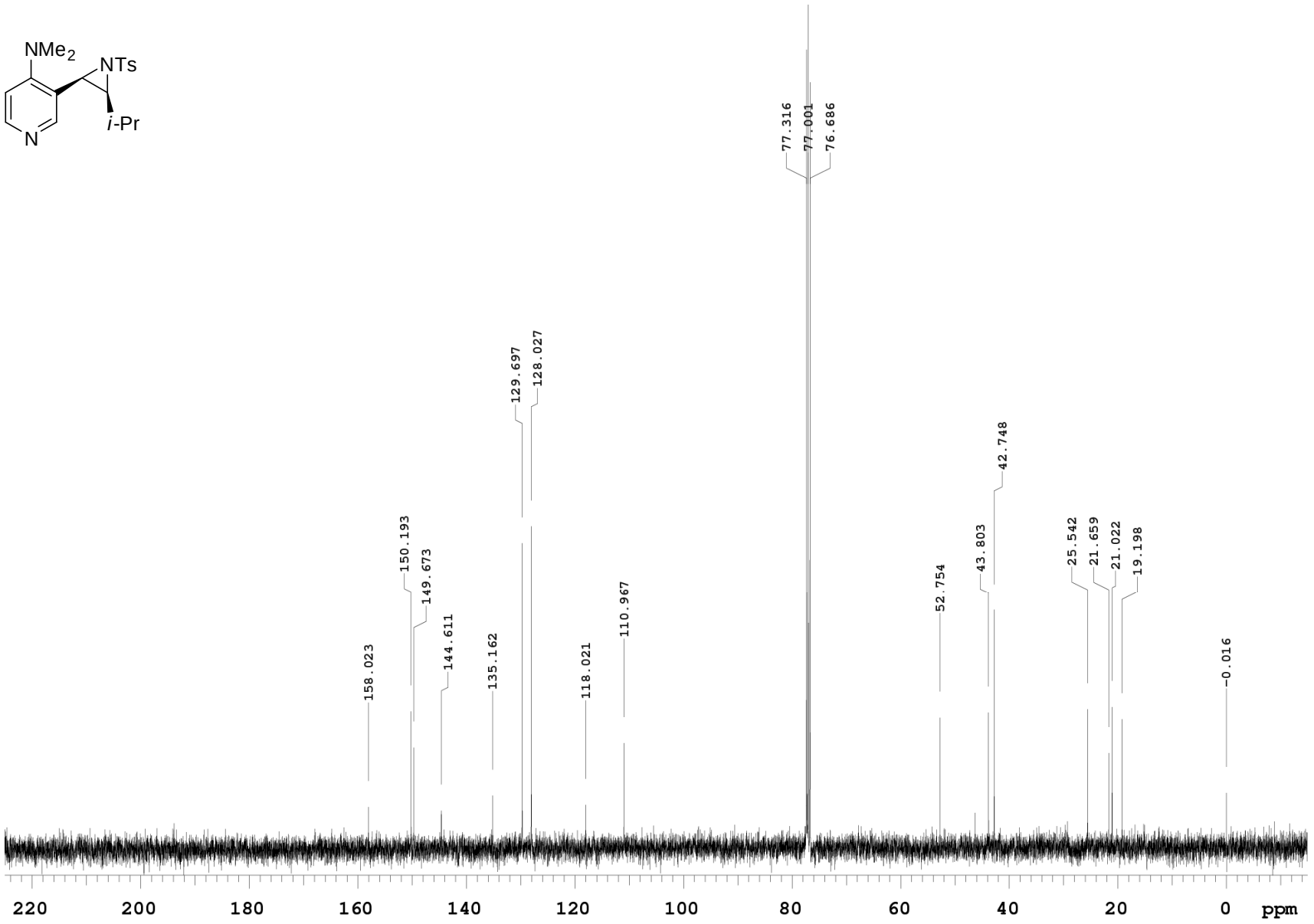
200
180
160
140
120
100
80
60
40
20
0
ppm

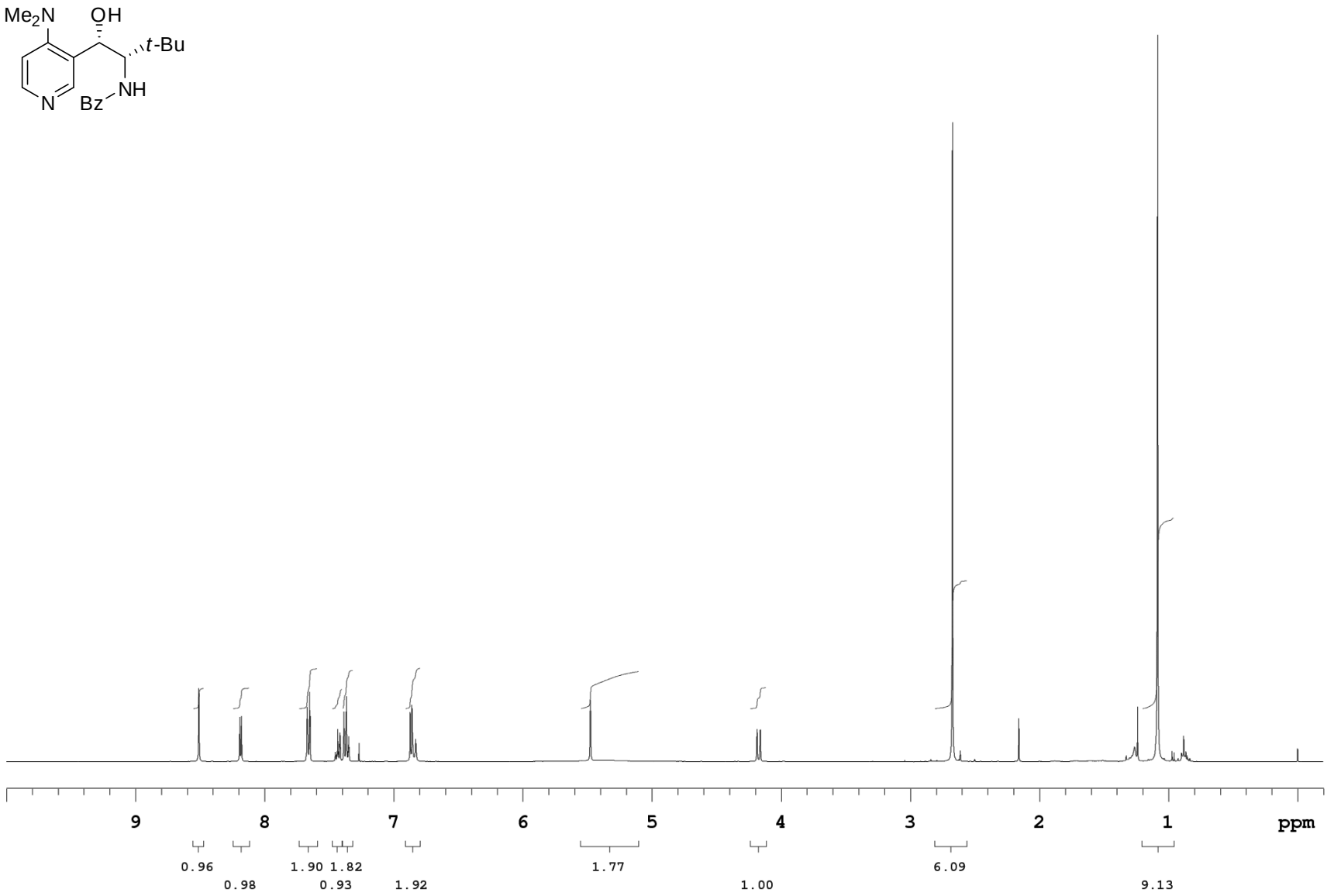

Me2N
OAc
i-Pr
NH
Ts
N
9
8
7
6
5
4
3
2
1
ppm
1.88
1.89
1.94
0.99
1.01
1.00
1.00
6.06
2.96
2.96
1.01
3.04
3.05

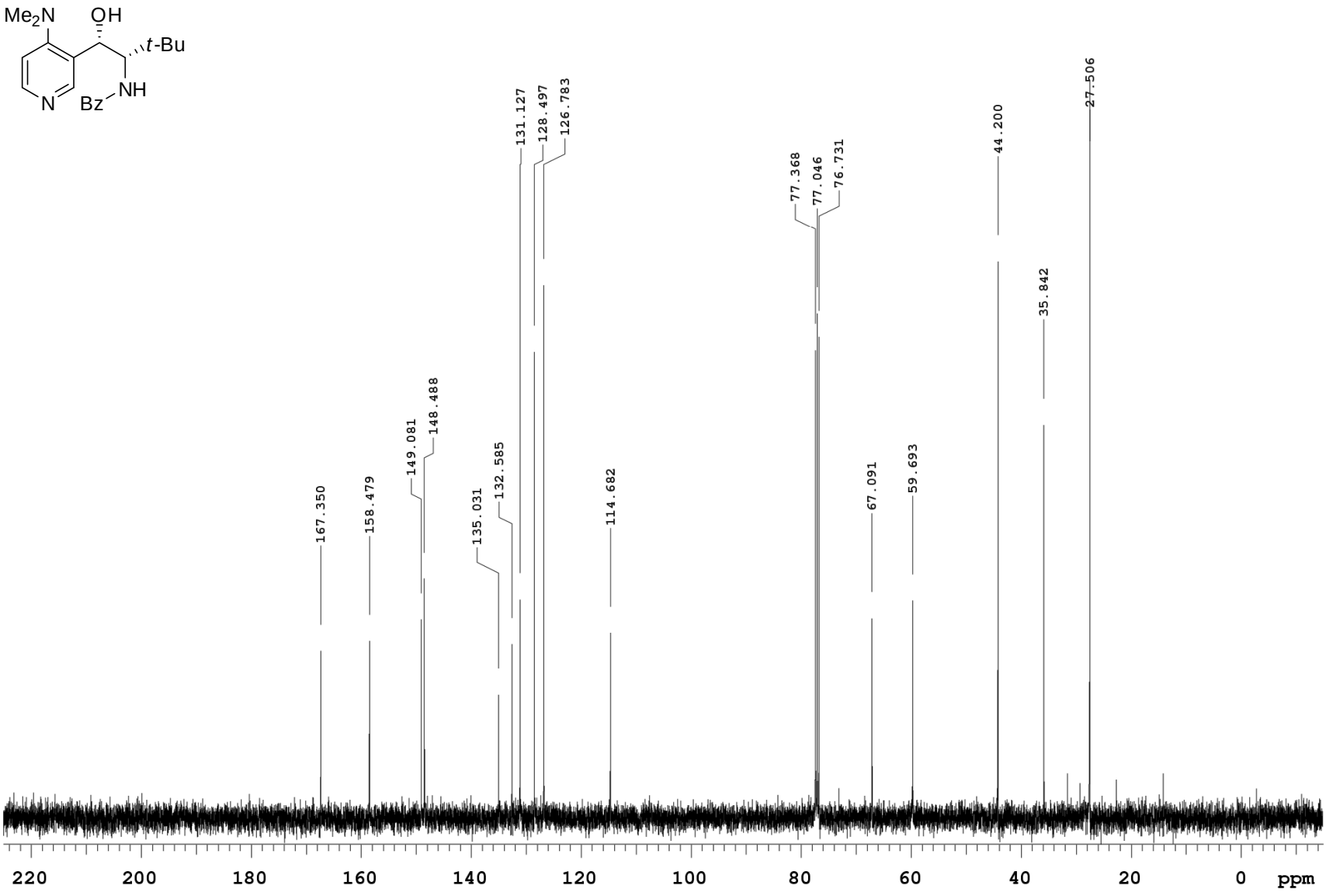
Me2N
OAc
i-Pr
NH
Ts
N
170.462
158.496
150.318
149.097
142.742
138.491
129.532
127.151
126.672
114.103
77.424
77.115
76.798
70.096
62.266
43.814
30.743
21.521
21.011
19.434
18.251
220
200
180
160
140
120
100
80
60
40
20
0
ppm


NMe2
NTs
i-Pr
N

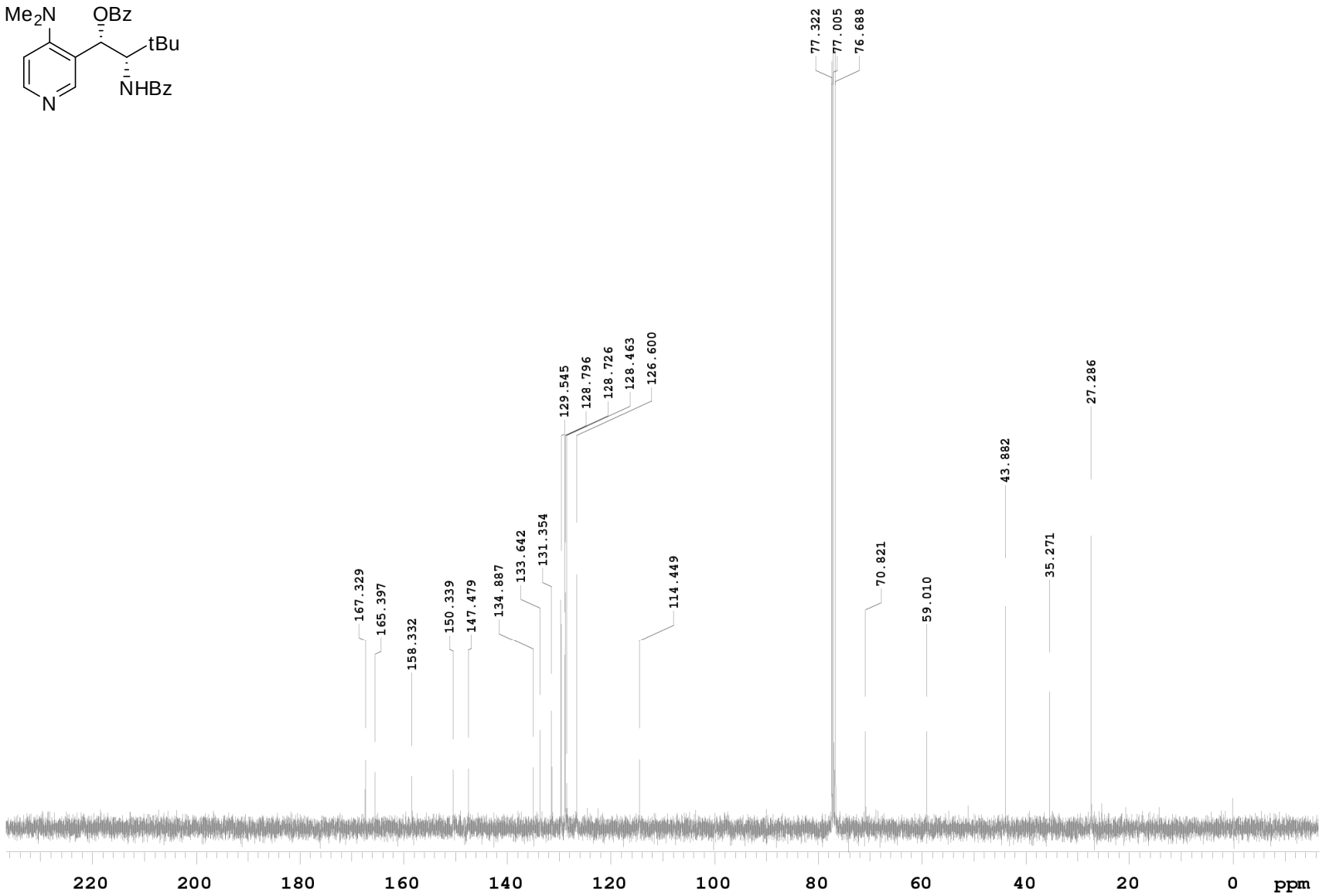
9
8
7
6
5
4
3
2
1
ppm
0.85
1.75
1.00
7.24
1.33
0.82
1.95
1.00
2.99
6.92


NMe2
NTs
i-Pr
N
158.023
150.193
149.673
144.611
135.162
129.697
128.027
118.021
110.967
77.316
77.001
76.686
52.754
43.803
42.748
25.542
21.659
21.022
19.198
0.016
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me2N
OH
t-Bu
NH
Bz
N
9
8
7
6
5
4
3
2
1
ppm
0.96
0.98
1.90
1.82
0.93
1.92
1.77
1.00
6.09
9.13


Me2N
OH
t-Bu
NH
Bz
N
167.350
158.479
149.081
148.488
135.031
132.585
131.127
128.497
126.783
114.682
77.368
77.046
76.731
67.091
59.693
44.200
35.842
27.506
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me2N
OBz
tBu
NHBz
N
9
8
7
6
5
4
3
2
1
ppm
0.95 1.88 4.89 1.00 1.00 9.44
1.01 2.90 0.98 1.01 6.11


