The Pd-Catalyzed Carbonylation Reaction of Naphthyl and Binaphthyl Triflates Using Aryl Formates as CO Surrogates

by

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Abstract

In hopes of developing new methods of asymmetric catalysis using derivatives of 1,1'-binaphthyl-2,2'- dicarboxylic acid (BINCA), we have been working on an improved synthesis of the dicarboxylic acid from 1,1'-bi-2-naphthol. The proposed synthesis consists of three steps consisting of triflation, dicarbonylation, and hydrolysis; this thesis focuses on the second step of carbonylation through the use of a CO surrogate, namely aryl formates.

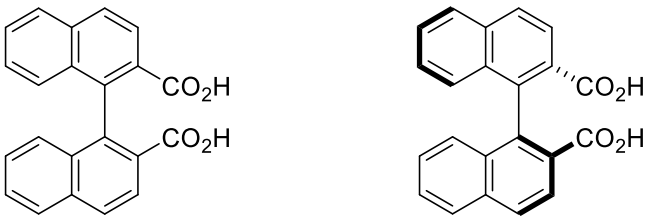
Chapter 1 details the two general methods of previous syntheses for BINCA, while Chapter 2 describes the history of the carbonylation reaction. Chapter 3 consists of our synthetic plans and designs, and finally, Chapter 4 presents our results on the Pd-catalyzed carbonylation using aryl formates as a CO surrogate.

Chapter 1

Introduction

1,1’-Binaphthyl-2,2’- dicarboxylic acid (1).

The compound 1,1’-binaphthyl-2,2’- dicarboxylic acid (BINCA, **1**), belongs to a class of C_2-symmetric, binaphthyl compounds with applications in catalytic asymmetric syntheses.[1] BINCA is particularly useful as a precursor for a variety of compounds, as its carboxylic groups can be transformed into different functional groups.[2-6]



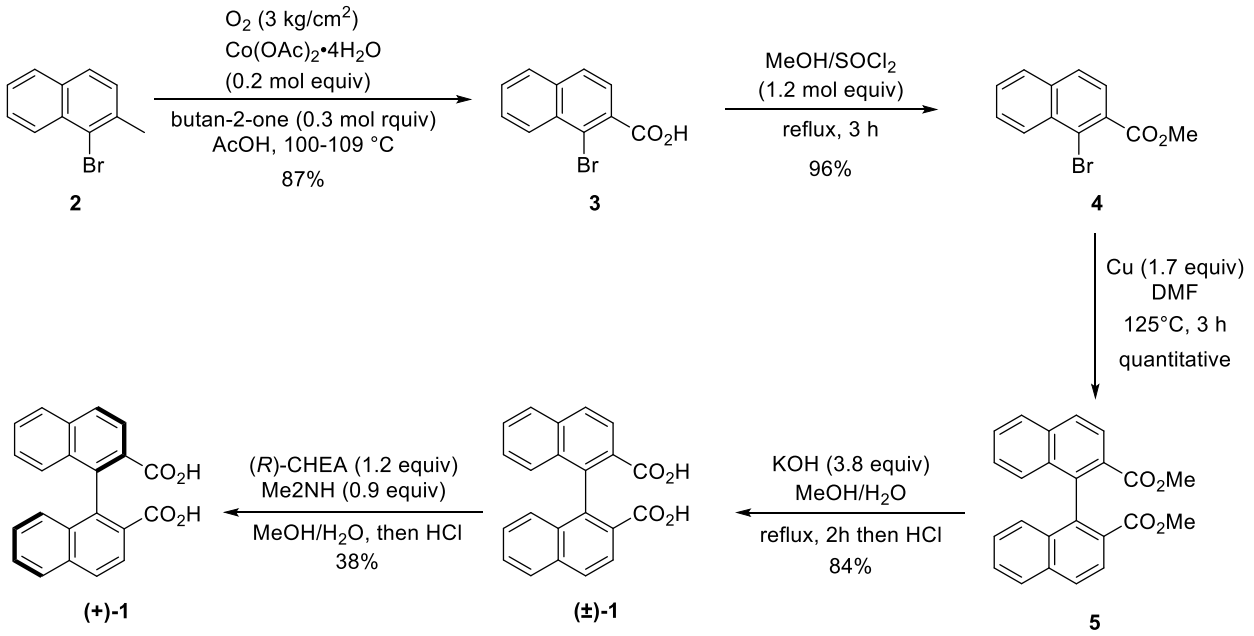
(±)-1 **(-)-1**

Figure 1.1. Structure of 1,1’-binaphthyl-2,2’-dicarboxylic acid (**1**)

There are over 40 different syntheses of **(±)-1** available in the literature, which can be categorized into two general synthetic routes:

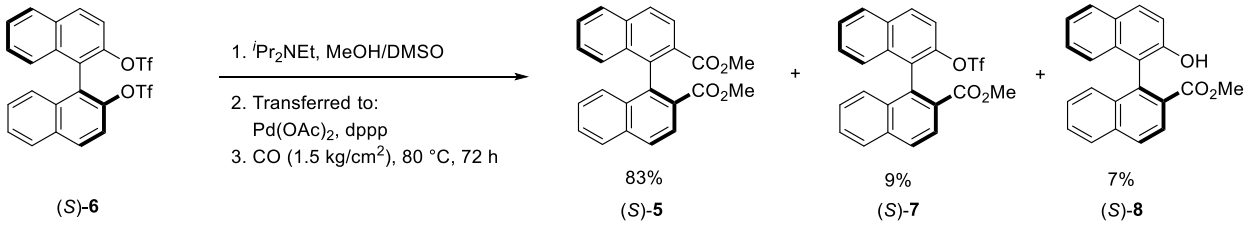
The first involves the use of a metal-halide exchange between two naphthyl structures with the appropriate substituents to create the dimer.[3-7] The shortest synthesis employing this technique was reported by Seki, et al. and consists of five steps (Scheme 1.1), starting with 1-bromo-2-methylnaphthalene (**2**).[7] The methyl group of **2** was oxidized to a carboxylic acid under O_2 then esterified. The resulting methyl 1-bromo-2-naphthoate (**4**) reacted with Cu powder for an Ullman coupling to provide dimethyl 1,1'-binaphthalene-2,2'-dicarboxylate (**5**) in quantitative yields.

The most difficult part of the synthesis remains the optical resolution of **(±)-1**, which for many years was achieved through the use of toxic quinines.[5-8] A non-toxic method was developed by Seki through the use of a non-toxic resolving agent (*R*)-(–)-1-cyclohexylethylamine [(*R*)-CHEA].[6] The maximum yield of a single, pure enantiomer from a racemic mixture is inherently limited to 50 percent, and resolution to (*R*)-**1** with the resolving agent R-CHEA was achieved with 38 percent efficiency for a total yield of 27 percent.



Scheme 1.2. Five-step synthesis of (*R*)-**1** by Seki, et al.

Another method for the synthesis of **1** consists of starting with the binaphthyl structure and converting the functionalities in the 2,2' positions to the carboxylic acid group.[9-11] Takaya et al. reported a Pd-catalyzed methoxycarbonylation under CO gas in methanol to afford **5** from 1,1'-binaphthalene-2,2'-diyl bis(trifluoromethanesulfonate) (**6**) in 83% yield, after which hydrolysis of **5** would afford the desired diacid **1**.[10] The synthetic plan has several advantages, such as the use of 1,1'-binaphthalene-2,2'-diol as a starting material, which is commercially available in its optically active forms and thereby bypasses the need for optical resolution in the synthesis.



Scheme 1.3. Methoxycarbonylation results using CO gas (1.5 kg/cm^2) by Takaya et al.

Despite its simplicity, a major drawback to the synthesis is the use of external CO gas, which requires the use of high-pressure resistant equipment. The efficiency of the methoxycarbonylation reaction drops considerably when using a CO balloon, as demonstrated by Procter and

Rayner.[11] Monomethoxyester **7** is the major product at 15% yield, and only re-subjecting **7** with the same conditions resulted in a satisfactory yield of dimethoxyester **5**.

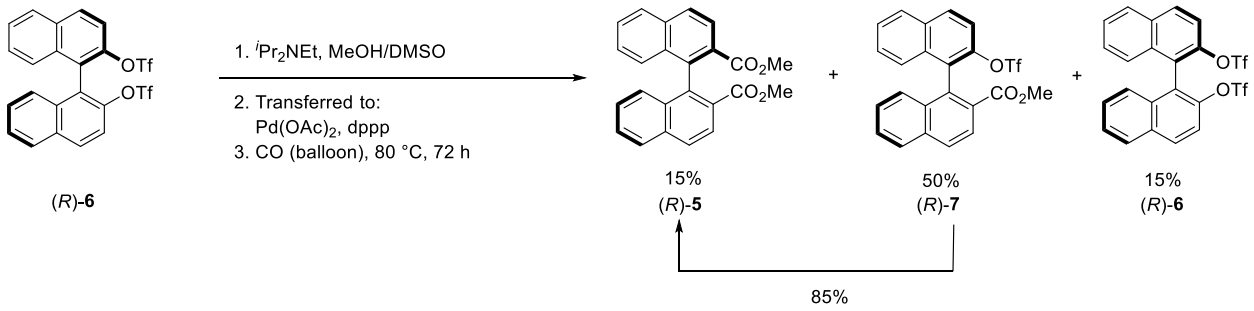


Figure 1.4. Methoxycarbonylation results using a CO balloon by Procter et al.

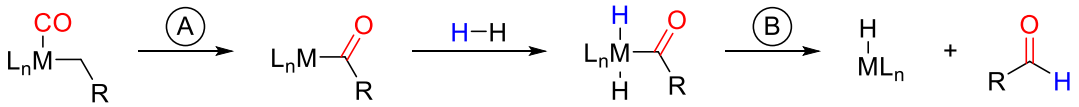
In addition, CO itself is toxic and difficult to handle at small scales, and the use of the gas severely limits the practicality of the synthesis and detracts from the overall method. To circumvent the problems associated with working with CO gas, we have worked on an alternative method of carbonylation through the use of a CO surrogate, which is described in the next chapter.

Chapter 2

Pd-Catalyzed Carbonylation Using Aryl Formates

Introduction

CO is one of the most important C_1 units,[12-13] and carbonylation chemistry involves the incorporation of CO into substrates to form compounds with carbonyl groups. CO by itself is inert to most organic compounds and reacts via a transition metal complex. From a metal carbonyl complex, insertion of CO into a C-metal bond (Step A, Scheme 2.1) results in an acyl complex and affords the carbonylated product upon reductive elimination (Step B, Scheme 2.1).