Me2N
OBz
tBu
NHBz
N
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77.005
76.688
167.329
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158.332
150.339
147.479
134.887
133.642
131.354
129.545
128.796
128.726
128.463
126.600
114.449
70.821
59.010
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35.271
27.286
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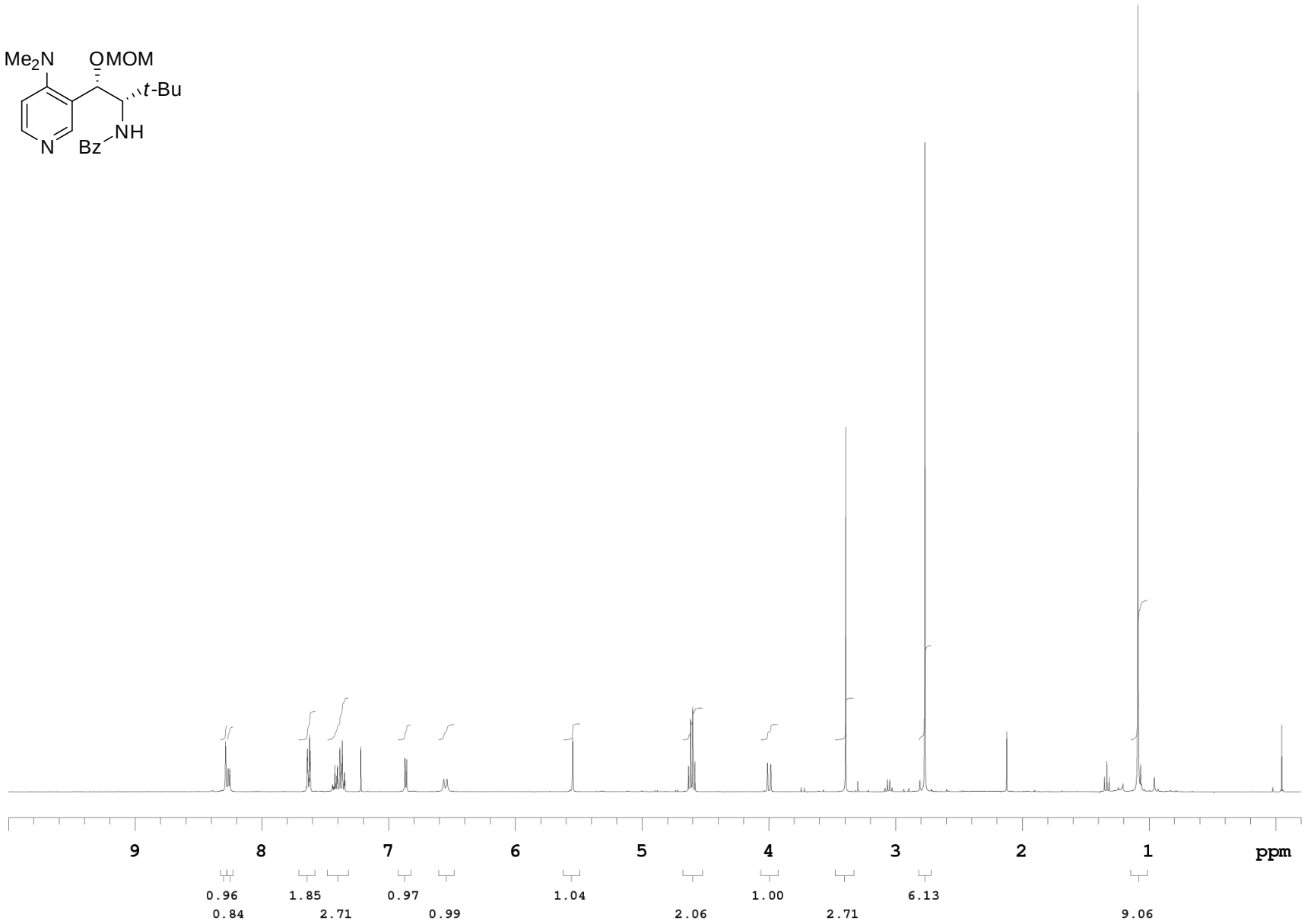
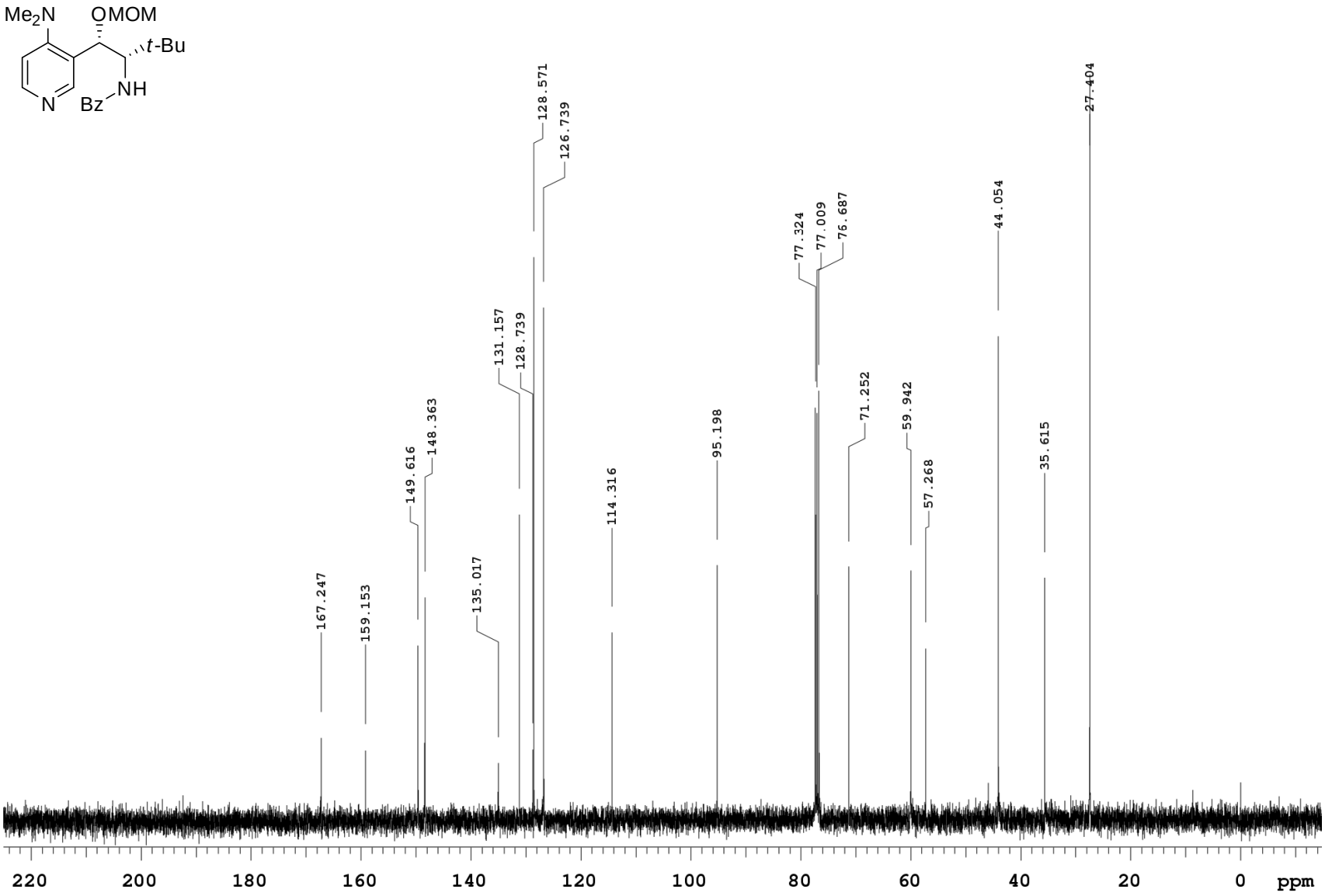
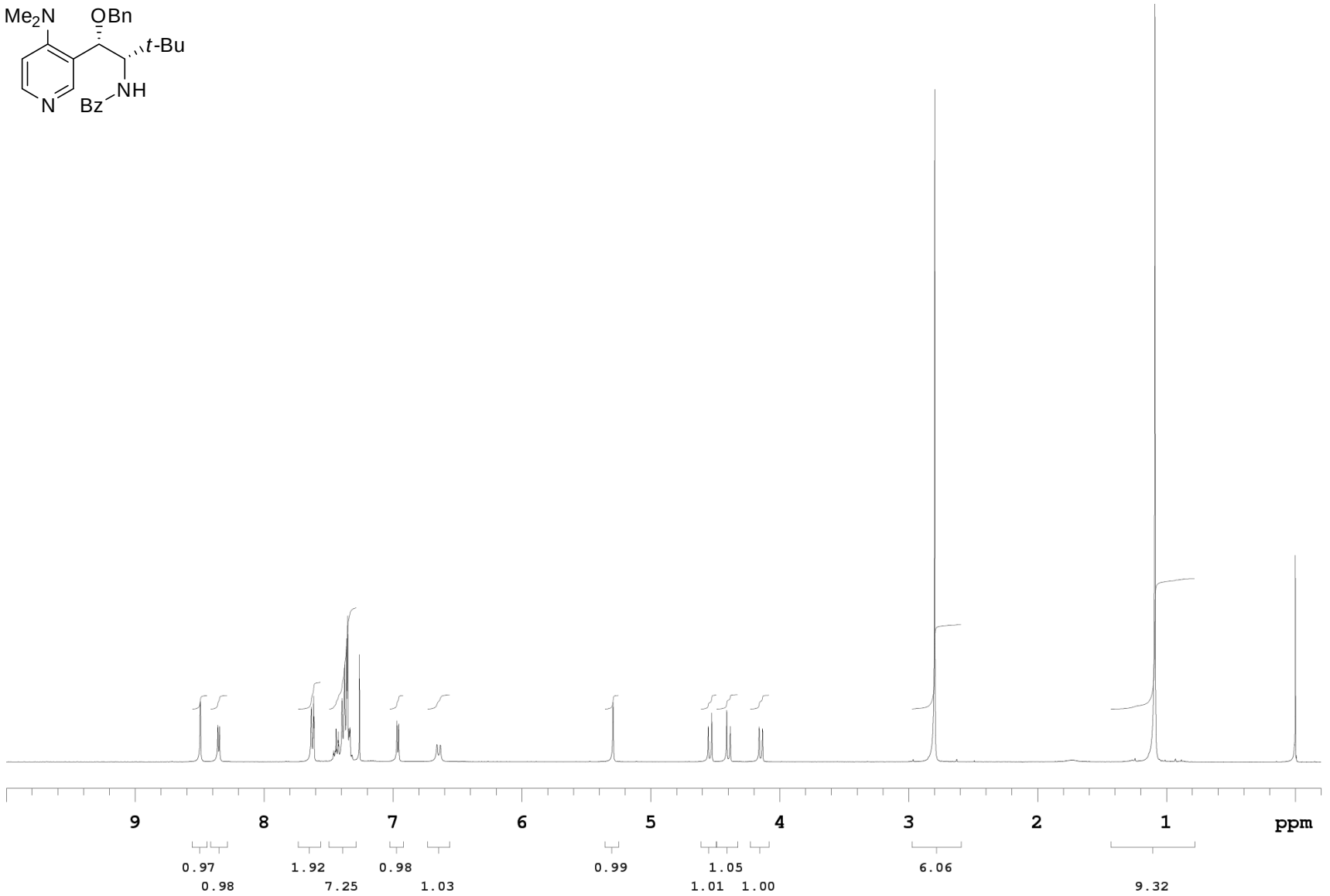
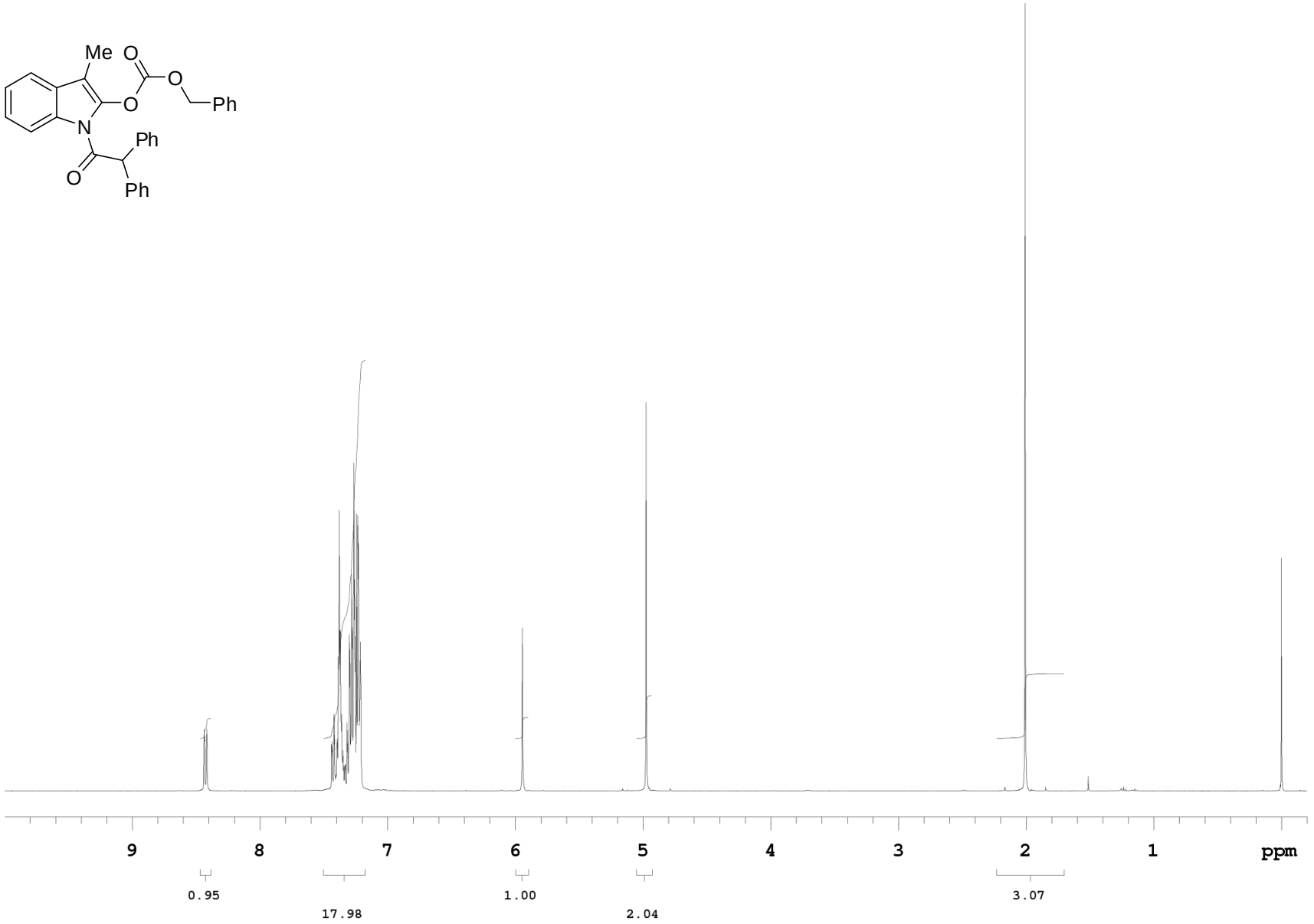
200
180
160
140
120
100
80
60
40
20
0
ppm


Me2N
OMOM
t-Bu
NH
N
Bz
9
8
7
6
5
4
3
2
1
ppm
0.96
0.84
1.85
2.71
0.97
0.99
1.04
2.06
1.00
2.71
6.13
9.06


Me2N
OMOM
t-Bu
NH
N
Bz
167.247
159.153
149.616
148.363
135.017
131.157
128.739
128.571
126.739
114.316
95.198
77.324
77.009
76.687
71.252
59.942
57.268
44.054
35.615
27.404
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me2N
OBn
t-Bu
NH
N
Bz
9
8
7
6
5
4
3
2
1
ppm
0.97
0.98
1.92
7.25
0.98
1.03
0.99
1.05
1.01
1.00
6.06
9.32

Me2N
OBn
t-Bu
NH
Bz
N
128.556
128.494
77.337
77.221
77.020
76.703
27.580
128.108
126.709
131.099
128.803
74.021
71.037
44.269
35.681
59.852
137.206
135.003
167.299
149.744
148.569
114.681
159.592
29.690
220
200
180
160
140
120
100
80
60
40
20
0
ppm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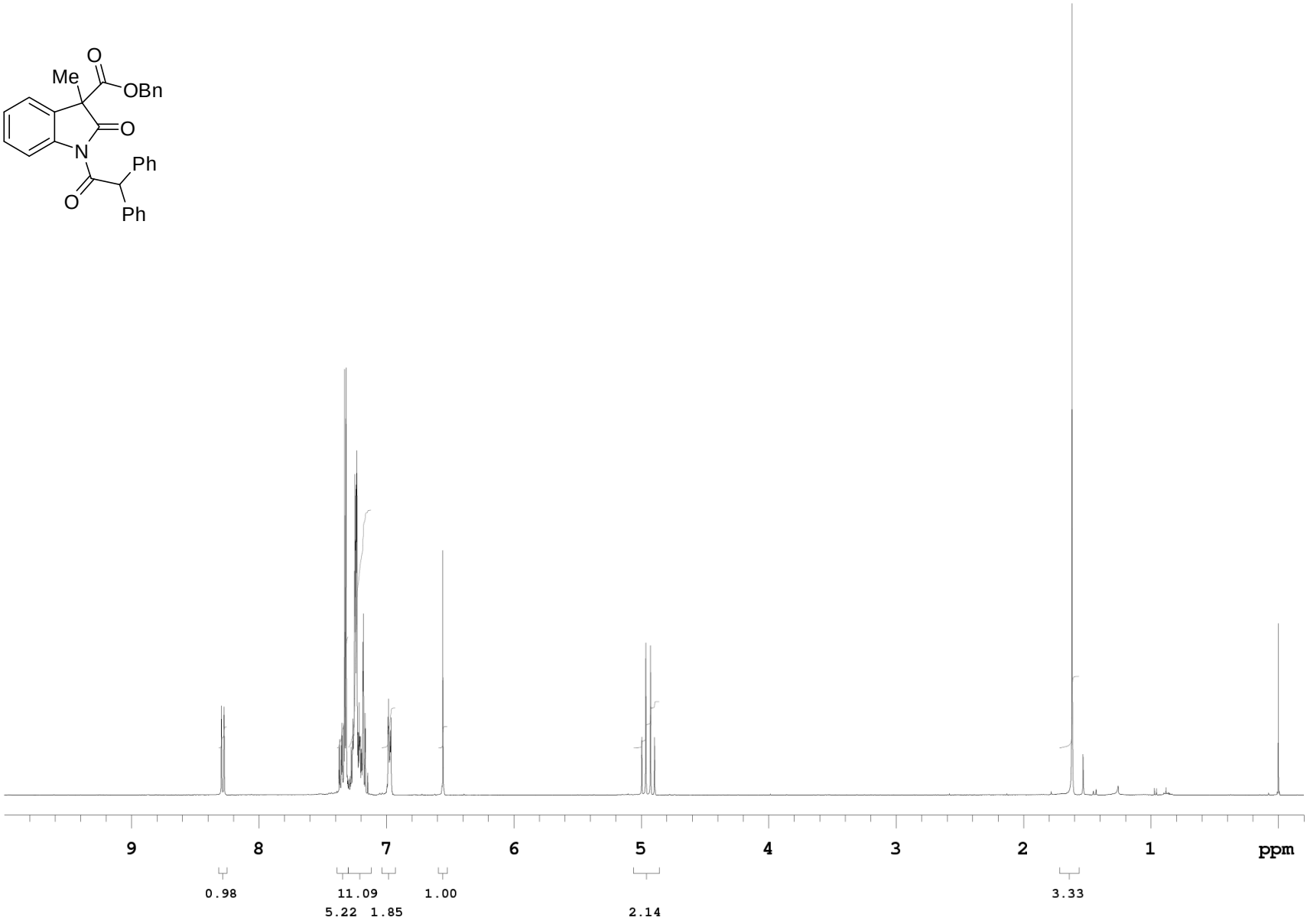
O
O
O
Ph
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.95
17.98
1.00
2.04
3.07

Me
O
O
O
Ph
N
Ph
O
Ph
170.433
151.123
138.786
136.892
133.971
132.950
129.147
129.054
128.784
128.560
128.482
128.227
127.307
125.328
123.922
118.495
116.748
105.872
77.341
77.024
76.707
71.366
58.310
7.377
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
Me
OBn
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.98
11.09
5.22
1.85
1.00
2.14
3.33