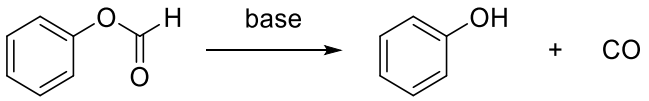
Scheme 2.1. General mechanism for the hydroformylation reaction

Some of the first organometallic catalyses involved carbonylation chemistry, such as the Roelen reaction in 1938 for the hydroformylation reaction with CO and H_2, and the Reppe reaction with hydrocarboxylation with CO and water.[14] These reactions are useful in their ability to transform alkenes into a variety of useful products, including secondary alcohols, aldehydes, and carboxylic acids. Today, industrial processes use carbonylation chemistry for the mass production of other C_1 units, including methanol, formaldehyde, and formic acid.[12-13]

Despite the versatility of the reaction, carbonylation with CO is seldom used in complex organic syntheses. As a colorless, odorless, flammable, and toxic gas, CO necessitates the use of high-pressure-resistant equipment and safe handling. The difficulty in storing and transporting CO safely further reduces its potential for practical applications in the laboratory setting. An alternate method to using external CO would be to use a surrogate that produces CO in situ; such examples include metal carbonyls and formic acid, formaldehydes, formic esters (formates), and other derivatives.[12-14]

Using CO surrogates has its own set of disadvantages. They often require severe conditions, longer reaction times, or extra reagents to prompt the additional decarbonylation process. For instance, formic acid requires high temperatures or acidic conditions for its decarbonylation,

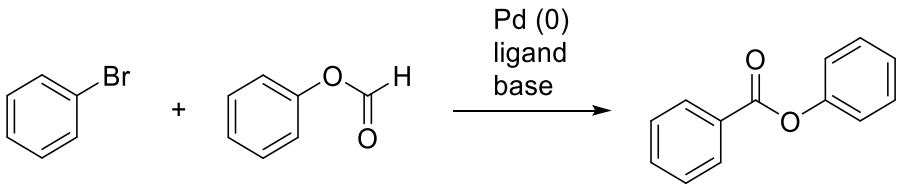
and the harshness limits the potential substrate scope.[15] Similarly, formaldehydes require high reaction temperatures or microwave irradiation for its decarbonylation.[16] Metal carbonyls rely on the efficient release of CO and some, such as $Ni(CO)_4$, can be just as toxic as gaseous CO.[17-18] An excess is often required for high yields, and combined with poor atom economy, these reactions produce high levels of byproduct waste.[14] Therefore, efforts in this area strive for the development of environmentally benign and efficient synthetic methods in addition to improving chemical yields and the scope of applicable substrates by developing better ligand and catalyst systems with improved efficiency.[12,14]



9a

Scheme 2.2. Decomposition of phenyl formate to phenol and CO

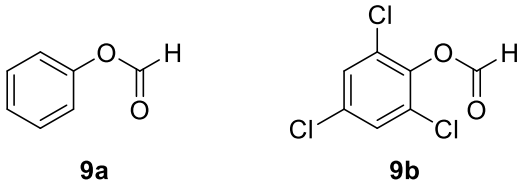
Alkyl formates, particularly methyl formate, have been widely utilized as a C_1 building block in organic synthesis. For instance, Mortreux, et al.[19] demonstrated the decarbonylation of methyl formate for the Heck-type esterification of alkyl and vinyl halides. In 1983, Ru-catalyzed reaction of methyl formate to ethylene was achieved for the hydroesterifications of alkenes, alkynes, and dienes.[20]



Scheme 2.3. Carbonylation of phenyl bromide with phenyl formate

Formates readily undergo decarbonylative decomposition by various transition metal catalysts or bases to yield CO and a corresponding alcohol (Scheme 2.2). Formates are advantageous in that they exist as a stable liquid or solid at room temperature, making them convenient to handle in the laboratory setting. Moreover, they can be prepared efficiently from alcohols by formylation using acetic formic anhydride or other formylating agents and are therefore readily accessible. However, the generation of CO from methyl formate was found to result in low yields. Moreover,

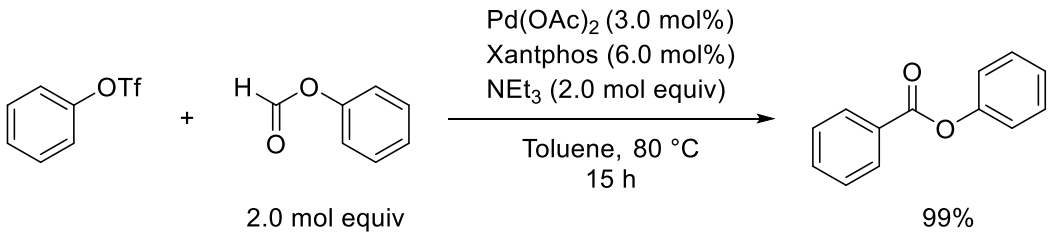
such a reaction required a Ru co-catalyst with overall harsher conditions of higher temperatures and strong bases, thereby limiting the substrate scope.[21-22]



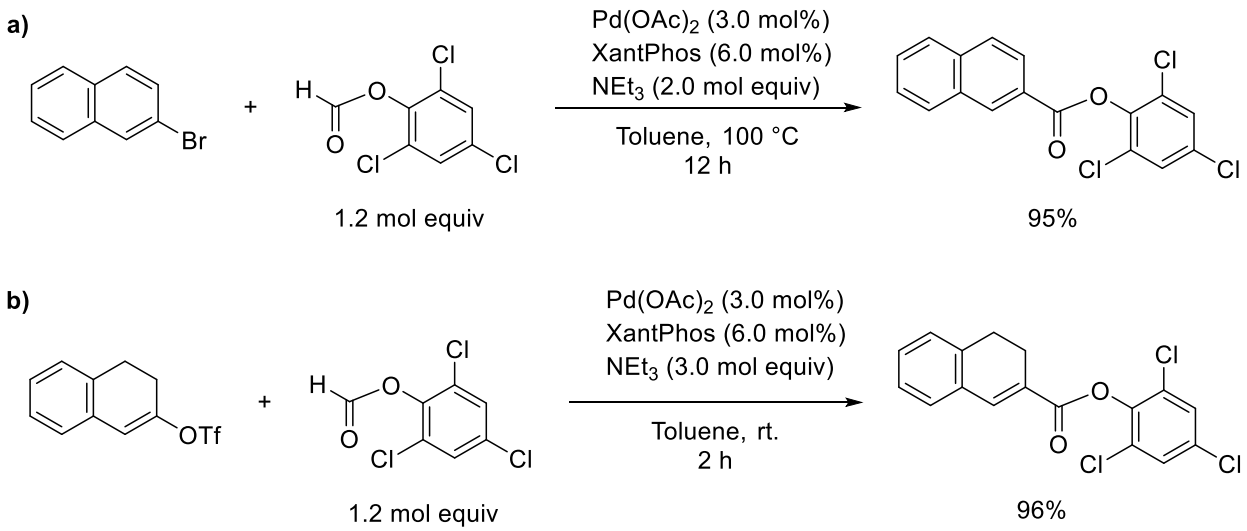
9a **9b**

Figure 2.1. Phenyl formate (**9a**) and 2,4,6-trichlorophenyl formate (**9b**)

In 2012, Tsuji's[23] and Manabe's[24] groups found that aryl formates made efficient sources of CO for aryl, alkenyl, and allyl halides (Scheme 2.3), with one example of an aryl triflate (Scheme 2.4).[24] A slight excess of phenyl formate (**9a**, 1.5-2.0 equiv) was sufficient for high-yielding Pd-catalyzed carbonylation under milder conditions (80°C) using NEt_3 as the base. In addition, Manabe demonstrated that 2,4,6-trichlorophenyl formate (**9b**) had great reactivity at room temperature for 2-bromonaphthalene and 3,4-dihydronaphthalen-2-yl trifluoromethanesulfonate using 1.2 equivalents of **9b** (Scheme 2.5).[24-25]

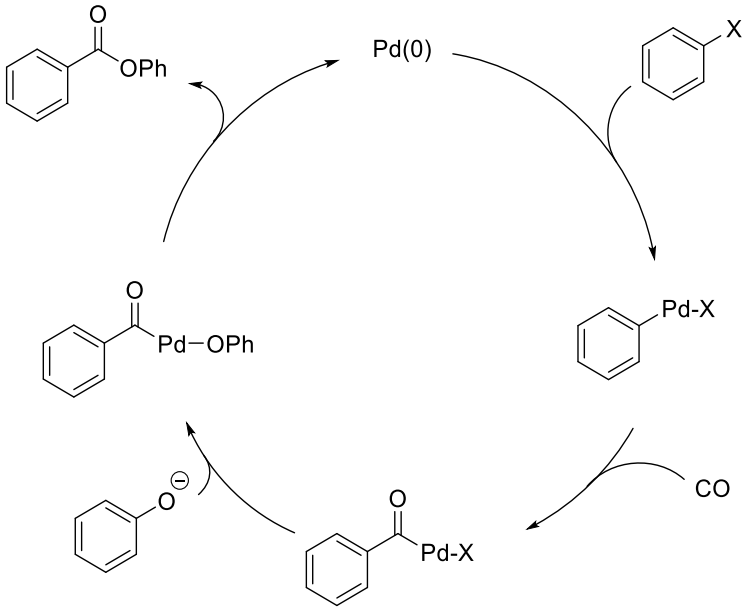


Scheme 2.4. Carbonylation reaction of phenyl triflate with phenyl formate



Scheme 2.5. Carbonylation reaction of **a)** 2-bromonaphthalene and **b)** 3,4-dihydronaphthalen-2-yl triflate using 2,4,6-trichlorophenyl formate by Manabe

A plausible mechanism for the reaction is presented in Scheme 2.5, in which the Pd catalyst inserts between the C-X bond. CO generated from the decarbonylation of phenyl formate adds and inserts to form an acyl complex. Phenoxide also coordinates to the metal center and reductively eliminates with the carbonyl compound to form the ester product**.**