Me
O
OBn
O
N
Ph
O
Ph
129.302
129.147
128.830
128.544
128.482
128.444
128.134
127.307
127.230
127.191
125.599
129.472
122.677
116.841
140.224
138.206
138.106
135.014
174.970
173.030
168.477
77.325
77.008
76.691
67.385
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20.263
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200
180
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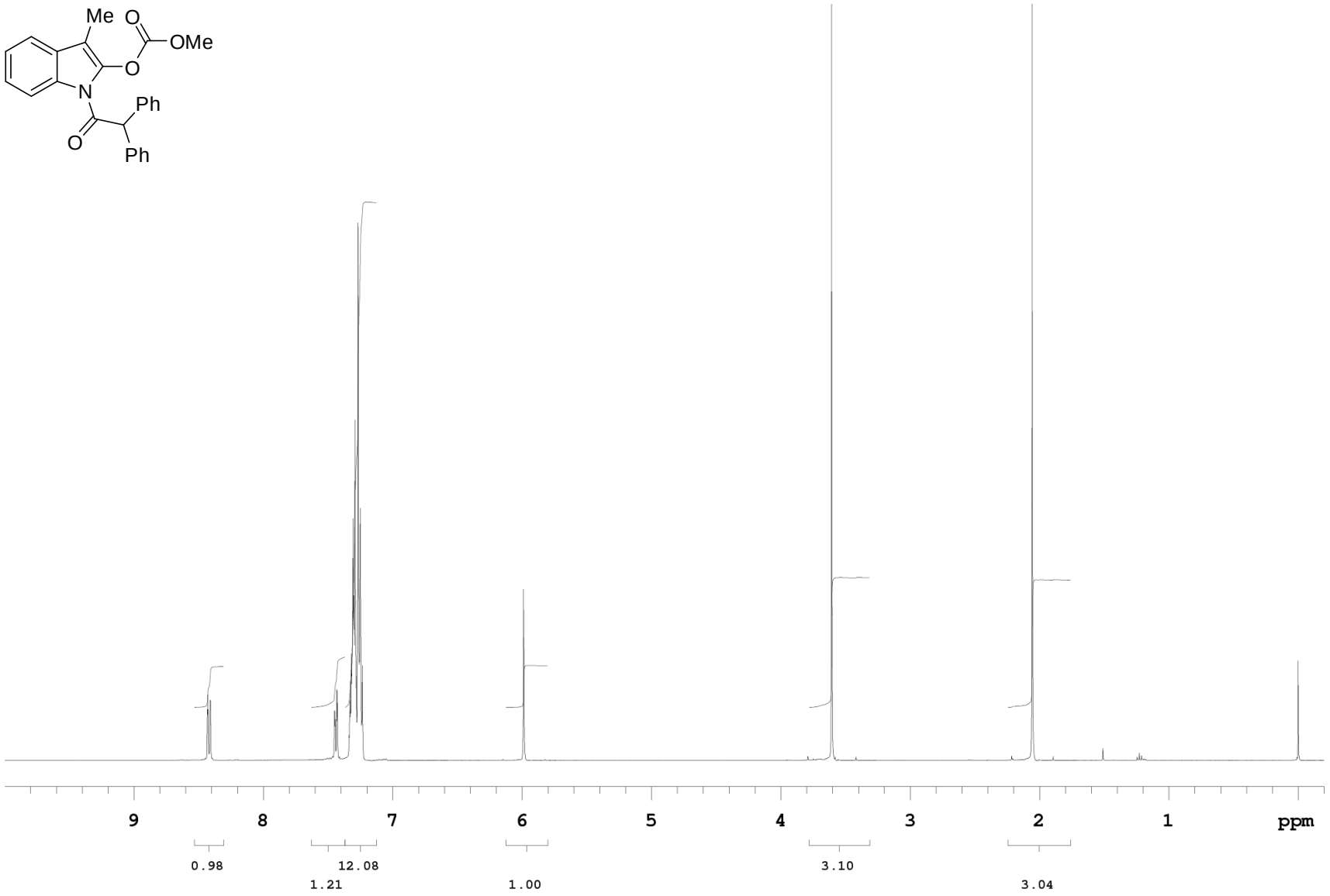
120
100
80
60
40
20
0
ppm


Me
O
OMe
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.98
12.08
1.21
1.00
3.10
3.04

Me
O
OMe
O
N
Ph
O
Ph
170.445
151.676
138.829
136.920
132.923
129.167
128.571
128.247
127.327
125.340
123.941
118.522
116.729
105.876
77.345
77.028
76.711
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7.366
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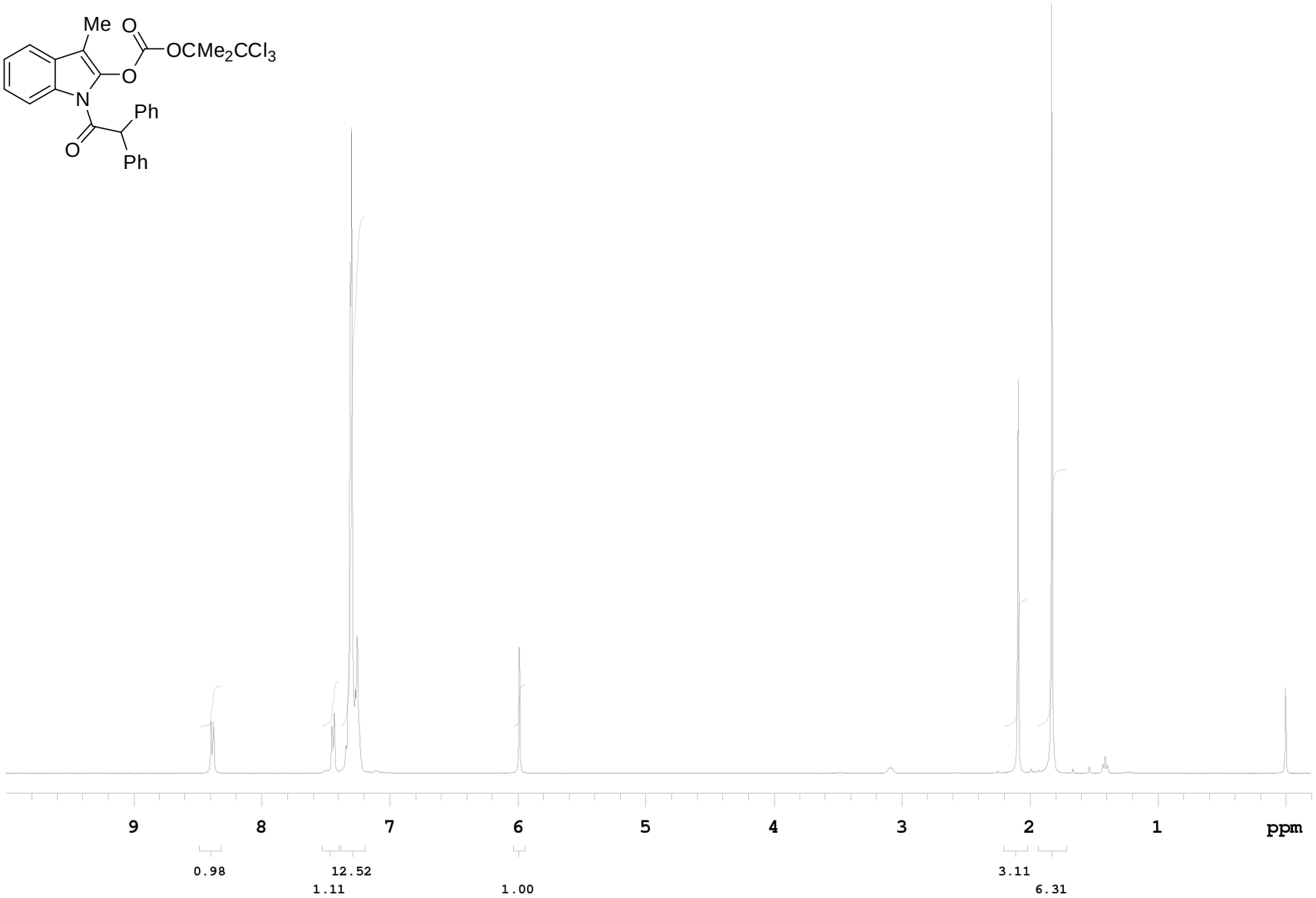
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
OCMe2CCl3
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.98
12.52
1.11
1.00
3.11
6.31

Me
O
OCMe2CCl3
O
N
Ph
O
Ph
129.077
128.675
128.111
77.333
77.209
77.008
76.691
20.850
127.369
138.747
136.753
132.965
125.390
123.929
118.510
116.578
105.934
104.612
92.081
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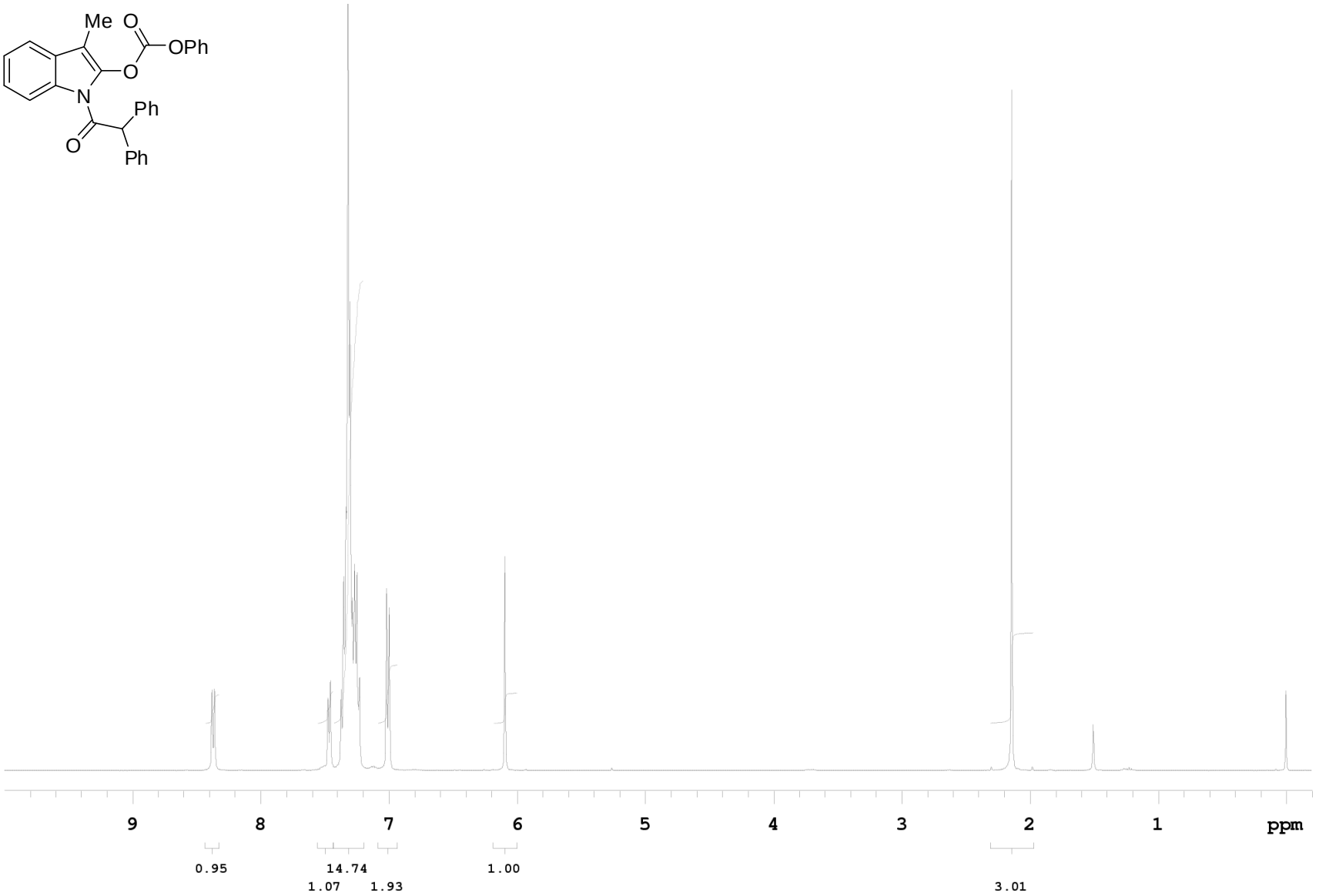
170.510
148.255
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
OPh
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.95
14.74
1.07
1.93
1.00
3.01

Me
O
OPh
O
N
Ph
O
Ph
129.137
128.759
128.187
129.547
127.445
126.602
125.443
123.982
120.387
138.815
136.883
132.848
118.687
116.522
106.118
170.539
150.696
149.591
77.354
77.037
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58.416
7.553
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200
180
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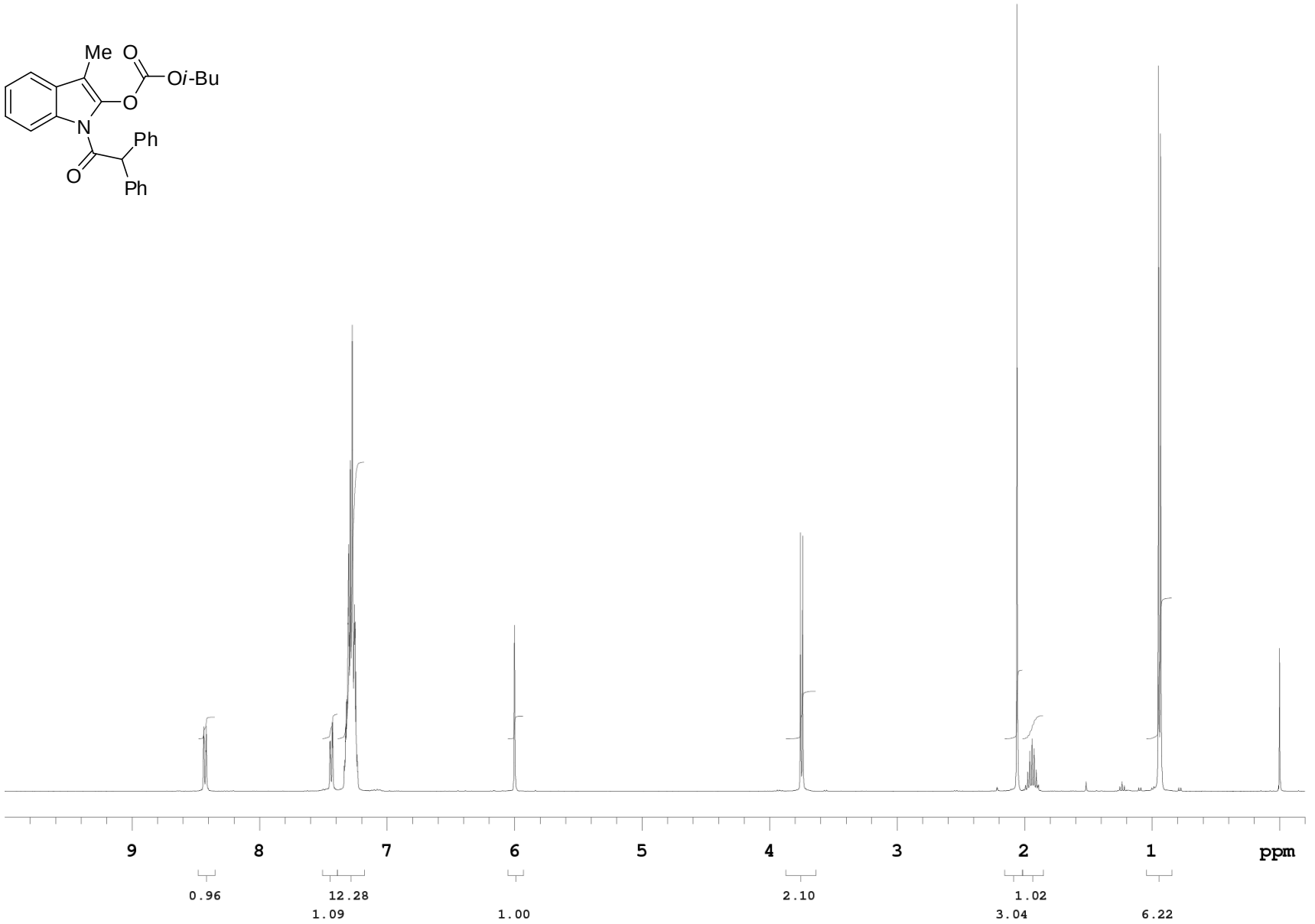
140
120
100
80
60
40
20
0
ppm


Me
O
Oi-Bu
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.96
12.28
1.09
1.00
2.10
1.02
3.04
6.22

Me
O
Oi-Bu
O
N
Ph
O
Ph
77.321
77.004
76.687
129.127
128.555
138.820
136.988
132.945
128.269
127.287
125.254
123.886
118.444
116.736
105.736
170.490
151.188
75.806
58.220
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18.759
7.380
220
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180
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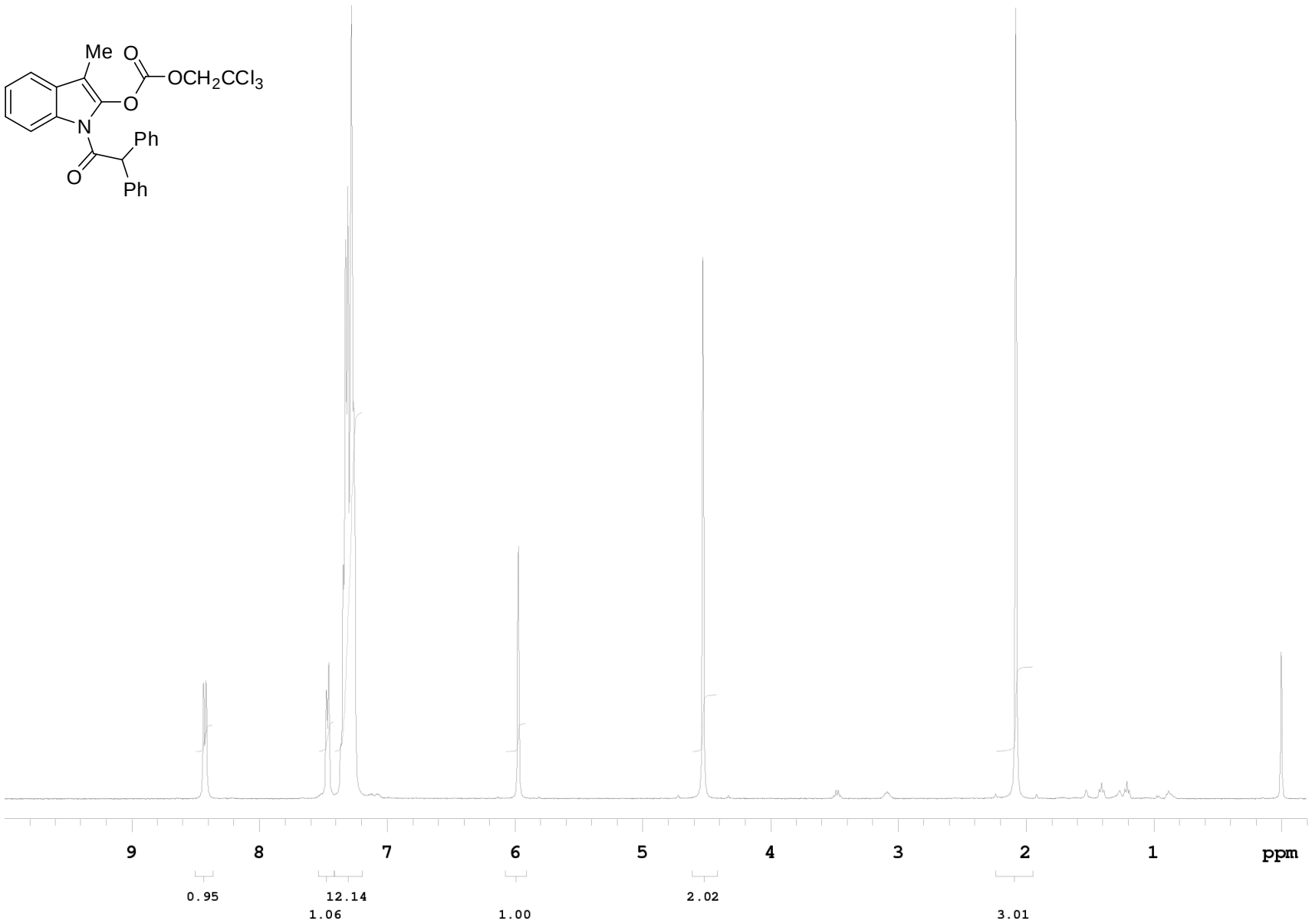
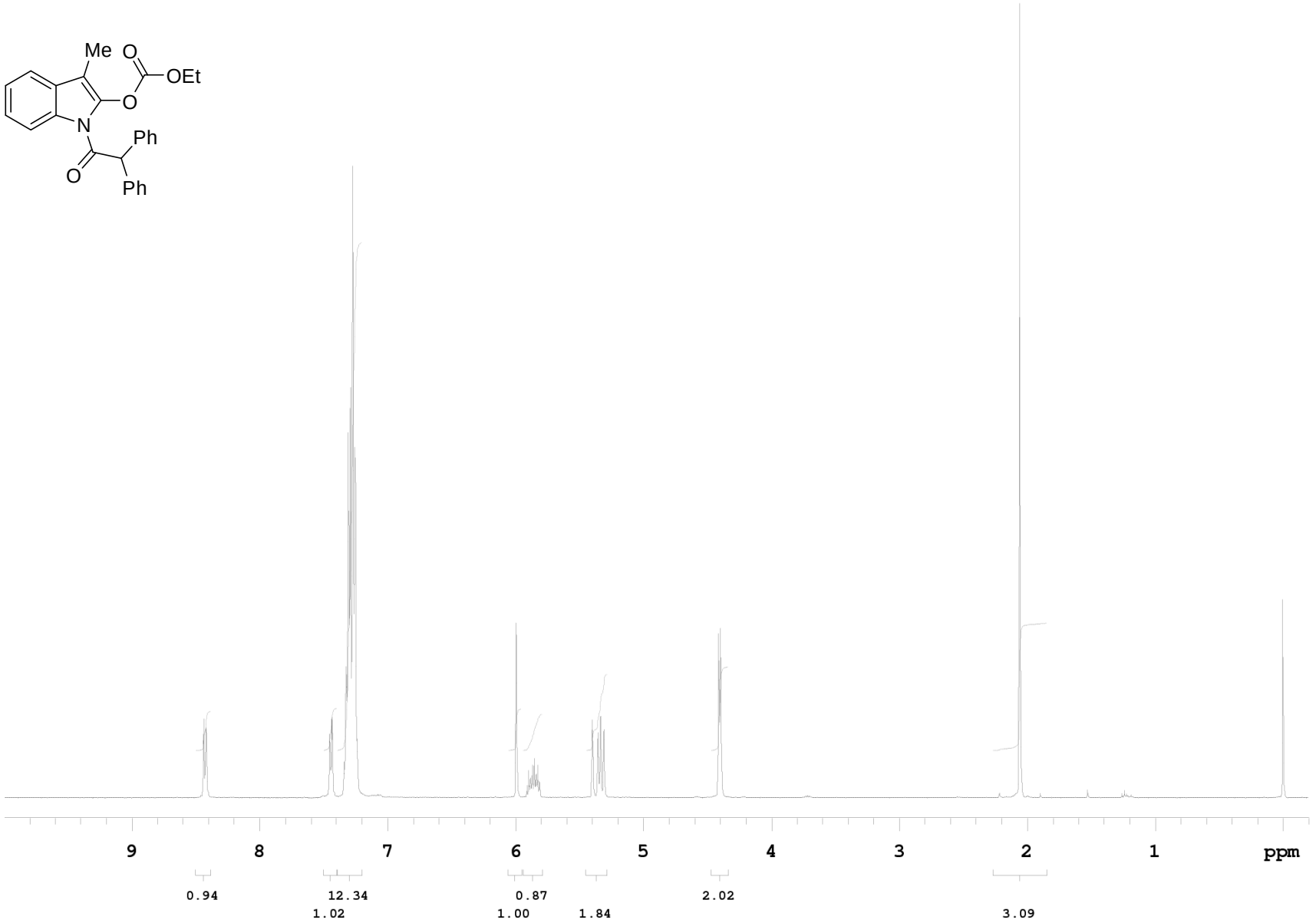
140
120
100
80
60
40
20
0
ppm