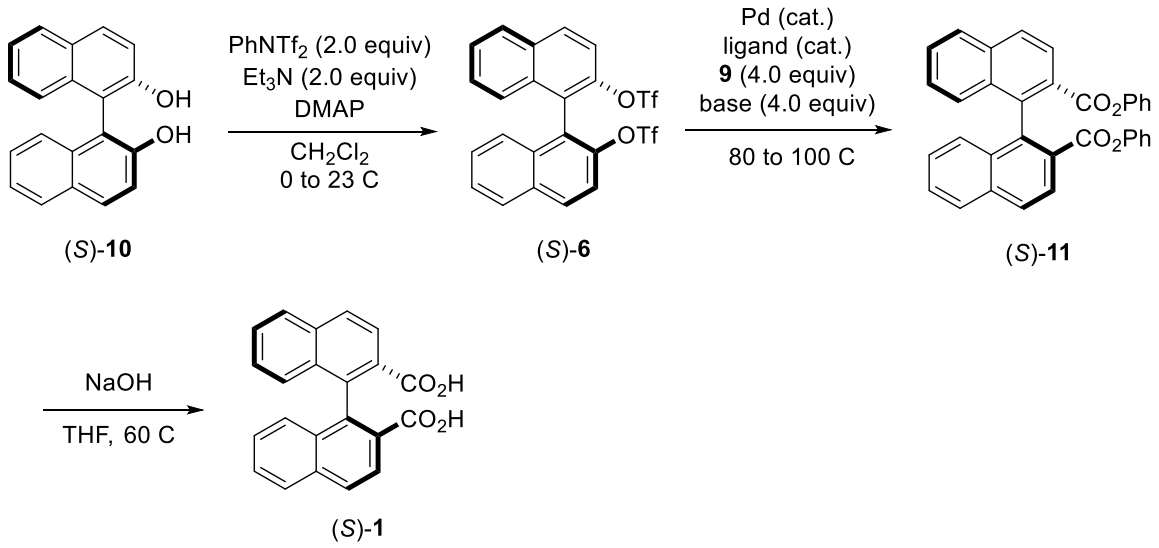


Scheme 2.6. Catalytic cycle for the esterification with phenyl formate

Chapter 3

Synthetic Plans and Design

The general availability of the binaphthyl system led us to begin with 1,1'-binaphthalene-2,2'-diol (**10**) as an inexpensive starting material, which is also commercially available in its enantiopure forms. Considering that Pd inserts between C-OTf as well as it does between C-Br,[12] we reasoned that we could extend Manabe's and Tsuji's method of carbonylation using aryl formates as a CO surrogate to naphthyl and binaphthyl triflates, which could be synthesized from their respective phenols by use of a triflating agent. Chapter 4 details the results of the experiments performed for the Pd-catalyzed carbonylation reaction of racemic bistriflate **6** using aryl formates as a CO surrogate for the improved, direct synthesis of racemic diacid **1**.



Scheme 3.1. Proposed route of synthesis

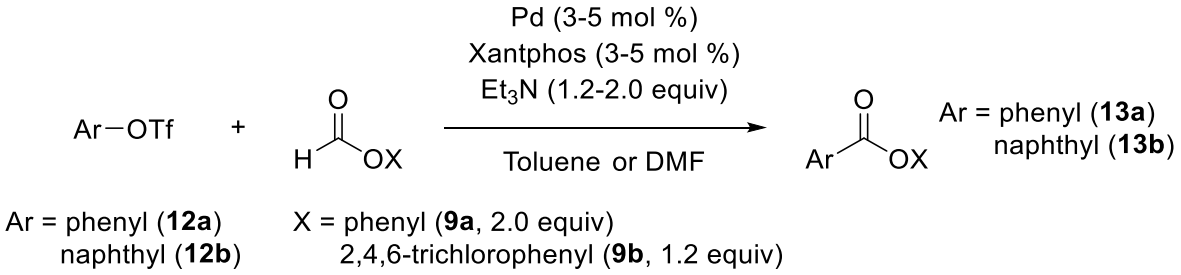
Chapter 4

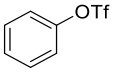
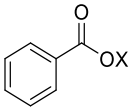
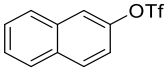
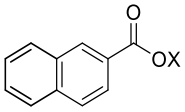
Results and Discussion

Substrate Tests

Following procedures by Manabe and Tsuji,[23-24] we first tested the carbonylation reaction using phenyl formate (**9a**) with phenyl triflate and 2-naphthyl triflate before using the binaphthyl system (Table 4.1). The combination of $PdCl_2(PhCN)_2$, Xantphos, and phenyl formate in DMF, which were conditions employed by Tsuji, worked well at 80 °C with phenyl triflate and 2-naphthyl triflate, seen in entries 2 and 3. Raising the temperature resulted in a significant improvement in the yield from a 50% yield at 60 °C to a quantitative conversion at 80 °C (Entries 1 & 2, Table 4.1).

Table 4.1. Carbonylation Results of Phenyl Triflate and 2-Naphthyl Triflate

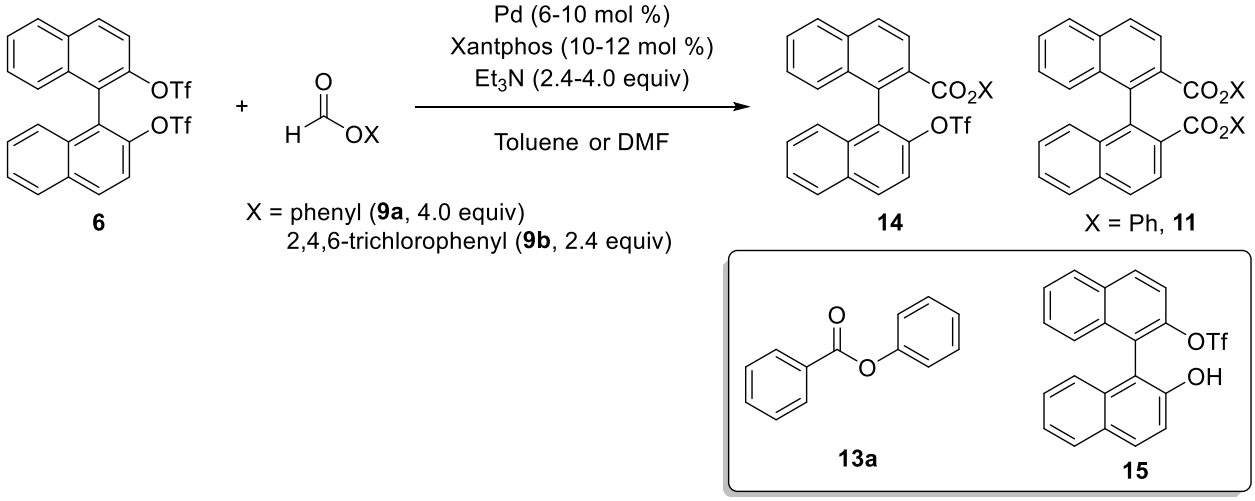


Entry	Substrate	Pd	Solvent	9	T (°C)	Product	Yield (%)[a]
1[b]		$PdCl_2(PhCN)_2$	DMF	**9a**	60		50
2[b]		$PdCl_2(PhCN)_2$	DMF	**9a**	80		99
3[b]		$PdCl_2(PhCN)_2$	DMF	**9a**	80		99
4[c]		$Pd(OAc)_2$	Toluene	**9b**	Rt		14
5[c]		$Pd(OAc)_2$	Toluene	**9b**	45		83