Me
O
OCH2CCl3
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.95
12.14
1.06
1.00
2.02
3.01

Me
O
OCH2CCl3
O
N
Ph
O
Ph
77.320
77.003
76.686
129.203
128.624
128.021
127.418
138.672
136.354
132.883
125.624
124.063
118.691
116.758
106.269
93.599
77.443
58.505
7.402
170.242
150.244
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
OEt
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.94
12.34
1.02
0.87
1.00
1.84
2.02
3.09

Me
O
OEt
O
N
Ph
O
Ph
77.325
77.008
76.692
129.132
128.536
128.266
127.300
138.871
136.962
132.935
125.251
123.891
118.457
116.710
105.787
170.487
151.000
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13.893
7.385
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200
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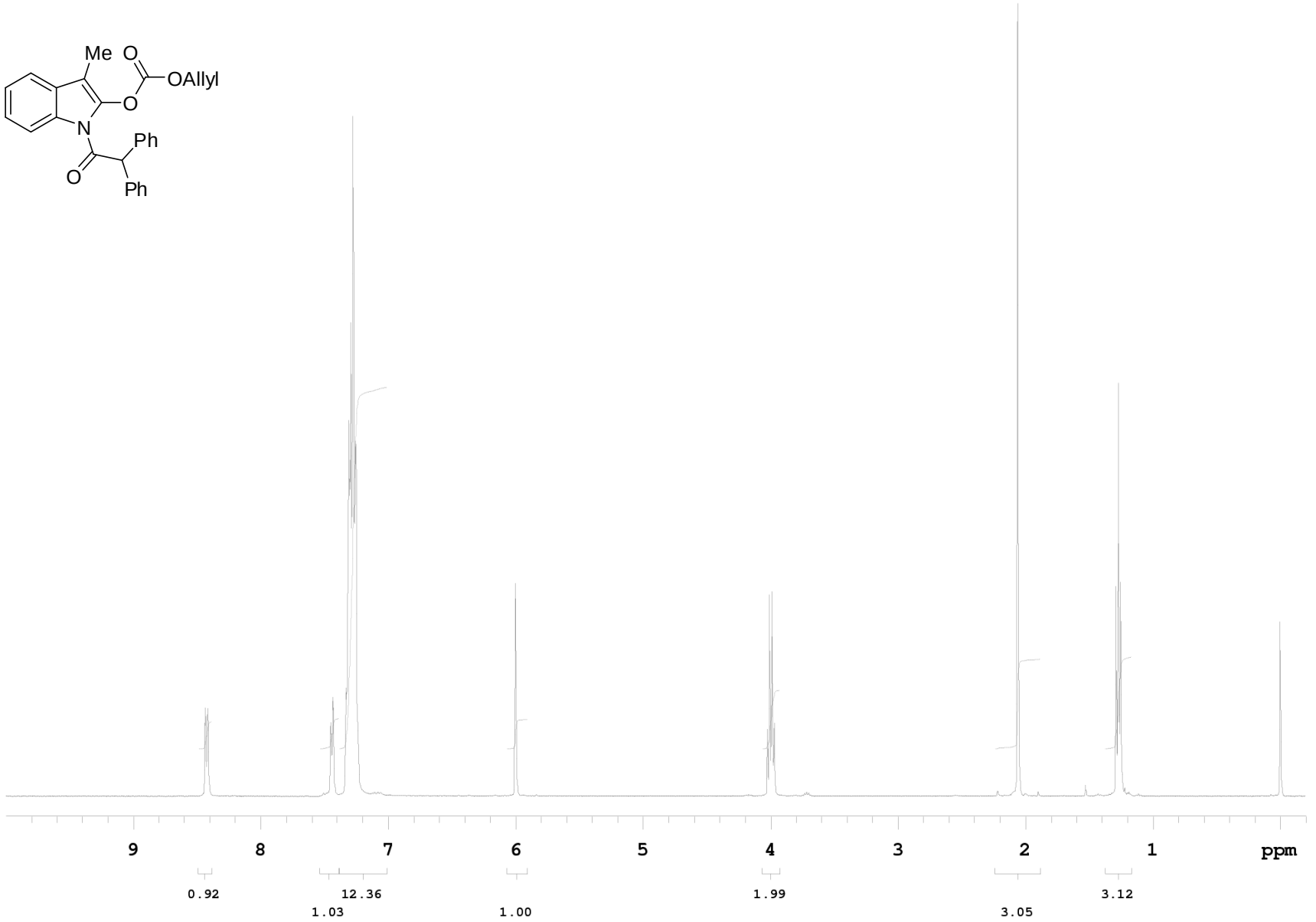
160
140
120
100
80
60
40
20
0
ppm


Me
O
OAllyl
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.92
12.36
1.03
1.00
1.99
3.05
3.12

Me
O
OAllyl
O
N
Ph
O
Ph
129.153
128.566
128.225
77.324
77.007
76.690
127.321
138.823
136.883
132.933
130.328
125.327
123.928
120.148
118.493
116.739
70.127
58.293
7.406
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150.867
170.454
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180
160
140
120
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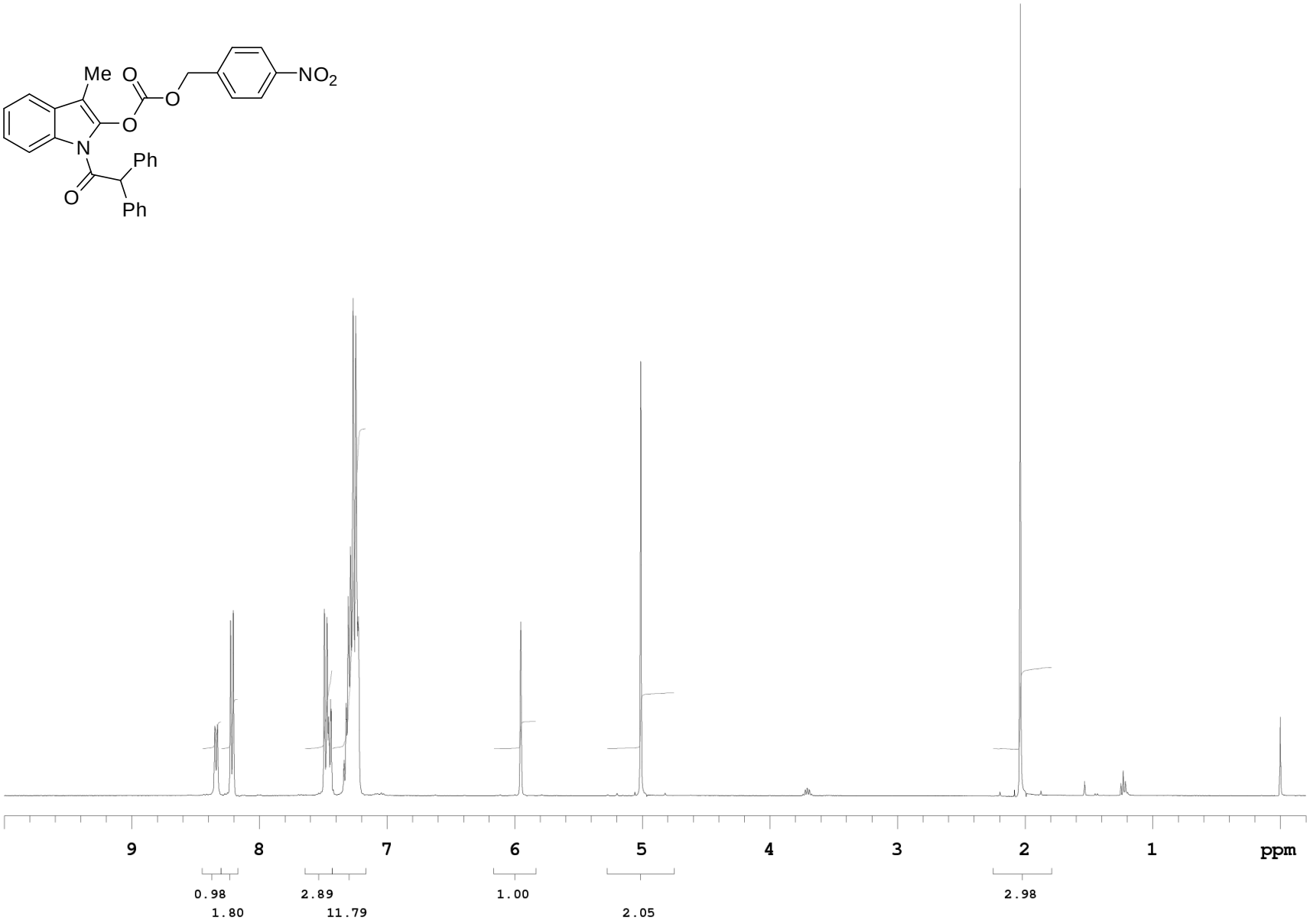
60
40
20
0
ppm


Me
O
O
O
N
O
Ph
Ph
NO2
9
8
7
6
5
4
3
2
1
ppm
0.98
1.80
2.89
11.79
1.00
2.05
2.98

Me
O
O
O
N
Ph
O
Ph
NO2
129.139
128.604
128.449
128.069
127.411
125.465
123.993
123.939
138.747
136.841
132.757
118.685
116.492
77.343
77.026
76.708
69.401
58.381
7.345
170.348
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141.002
106.077
220
200
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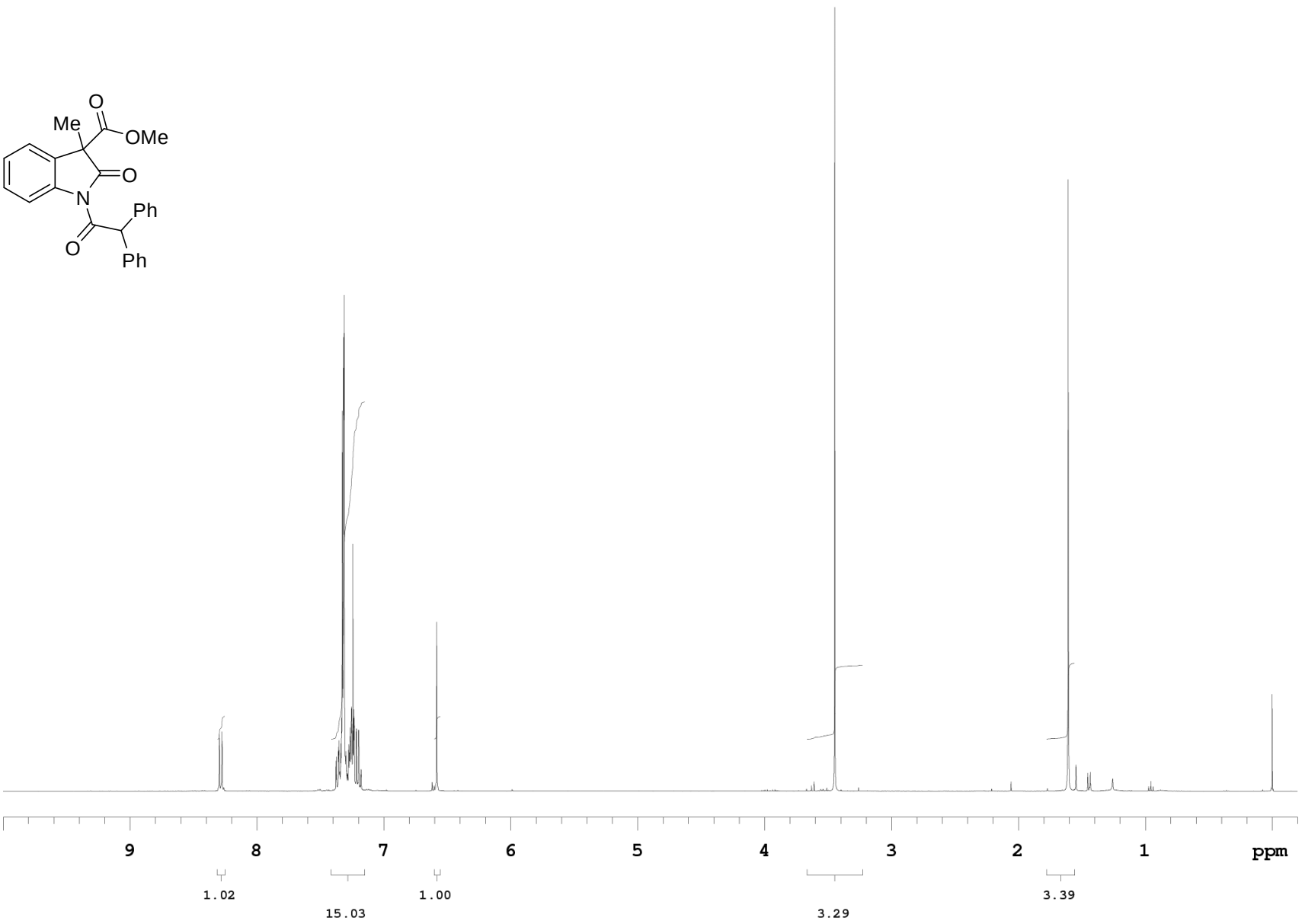
120
100
80
60
40
20
0
ppm


O
Me
OMe
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
1.02
15.03
1.00
3.29
3.39

Me
OMe
O
O
N
Ph
O
Ph
129.323
129.279
128.913
128.598
128.524
127.323
127.220
125.631
122.716
116.804
129.477
77.344
77.227
77.029
76.707
57.691
55.647
53.127
20.413
175.075
173.054
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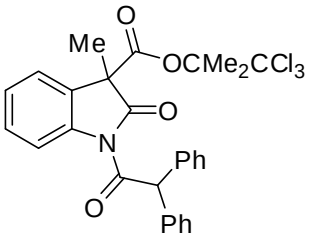
138.128
138.032
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
OCMe2CCl3
O
N
Ph
O
Ph

9
8
7
6
5
4
3
2
1
ppm
0.98
12.52
1.11
1.00
3.11
6.31

Me
O
OCMe2CCl3
O
N
Ph
O
Ph
129.077
128.675
128.111
77.333
77.209
77.008
76.691
20.850
127.369
138.747
136.753
132.965
125.390
123.929
118.510
116.578
105.934
104.612
92.081
58.054
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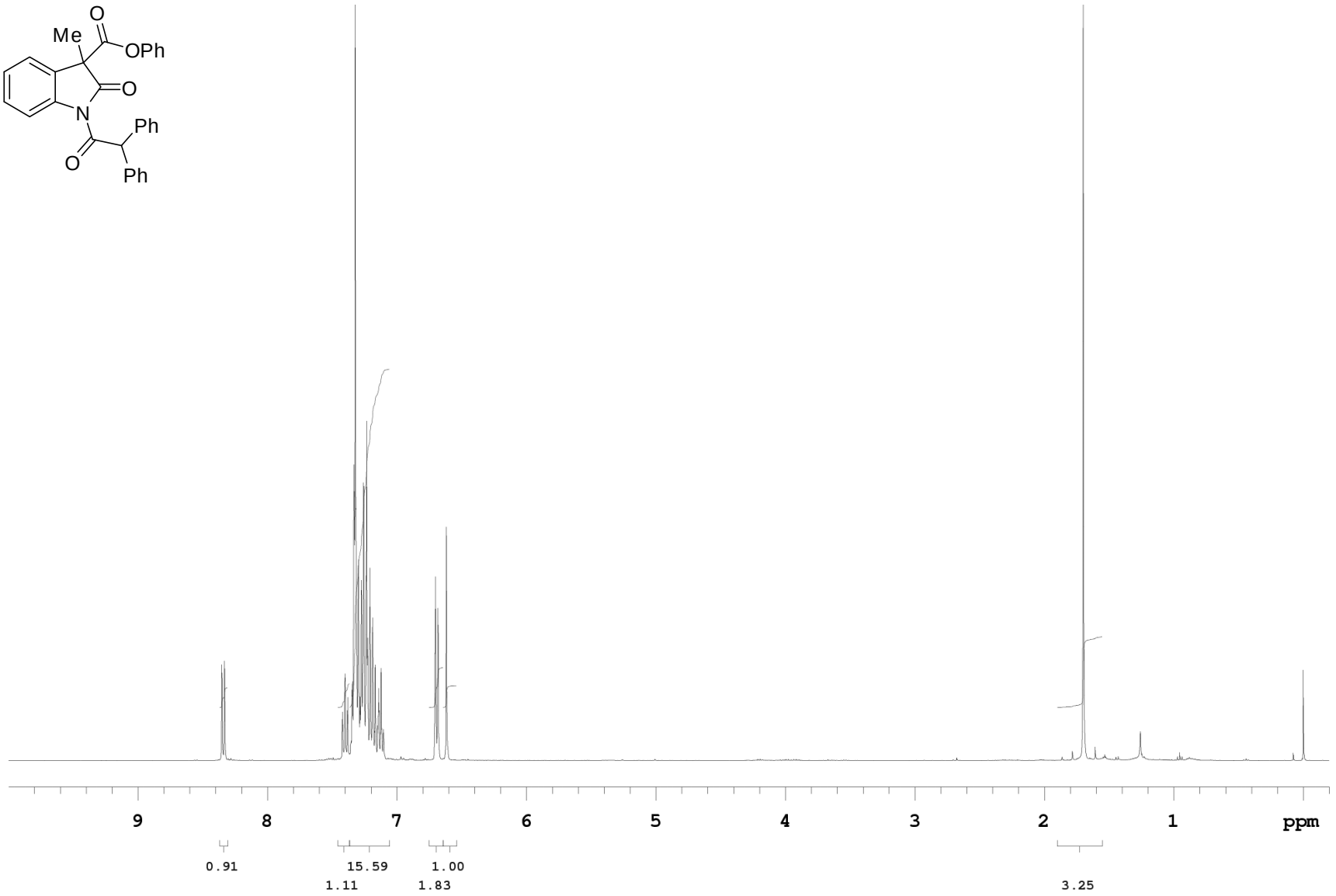
170.510
148.255
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
Me
OPh
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.91
15.59
1.11
1.00
1.83
3.25