[a]Yields based on ^{1}H-NMR analysis; [b]Conditions: 5.0 mol % $PdCl_2(PhCN)_2$, 5.0 mol % Xantphos, 2.0 equiv Et_3N; [c]Conditions: 3.0 mol % $Pd(OAc)_2$ 6.0 mol % Xantphos, 1.2 equiv Et_3N

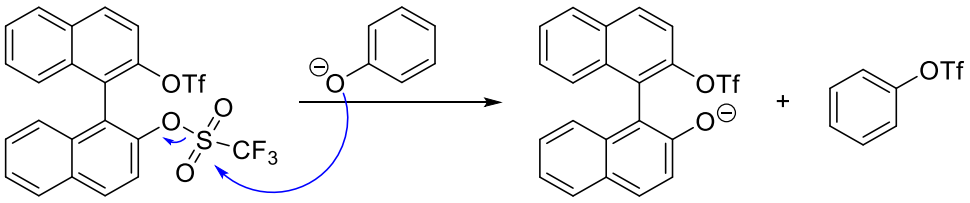
Using 2,4,6-trichlorophenyl formate (**9b**), $Pd(OAc)_2$, and Xantphos at room temperature, which were conditions set by Manabe,[25] with 1-naphthyl triflate was low-yielding at room temperature but provided satisfactory yields at 45 °C (Entries 4 & 5, Table 4.1). However, the reactivity of formate **9b** with the binaphthalene bistrfilate **6** produced low yields even at an elevated temperature (Entry 4, Table 4.2). Using phenyl formate provided more successful results in which the desired diester **11** was formed with the monoester **14a** as the major product (Entry 3, Table 4.2). A general trend in all of these reactions is raising the temperature increases the yield (Entries 1&2 and 4&5, Table 4.1). However, in the case of the bistriflate, raising the temperature also drove side reactions that produced phenyl benzoate (**13a**) and BINOL monotriflate (**15**). The formation of these products is most likely the result of phenoxide attacking the sulfur in the triflate group to form the alkoxide of BINOL-monotriflate and phenyl triflate (Scheme 4.1), the latter of which can oxidatively add to Pd(0) and undergo carbonylation to form phenyl benzoate (Scheme 2.5).

Table 4.2. Carbonylation Results of Bistriflate 6



Entry	Pd	Solvent	9	T (°C)	Products[a]
1[b]	$PdCl_2(PhCN)_2$	DMF	**9a**	80	**6**
2[b]	$PdCl_2(PhCN)_2$	DMF	**9a**	120	**14a** (50 %); **13a**, **15**
3[c]	$Pd(OAc)_2$	Toluene	**9a**	90	**14a** (70 %), **11** (10%)
4[c]	$Pd(OAc)_2$	Toluene	**9b**	100	**14b** (10 %)

[a]Based on ^{1}H-NMR analysis; [b]Conditions: 10 mol % $PdCl_2(PhCN)_2$, 10 mol % Xantphos, 4.0 equiv Et_3N; [c]Conditions: 6.0 mol % $Pd(OAc)_2$ 12.0 mol % Xantphos, 2.4 equiv Et_3N

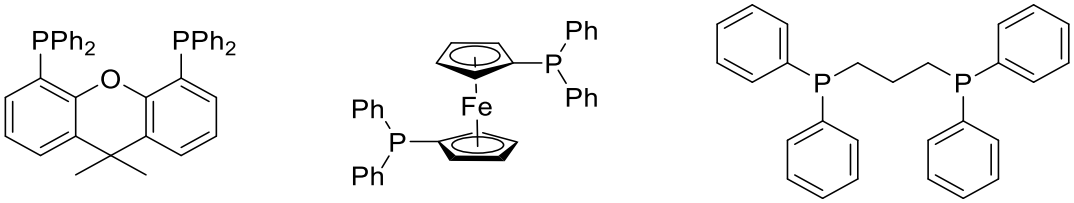


Scheme 4.1. Plausible mechanism for the formation of side products

The best conditions for the initial set of experiments with the bistriflate substrate was obtained with $Pd(OAc)_2$ and phenyl formate in toluene at 90°C, where the monoester was the major product, and the desired diester was also isolated in 10% yield (entry 3, Table 4.2).

Reaction Optimization

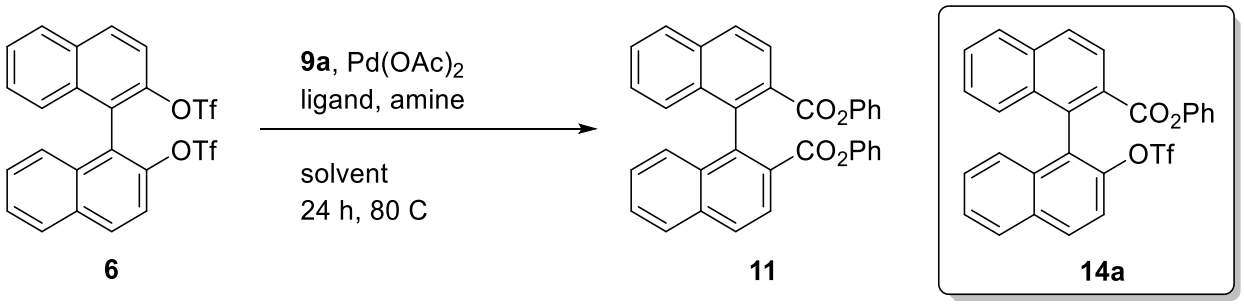
To optimize reaction conditions, we considered different catalyst-ligand and solvent systems (Table 4.3). Due to difficulties in separating the products by methods of silica gel flash chromatography and preparatory TLC, results are reported as a ratio determined by ^{1}H-NMR analysis (Tables 4.4 and 4.5). We found that the ligand 1,3-bis(diphenylphosphino)propane (dppp, **18**) led to the complete reaction of the starting material unlike the ligands 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, **16**) or 1,1'-bis(diphenylphosphino)ferrocene (dppf, **17**), which was an interesting observation considering that both Manabe and Tsuji reported the greatest efficiency using Xantphos and dppf in their ligand screening tests. We speculate that in the case of the bistriflate, the smaller ligand dppp, with a bite angle of 87.3°, compared to 109.0° for Xantphos and 99.07° for dppf, better allows for the coordination of the bulky substrate onto the Pd center.[26]