Me
O
OPh
O
N
Ph
O
Ph
77.333
77.016
76.699
129.356
129.217
129.124
128.699
128.560
128.536
127.354
127.230
126.225
125.831
122.600
120.969
174.700
173.053
167.341
150.033
140.433
138.168
137.905
129.750
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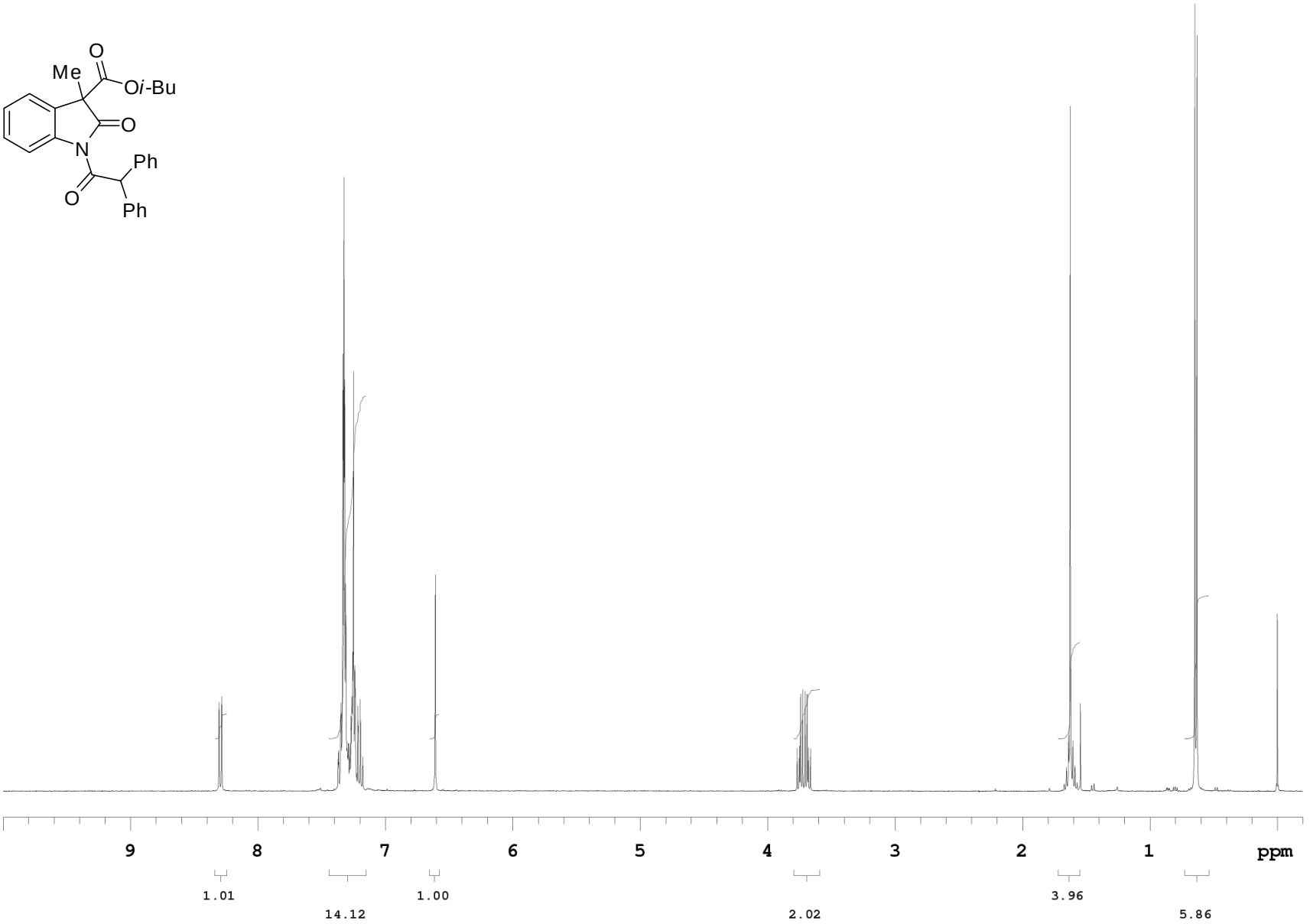
56.022
20.340
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
O*i*-Bu
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
1.01
14.12
1.00
2.02
3.96
5.86

Me
O
Oi-Bu
O
N
Ph
O
Ph
175.205
173.029
168.715
140.227
138.272
138.176
129.386
129.291
129.225
129.188
128.559
128.544
127.306
127.233
125.592
122.574
116.882
77.327
77.012
76.697
71.848
57.454
55.974
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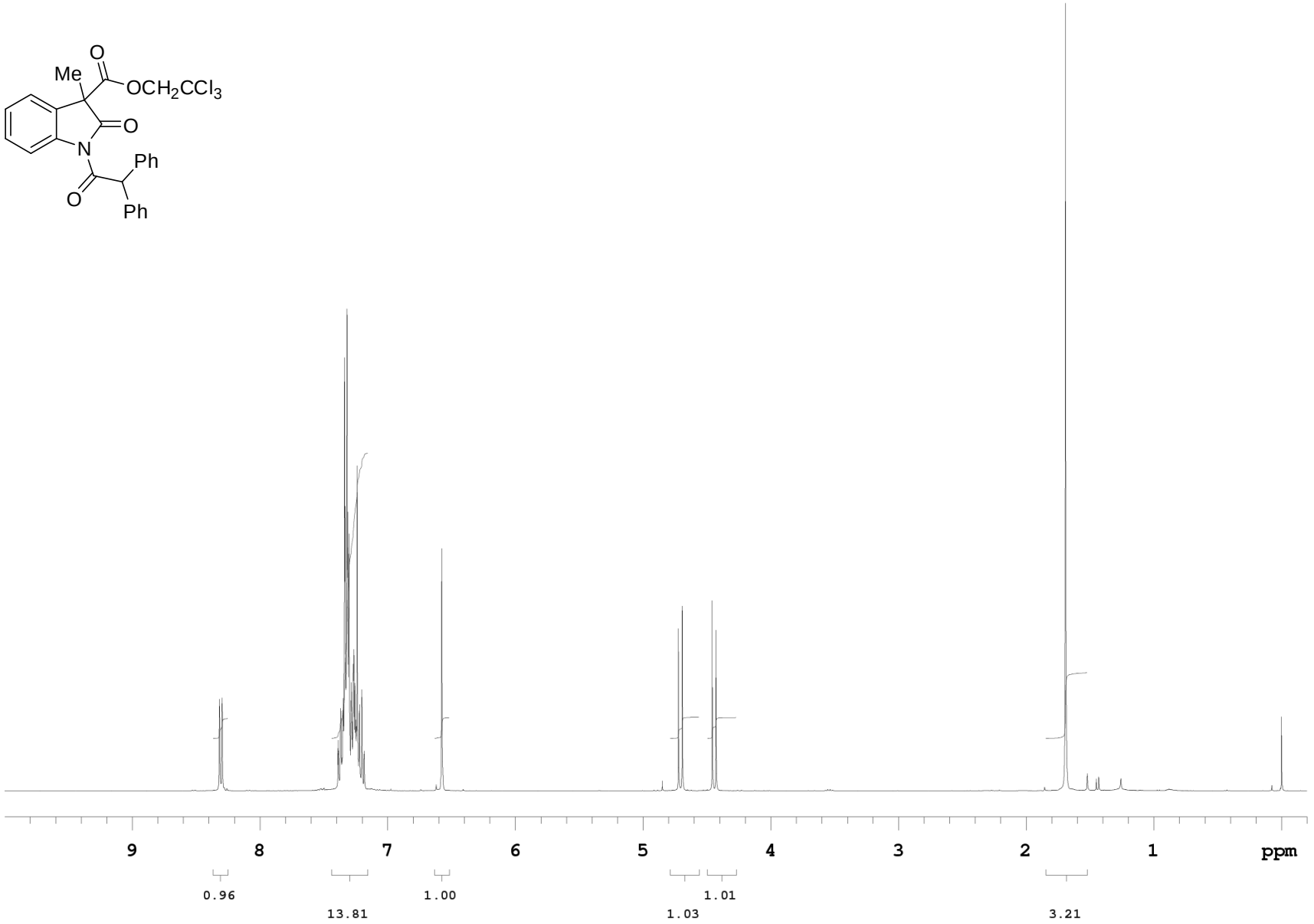
20.257
18.572
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
OCH2CCl3
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.96
13.81
1.00
1.03
1.01
3.21

Me
O
OCH2CCl3
O
N
Ph
O
Ph
174.236
172.906
167.139
140.409
138.175
138.144
129.842
129.294
129.255
128.598
128.119
127.369
127.315
125.668
122.970
117.088
94.053
77.356
77.240
77.039
76.722
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20.085
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160
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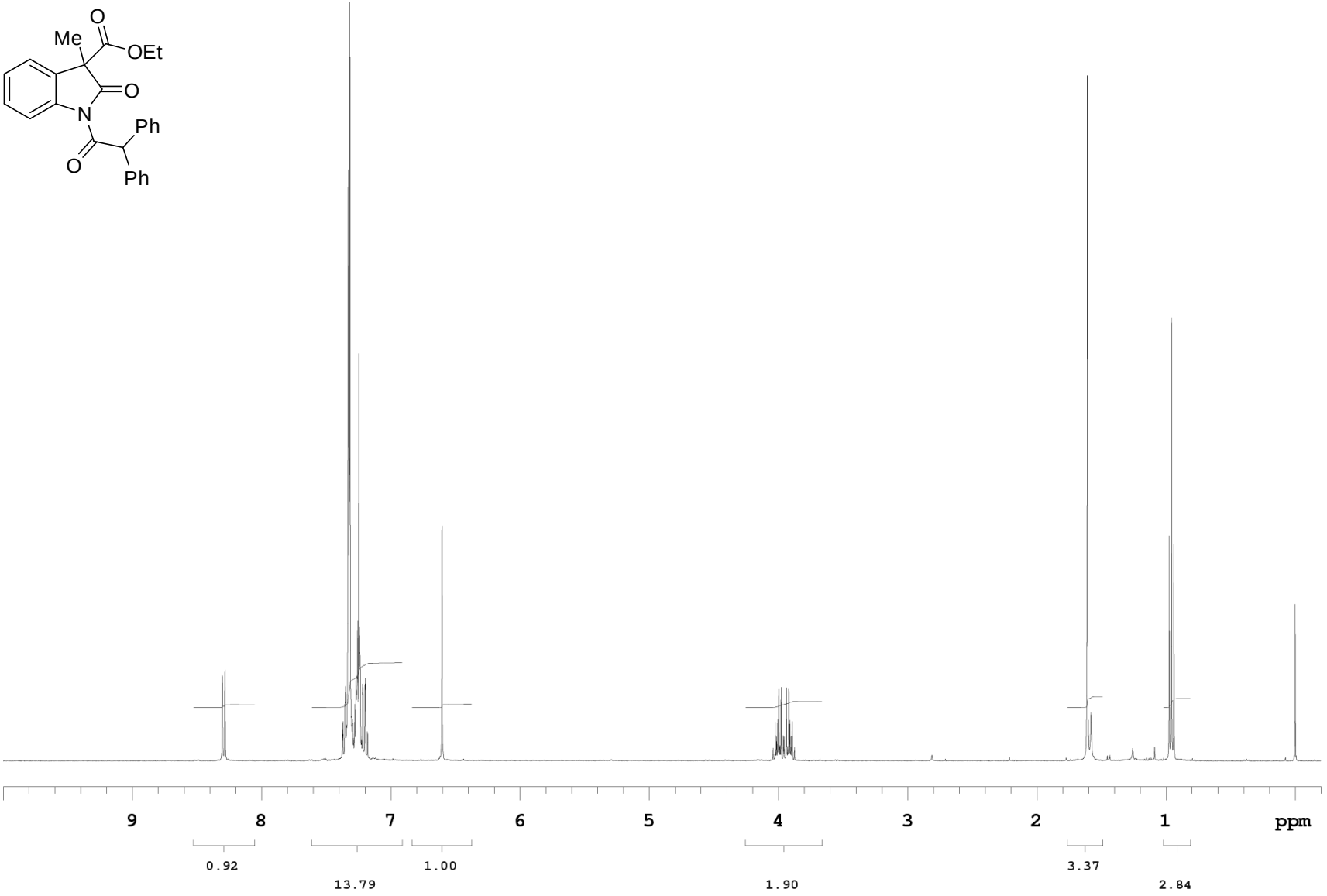
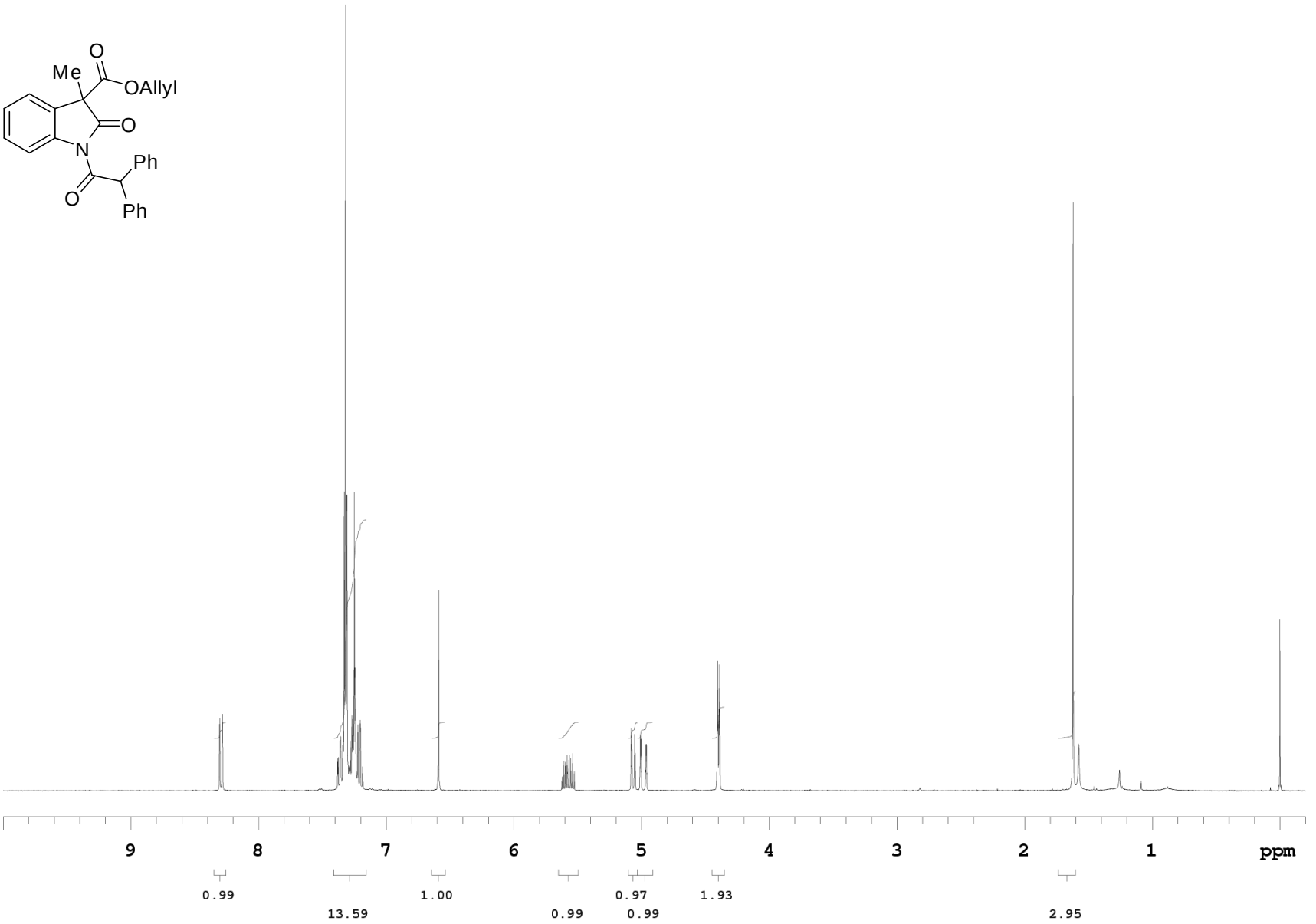
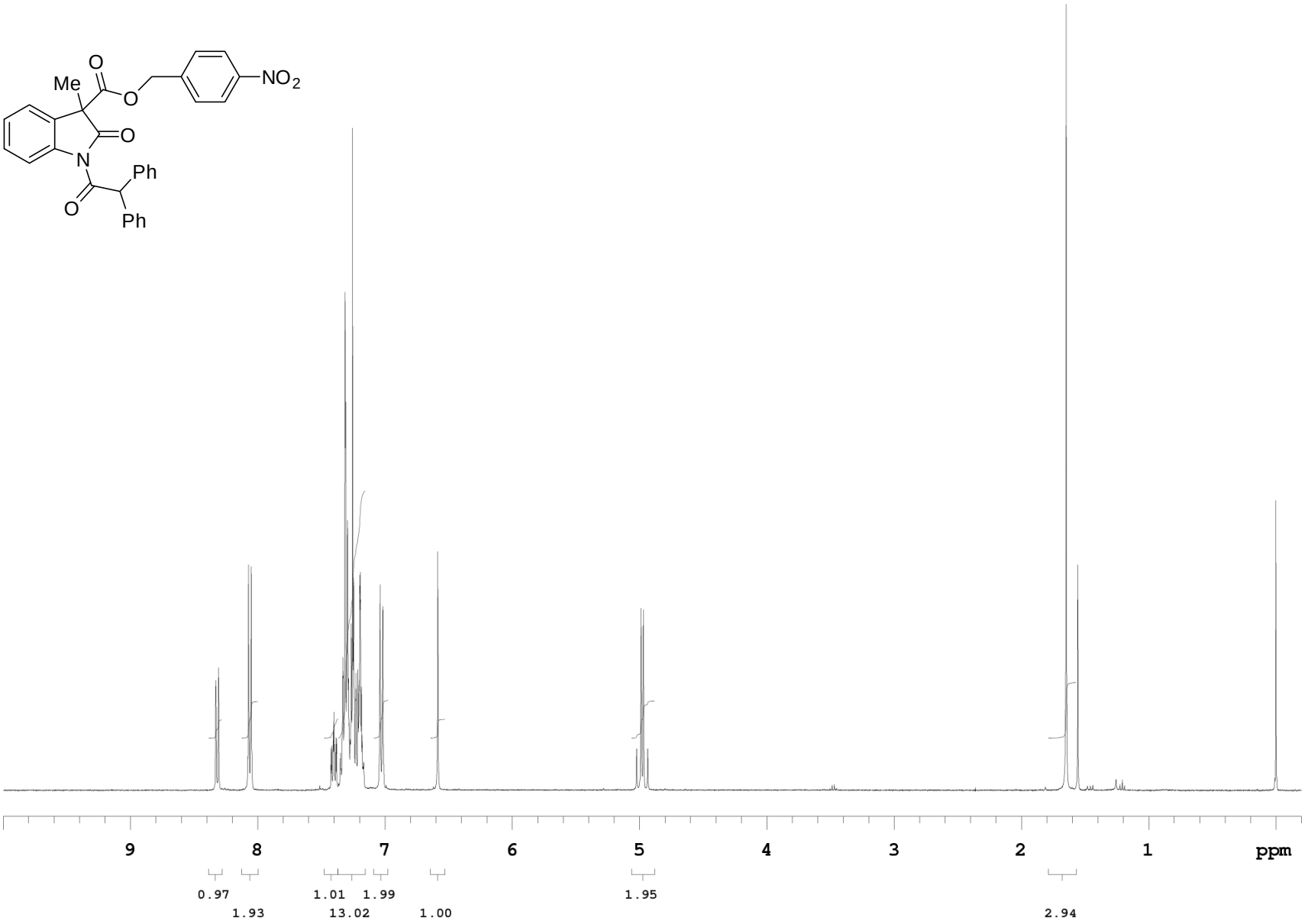
120
100
80
60
40
20
0
ppm


O
Me
OEt
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.92
13.79
1.00
1.90
3.37
2.84

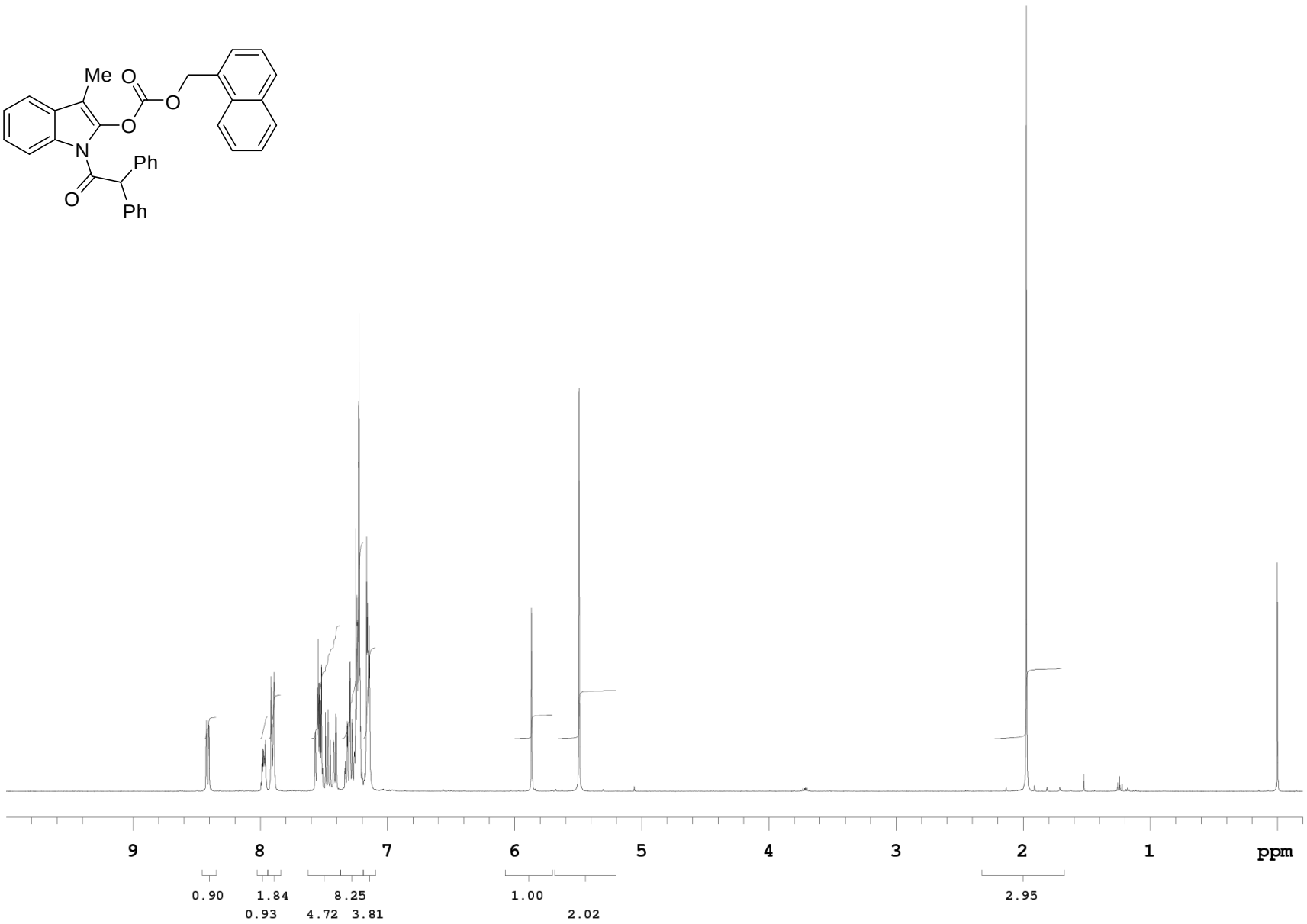
Me
OEt
O
O
N
Ph
O
Ph
129.328
129.210
129.115
128.544
128.529
129.379
127.313
127.255
125.621
122.618
116.853
77.341
77.224
77.026
76.711
62.222
57.578
55.842
20.477
13.650
175.212
173.073
168.737
140.198
138.242
138.154
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
Me
OAllyl
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.99
13.59
1.00
0.99
0.97
0.99
1.93
2.95

Me
O
OAllyl
O
N
Ph
O
Ph
175.041
173.056
168.404
140.217
138.181
138.122
130.892
129.479
129.317
129.208
128.951
128.541
127.318
127.237
125.640
122.674
118.235
116.872
77.338
77.016
76.701
66.248
57.590
55.839
20.437
220
200
180
160
140
120
100
80
60
40
20
0
ppm


O
Me
O
NO2
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.97
1.93
1.01
13.02
1.99
1.00
1.95
2.94

Me
O
O
O
N
Ph
O
Ph
NO2
129.309
129.141
128.569
128.547
128.503
127.419
127.361
127.295
125.756
123.720
77.338
77.220
77.023
76.700
129.800
122.621
116.996
138.107
138.019
147.571
142.231
140.297
174.798
172.967
168.271
65.661
57.648
55.853
20.180
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Me
O
O
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
0.90
1.84
0.93
8.25
4.72
3.81
1.00
2.02
2.95

Me
O
O
O
N
Ph
O
Ph
128.884
128.528
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128.141
127.253
126.951
126.224
125.312
125.212
123.898
123.163
118.494
116.724
105.887
77.325
77.216
77.008
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129.525
151.223
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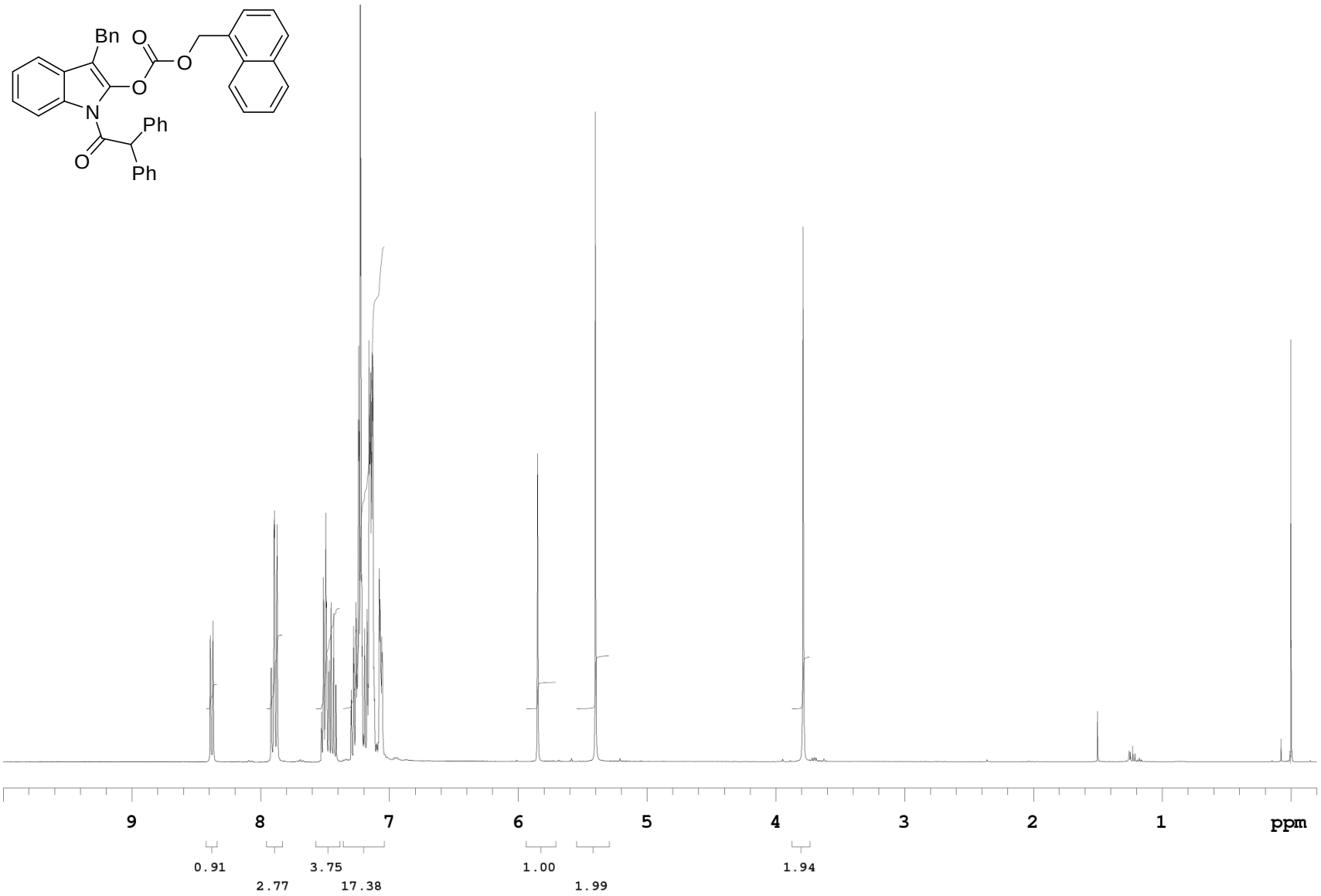
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3.75
17.38
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1.99
1.94

Bn
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O
O
N
Ph
O
Ph
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123.197
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133.085
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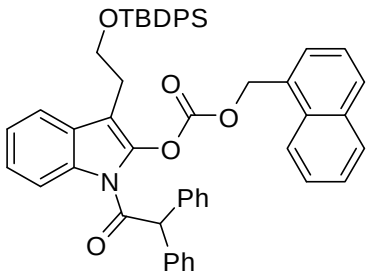
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O
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Ph

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ppm
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1.00
2.01
2.04
2.02
9.33

OTBDPS
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O
N
Ph
O
Ph
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77.215
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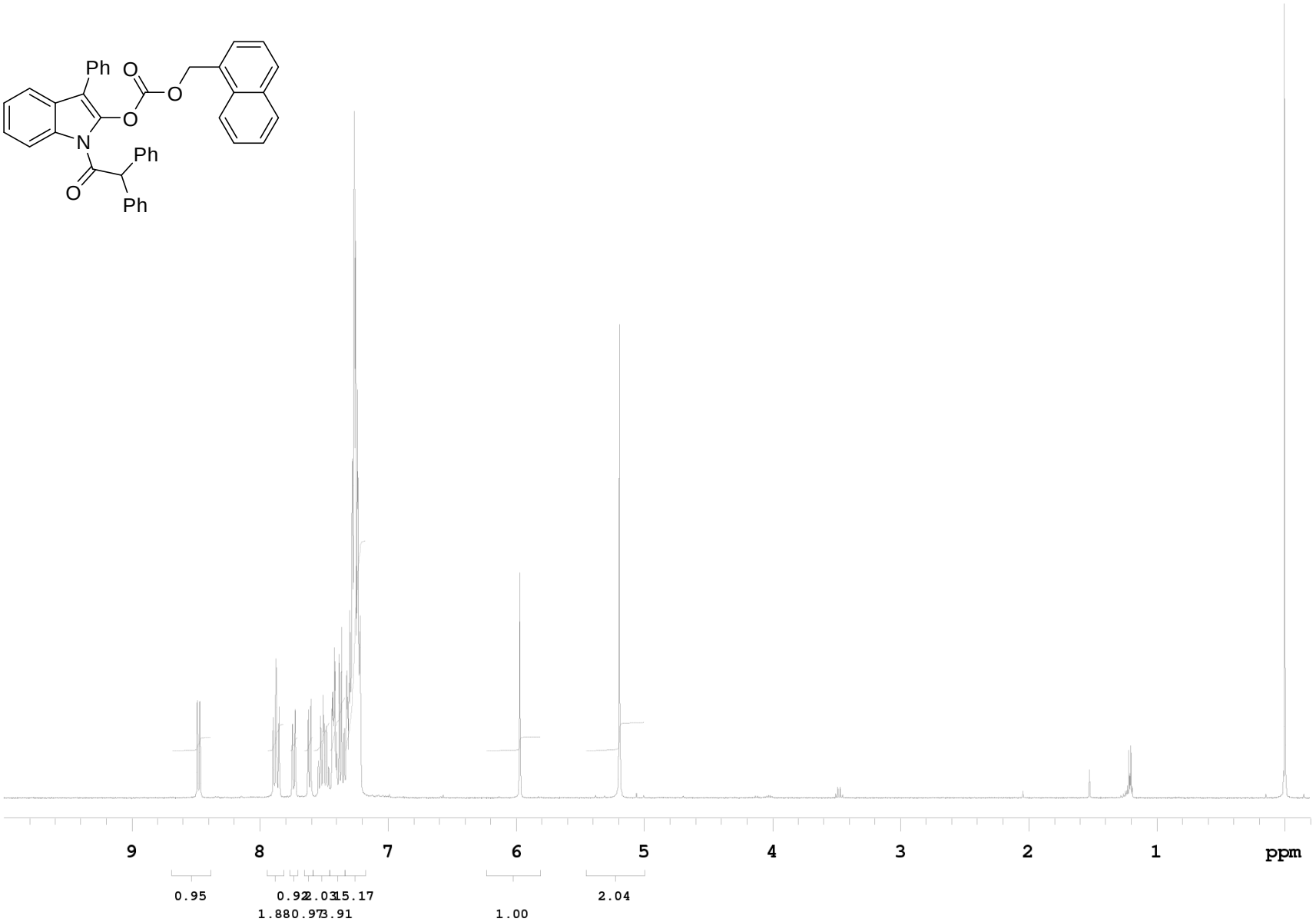
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Ph
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7
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5
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1
ppm
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2.03
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1.88
0.97
3.91
1.00
2.04

Ph
O
O
O
N
Ph
O
Ph
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125.588
125.107
124.324
123.131
119.411
116.761
111.244
77.326
77.210
77.008
76.691
69.592
58.689
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136.537
133.693
133.065
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130.524
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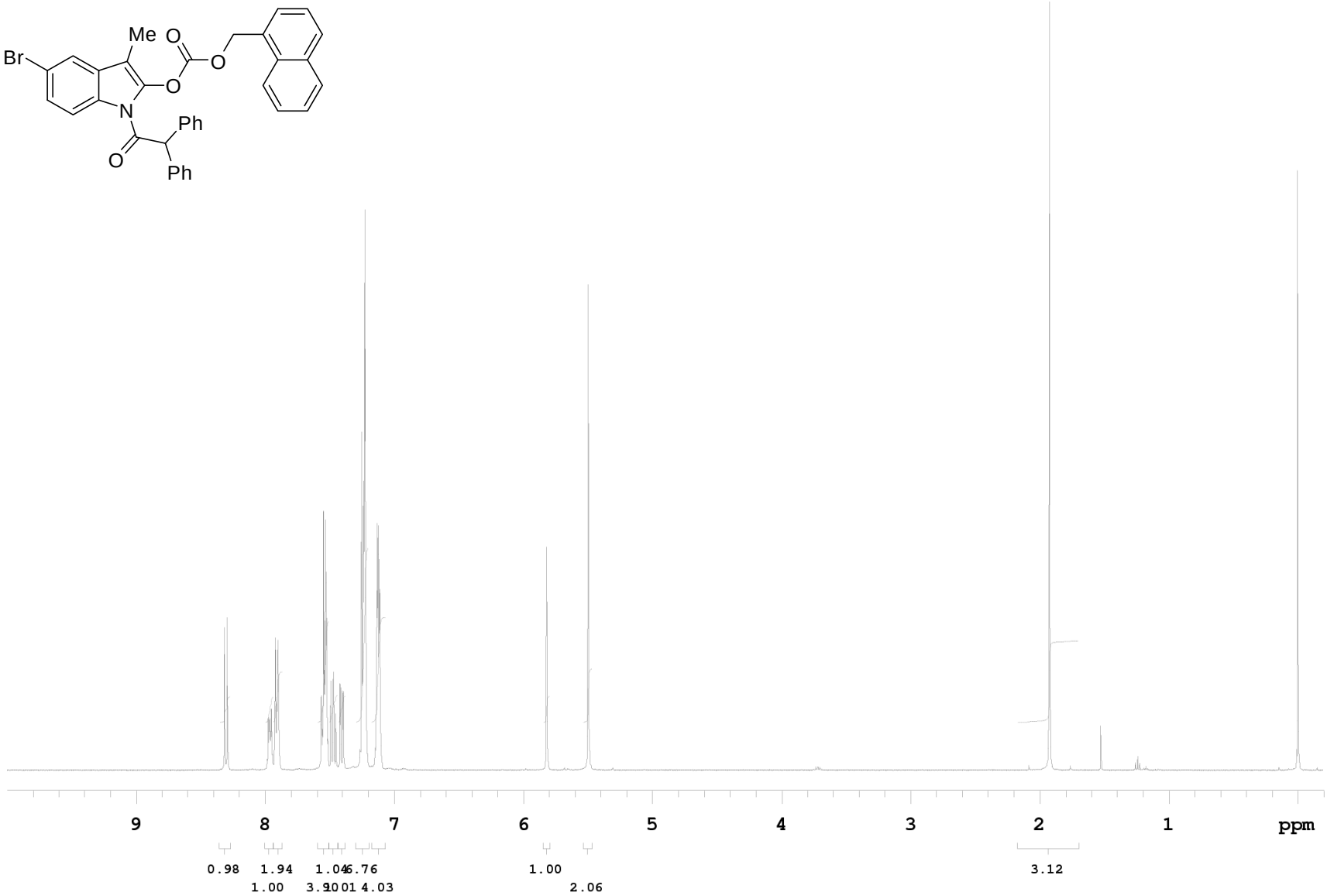
Br
Me
O
O
O
N
O
Ph
Ph
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8
7
6
5
4
3
2
1
ppm
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1.94
1.00
1.04
3.91
1.00
6.76
1.01
4.03
1.00
2.06
3.12