16 **17** **18**

Figure 4.1. Structures of the ligands Xantphos (**16**), dppf (**17**), and dppp (**18**)

Table 4.3. Select Screening Results for the Dicarbonylation of Bistriflate



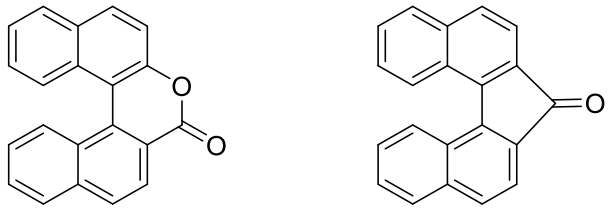
6 **11** **14a**

Entry	Ligand	Amine	Solvent	Product[a]
1	Xantphos	Et_3N	CH_3CN	**14a** trace
2	Xantphos	Et_3N	DMF	**6**
3	Xantphos	Et_3N	DMSO	**14a** trace
4	dppp	^{i}PrEtN	DMSO	**11** 22%
5	dppf	^{i}PrEtN	DMSO	**14a** trace

[a]Based on ^{1}H NMR analysis

Given the higher reactivity of the starting bistriflate **6** with dppp compared to Xantphos and dppf, we decided to use $Pd(OAc)_2$, dppp, and diisopropylethylamine in DMSO as the main conditions (entry 4, Table 4.3), which are similar to the conditions used by Takaya[10] and Procter and Rayner[11] in their Pd-catalyzed dicarbonylation using external CO gas (see Chapter 1).

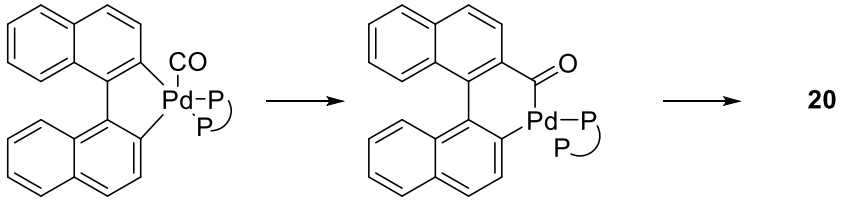
While using dppp improved the reaction of the starting material, it also produced two new side products in addition to the monoester and diester: lactone **19** and ketone **20** (Figure 4.1).



19 **20**

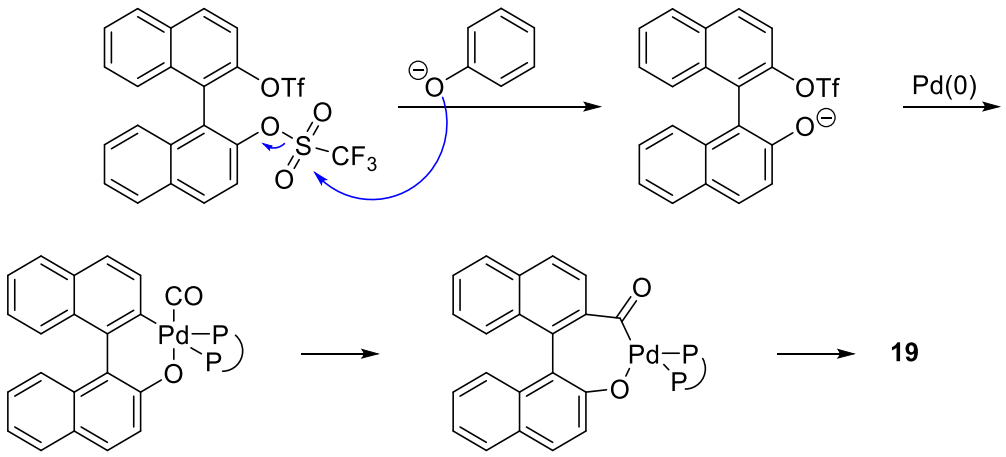
Figure 4.1. Structures of 4H-benzo[f]naphtho[2,1-c]chromen-4-one (**19**) and 7H-dibenzo[c,g]fluoren-7-one (**20**)

The ketone most likely is formed when the binaphthyl structure chelates to the metal center, and upon carbonylation on one side, reductively eliminates to result in the ketone (Scheme 4.1).



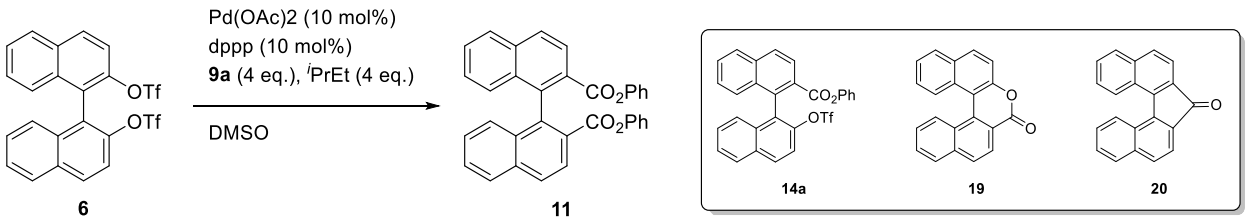
Scheme 4.1. Plausible scheme for the formation of ketone **20**

In the case of the lactone, we believe that the alkoxide of BINOL-monotriflate, formed from the reaction between bistriflate and phenoxide (Scheme 4.2), coordinates to the Pd, undergoes carbonylation, and then reductive elimination. We subjected BINOL-monotriflate **7** to the same reaction conditions in a separate experiment, and the formation of the lactone was indeed observed. We ascribe the formation of these products to the smaller bite angle of dppp compared to Xantphos or dppf, which allows chelation of the substrate to the Pd. Ketone formation was only observed in select cases, such as in the large scale (3.79 mmol) experiments, or when six equivalents of phenyl formate was used.