Br
Me
O
O
O
N
O
Ph
Ph
129.198
129.051
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128.588
128.472
127.382
127.250
126.609
125.967
125.704
125.009
122.937
118.454
118.338
132.352
131.146
130.551
129.933
129.623
139.085
137.972
137.763
133.604
174.078
172.842
167.887
77.330
77.214
77.013
76.696
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120
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20
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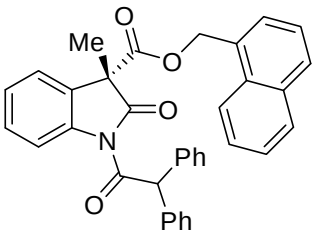
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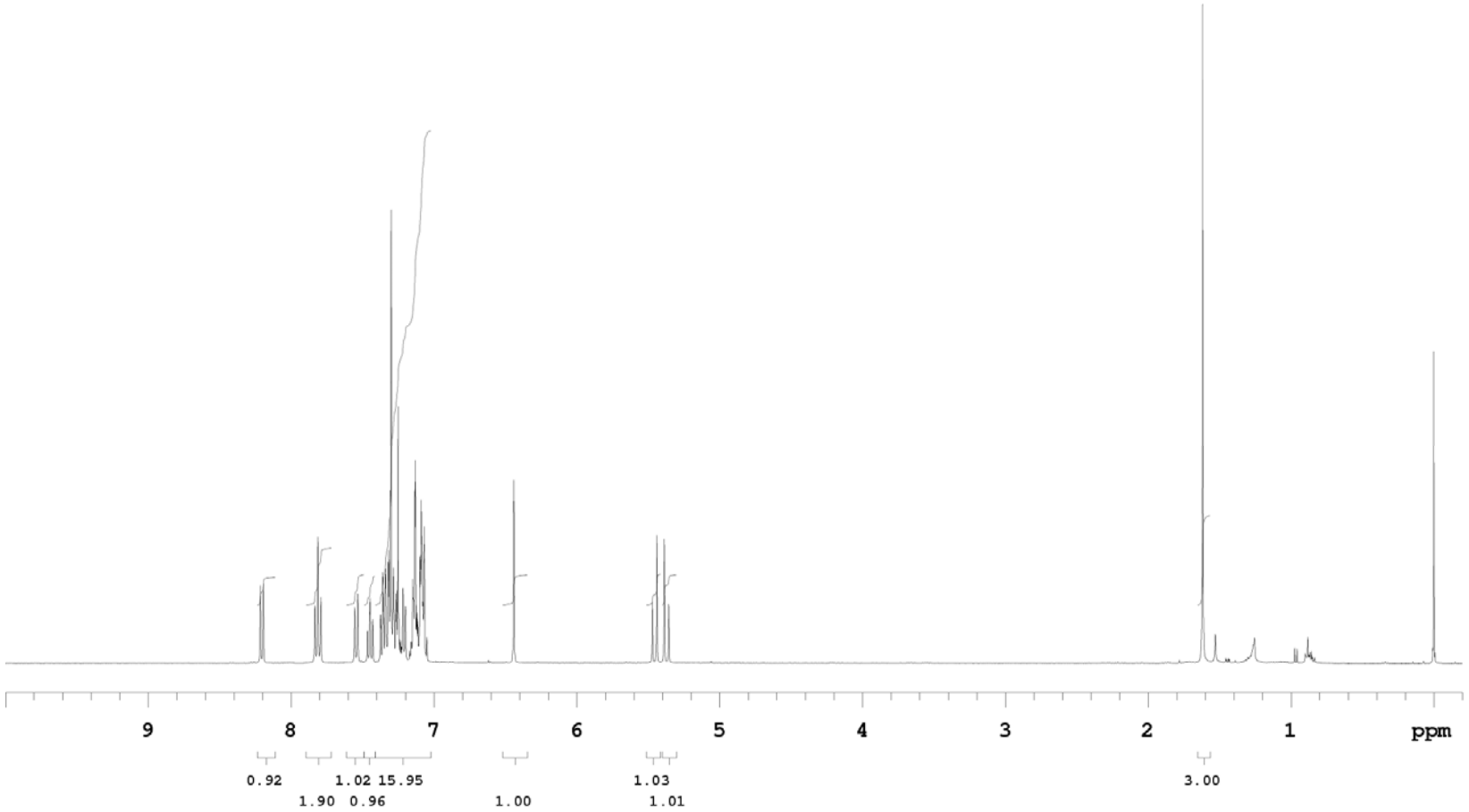
O
O
N
Ph
O
Ph


9
8
7
6
5
4
3
2
1
ppm
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1.90
1.02
0.96
15.95
1.00
1.03
1.01
3.00

Me
O
O
O
N
O
Ph
Ph
129.198
129.051
128.649
128.588
128.472
77.330
77.214
77.013
76.696
132.352
131.146
130.551
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127.382
127.250
126.609
125.967
125.704
125.009
122.937
118.454
118.338
139.085
137.972
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174.078
172.842
167.887
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120
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80
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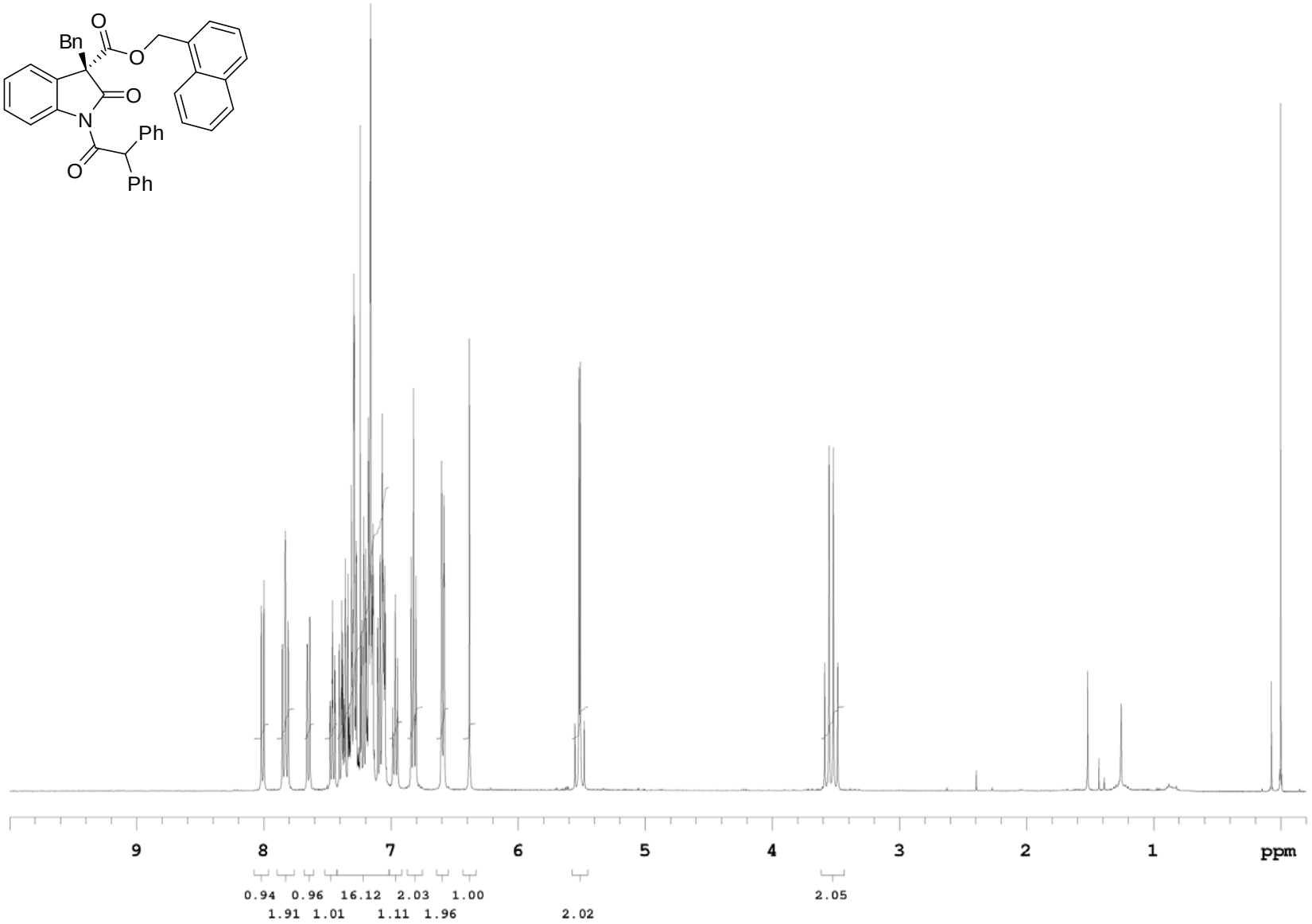
40
20
0
ppm


Bn
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O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
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0.96
16.12
2.03
1.00
1.91
1.01
1.11
1.96
2.02
2.05

Bn
O
O
O
N
O
Ph
Ph
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172.953
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140.147
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133.530
131.118
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129.387
129.286
129.232
129.023
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128.536
128.521
128.366
127.253
127.075
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125.468
125.027
123.063
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77.178
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66.403
57.475
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120
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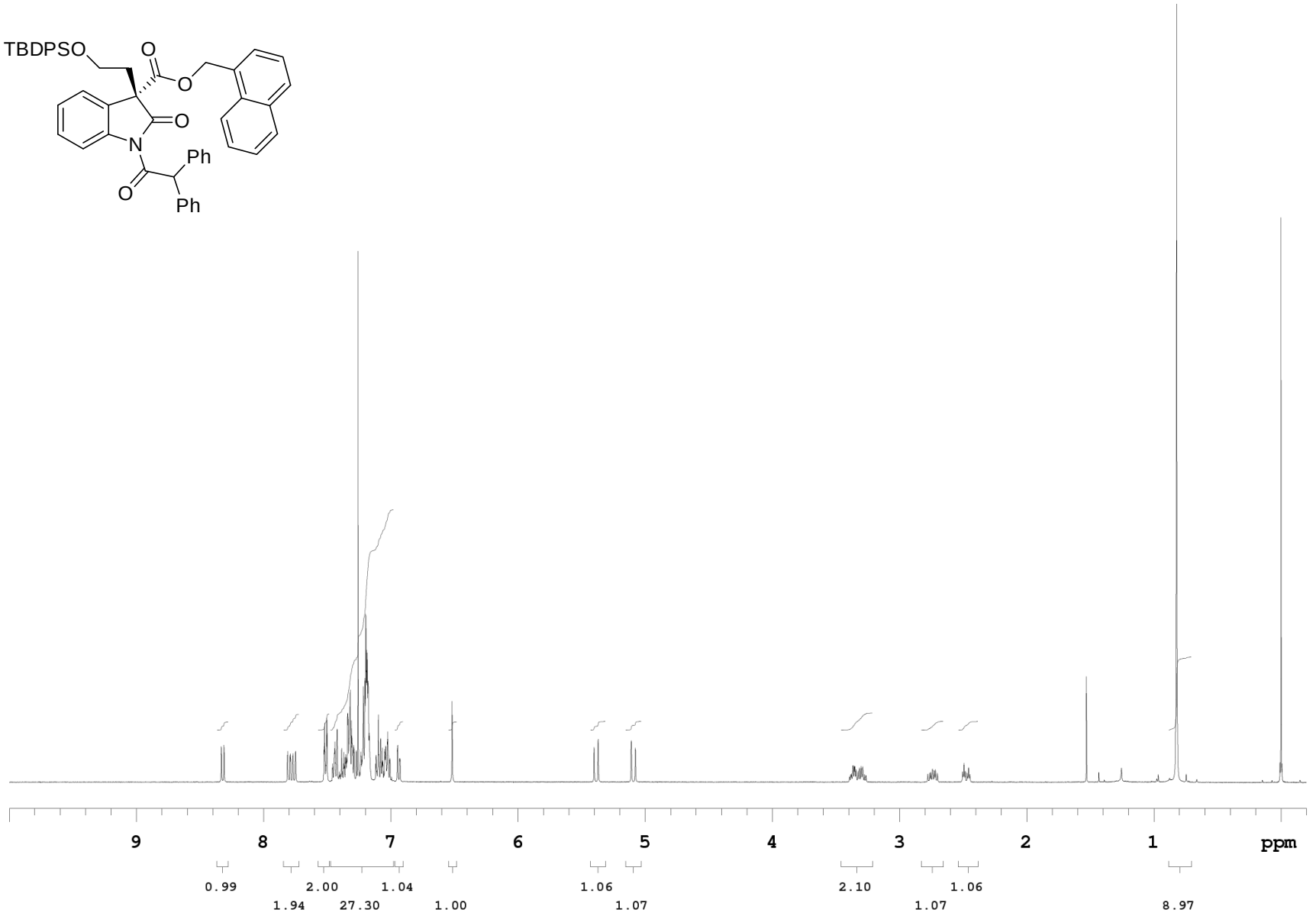
0
ppm


TBDPSO
O
O
O
N
Ph
O
Ph
9
8
7
6
5
4
3
2
1
ppm
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2.00
27.30
1.04
1.00
1.06
1.07
2.10
1.07
1.06
8.97

TBDPSO
O
O
O
N
O
Ph
Ph
135.478
135.315
135.261
133.437
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129.495
129.317
128.985
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57.537
44.682
35.066
26.570
26.524
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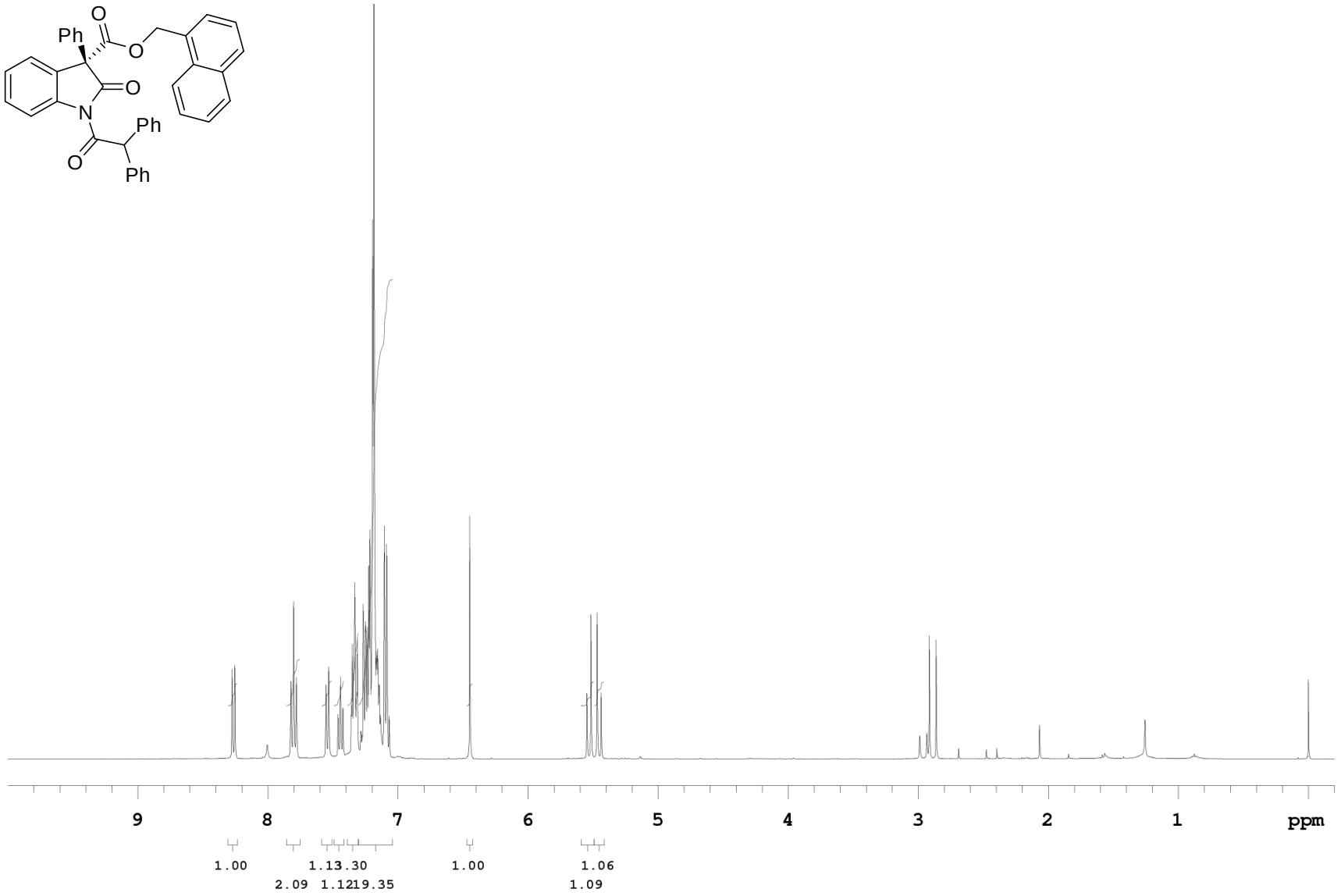
O
Ph
O
O
N
Ph
O
Ph
9
8
7
6
5
4
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2
1
ppm
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2.09
1.13
1.12
3.30
19.35
1.00
1.06
1.09

Ph
O
O
O
N
Ph
O
Ph
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130.082
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129.077
128.583
128.536
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127.315
127.160
126.465
126.032
125.885
125.498
125.344
125.050
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77.032
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120
100
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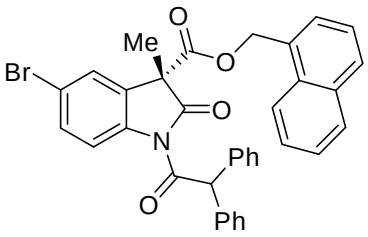
60
40
20
0
ppm


Me
O
O
Br
O
N
Ph
O
Ph

9
8
7
6
5
4
3
2
1
ppm
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1.99
1.08
0.50
6.00
1.00
1.06
1.05
3.35

Br
Me
O
O
O
N
O
Ph
Ph
174.078
172.842
167.887
139.085
137.972
137.763
133.604
132.352
131.146
130.551
129.933
129.623
129.198
129.051
128.649
128.588
128.472
127.382
127.250
126.609
125.967
125.704
125.009
122.937
118.454
118.338
77.330
77.214
77.013
76.696
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55.872
20.005
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200
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120
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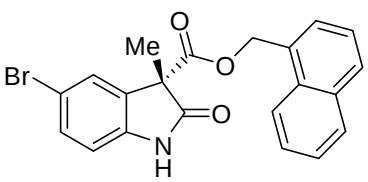
40
20
0
ppm


Me
O
O
Br
O
N
H

9
8
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ppm
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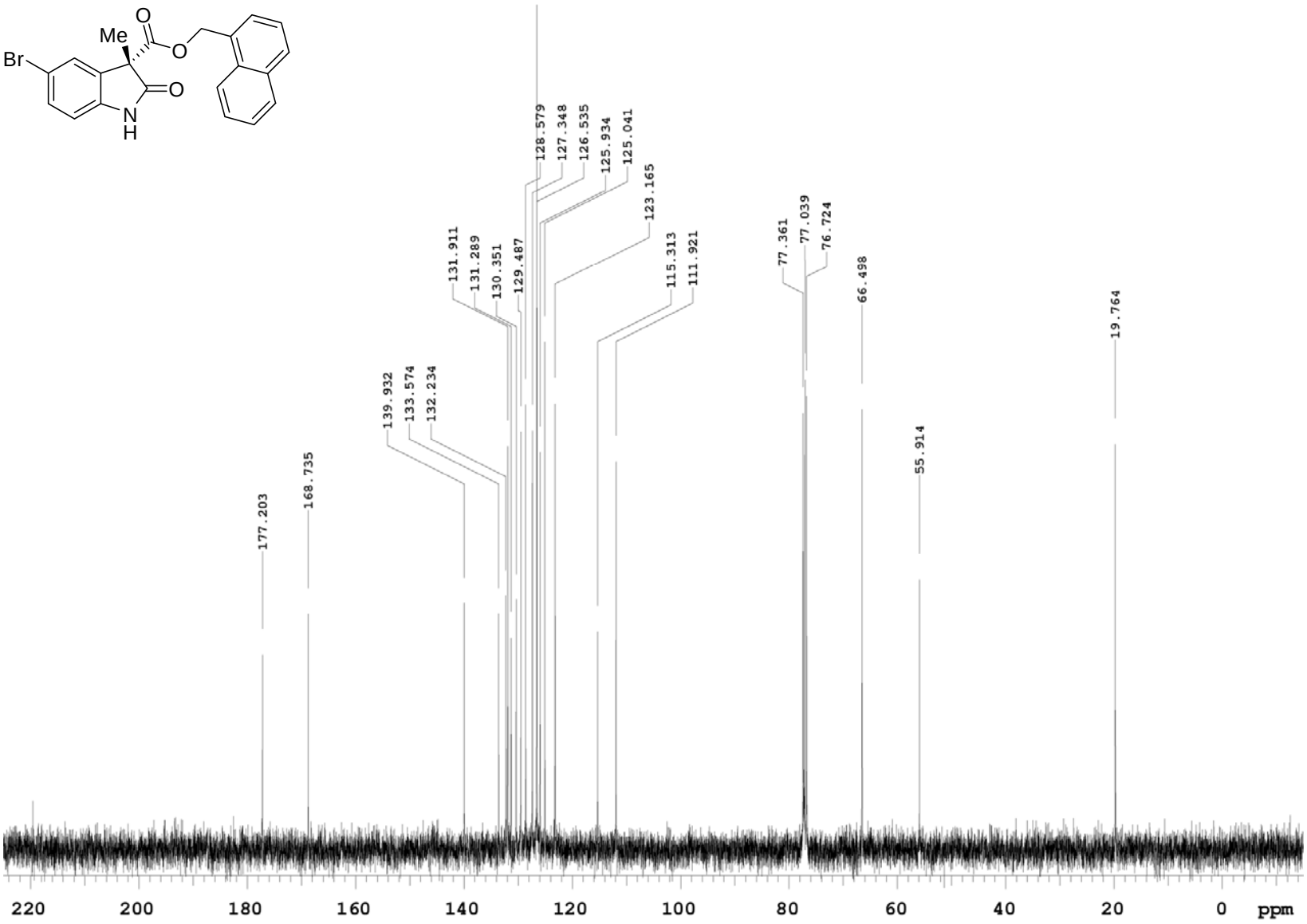
Br
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131.289
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126.535
125.934
125.041
123.165
115.313
111.921
77.361
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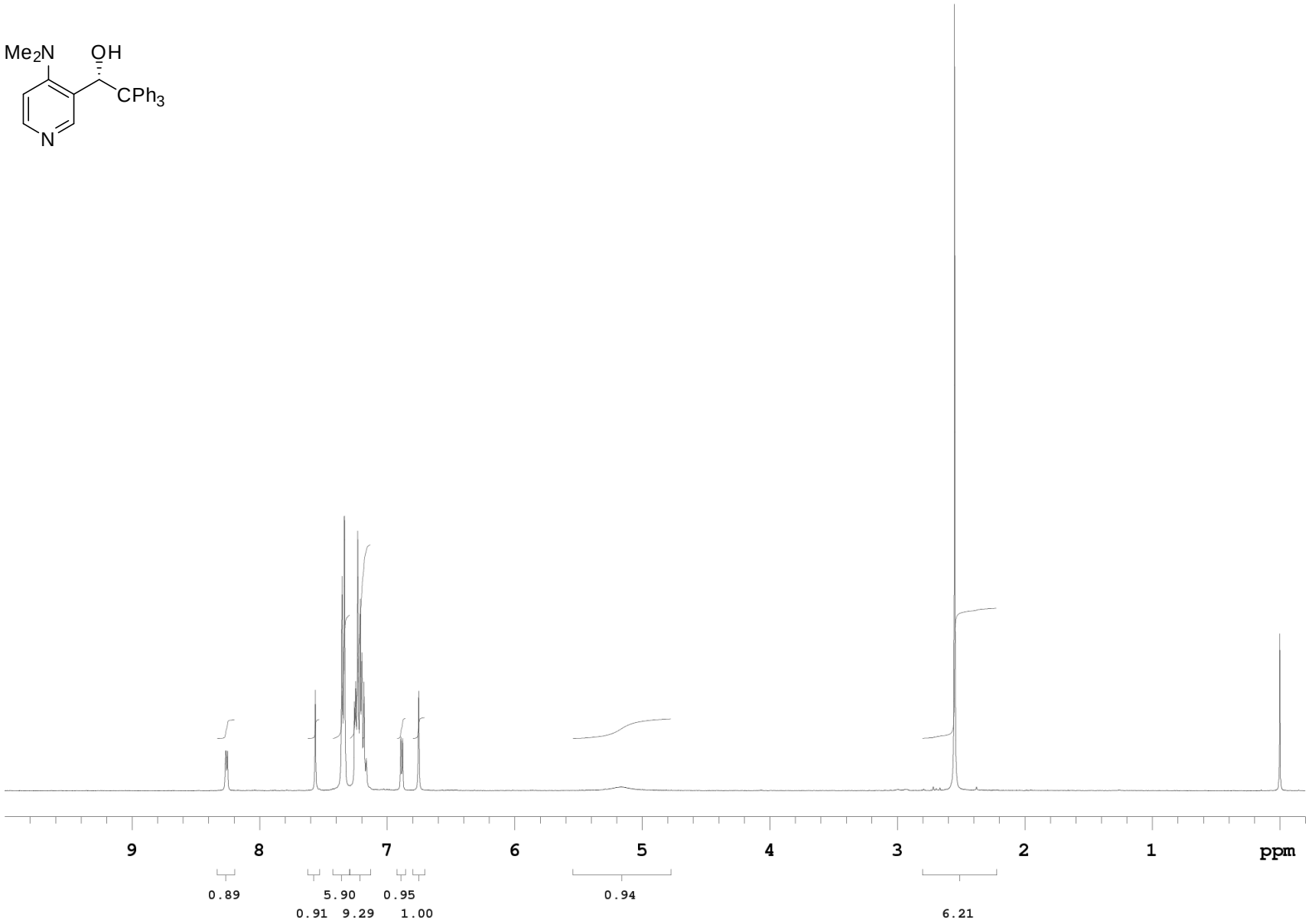
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7
6
5
4
3
2
1
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9.29
0.95
1.00
0.94
6.21

Me2N
OH
CPh3
N
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144.550
139.781
125.875
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122.953
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110.299
72.608
72.291
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60.078
39.825
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120
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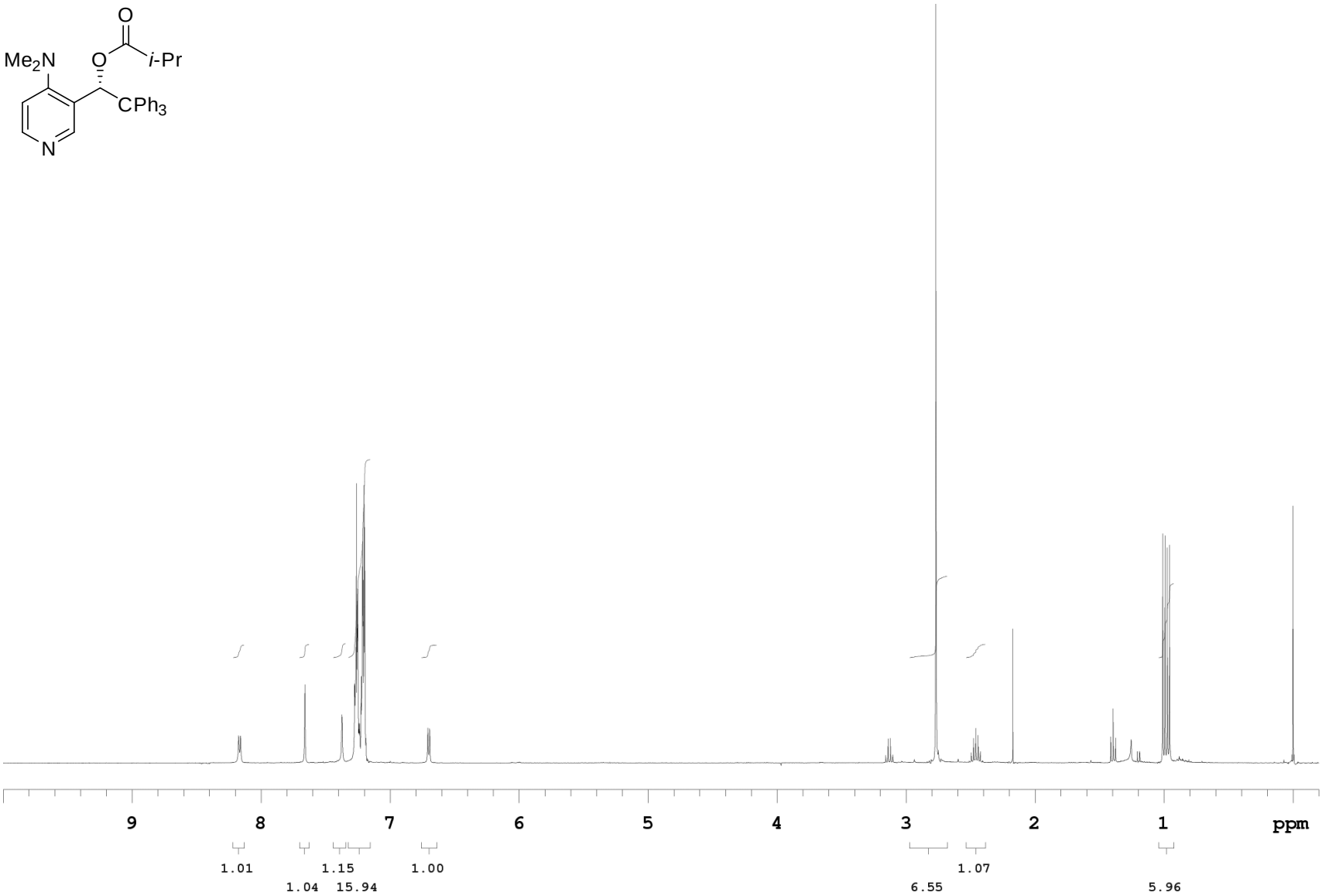
Me2N
O
O
i-Pr
CPh3
N
9
8
7
6
5
4
3
2
1
ppm
1.01
1.04
1.15
15.94
1.00
6.55
1.07
5.96

Me2N
O
O
i-Pr
CPh3
N
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159.259
151.539
148.807
143.218
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127.300
126.568
113.771
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77.226
77.028
76.706
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64.414
43.464
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120
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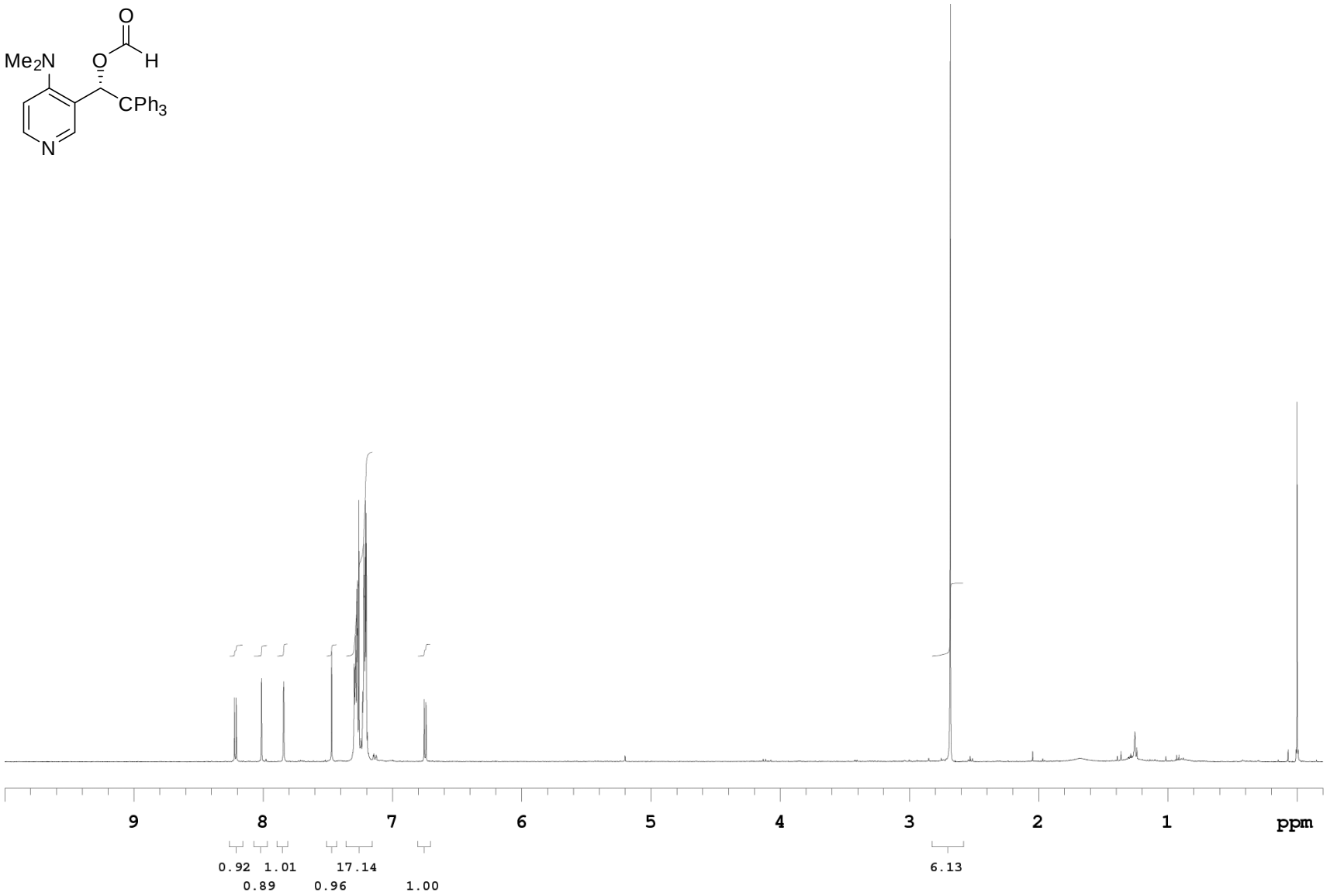
ppm


Me2N
O
O
H
CPh3
N
9
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3
2
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ppm
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0.89
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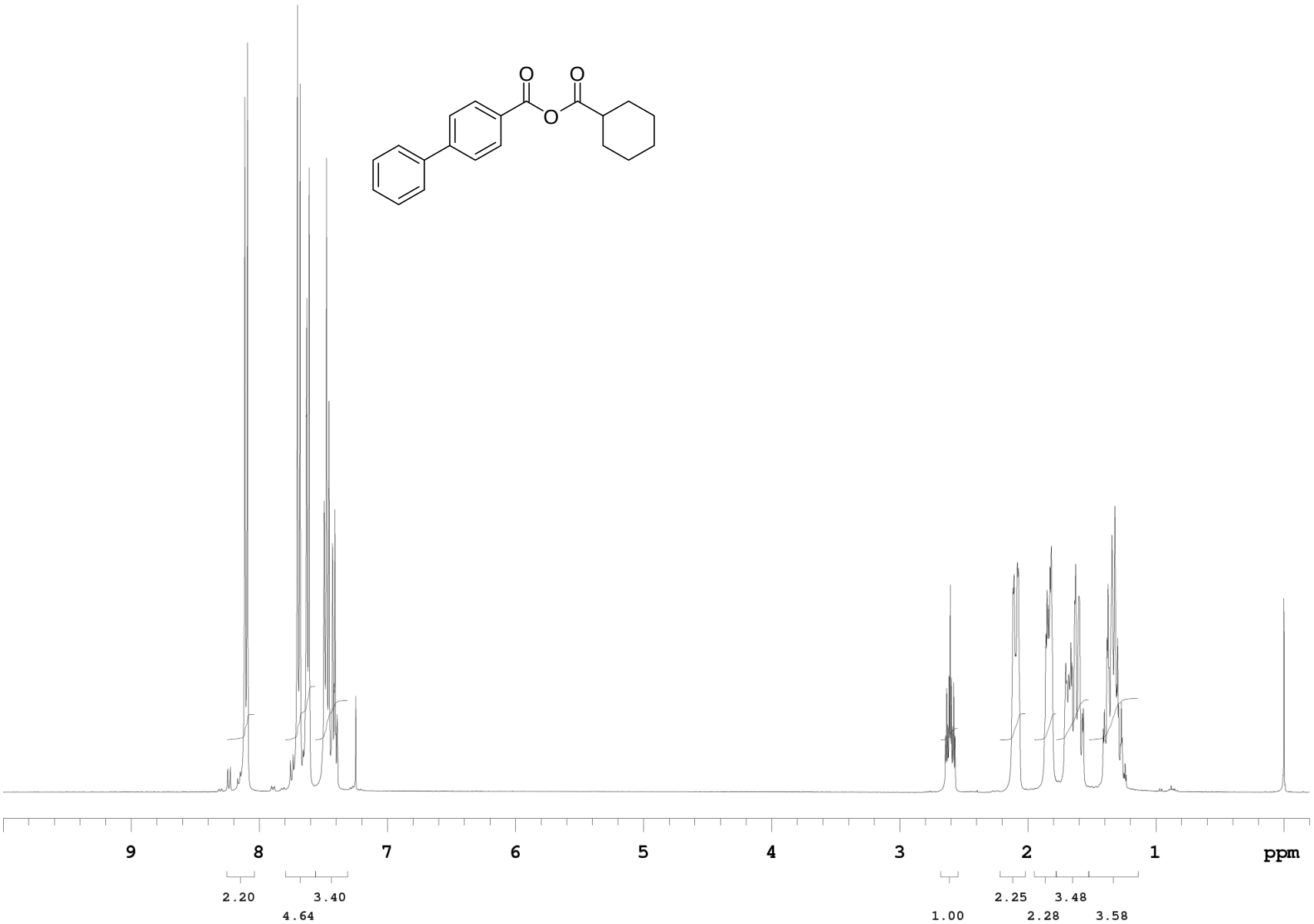
6.13


O
O
O
9
8
7
6
5
4
3
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2.28
3.58

O
O
O
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127.582
127.377
127.318
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25.602
25.206
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160
140
120
100
80
60
40
20
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ppm