Scheme 4.2. Plausible scheme for the formation of lactone **19**

Table 4.4. ^{1}H NMR Analysis of the Carbonylation Reaction of 6



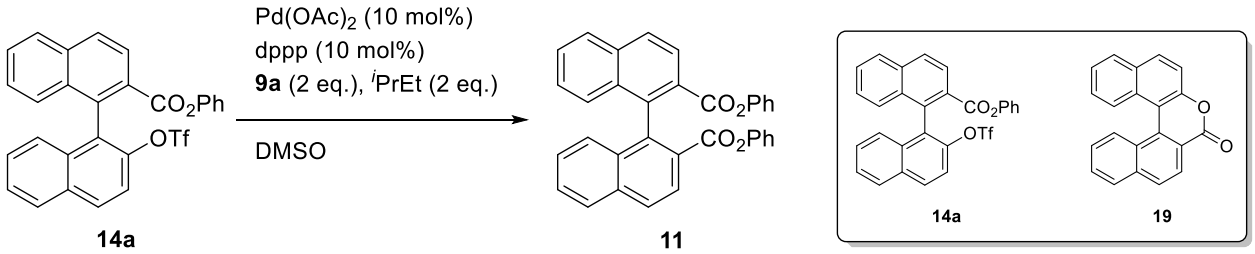
Entry	Substrate 6 mmol	T (°C)	Product ratio[a] 11:14a:19:20
1[b]	3.79 mmol	80	36:14:27:22
2[b]	0.50 mmol	80	38:32:40:0
3[c]	0.91 mmol	80	53:17:29:1
4[c]	0.91 mmol	80	64:33:3:0
5[d]	0.10 mmol	100	60:16:24:0
6[d]	0.50 mmol	100	73:7:20:3

[a]Due to difficulties in separating the products, results are reported as a ratio determined by ^{1}H-NMR analysis. [b]Using a RB-flask with septum and Ar balloon; [c]Using a test tube with septum and Ar balloon; [d]Using a test tube with septum only

The yield of the diester was further improved when making other changes to the experimental setup: namely, the reaction vessel. While previous experiments were performed using a round-bottomed flask capped by a rubber septum with an Ar balloon (entries 1-2, Table 4.4), we found that using a test tube with a septum and Ar balloon increased diester formation as the major product (entries 3-4, Table 4.4). Furthermore, tightly securing the flask with parafilm or Cu wire and avoiding the use of the balloon led to the highest yields of the diester obtained thus far. These results suggest that CO leakage between the seal was a contributing factor to the lower yield of the diester compared to the monoester.

Additionally, we resubjected the conditions with monoester **14a** to observe whether a greater ratio of diester **11** would be produced, as was the case for Procter and Rayner in the carbonylation of methoxymonoester **7** using a CO balloon.[11] The diester to monoester to lactone product ratio (**11**:**14a**:**19**) starting with the monoester **14a** substrate was comparable to the results obtained when starting with bistriflate **6**; which suggests that either the Pd insertion between the monoester-triflate C-OTf bond or the CO insertion to the C-Pd bond is the rate determining step in the catalytic cycle.

Table 4.5. ^{1}H NMR Analysis of the Carbonylation Reaction of 14a



Entry	Substrate 14a	T (°C)	Product ratio[a] 11:14a:19
1[b]	0.23 mmol	80	18:38:44
2[b]	0.38 mmol	80	58:38:4
3[c]	0.20 mmol	100	53:38:9

[a]Due to difficulties in separating the products, results are reported as a ratio determined by ^{1}H-NMR analysis. [b]Using a test tube with septum and Ar balloon; [c]Using a test tube with septum only.

Chapter 5

Conclusion

In summary, the best conditions obtained so far involved the use of $Pd(OAc)_2$, dppp, and phenyl formate in DMSO at 100°C, where the diester was the major product, isolated in 40% yield. Interestingly, Manabe's group recently observed that the use of DMF instead of DMSO resulted in the formation of biphenyl ester **11** in about 70% yield.[27] While 2,4,6-trichlorophenyl formate showed higher reactivity with 2-naphthyl triflate (**12b**), such success has not been met with 1,1-binaphthyl-2,2'-bistriflate (**6**). Future directions include optimizing reaction conditions for maximizing yield of the diester without using an excessive amount of phenyl formate, as well as using chiral 1,1'-bi-2-naphthol for the eventual synthesis of chiral BINCA. Currently, using different catalyst-ligand combinations and base loadings are considerations at hand.

Given the number of different byproducts that form in the reaction, there is great opportunity for performing a kinetic study to provide further insight on the mechanism of the catalytic cycle to help control the reaction to form one major product.

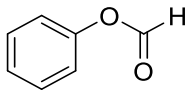
Chapter 6

Experimental

General. Palladium acetate was purchased from Fisher Chemical. Ligands were purchased from Acros (Xantphos) and Sigma Aldrich (dppp and dppf) and were used without purification. Aryl formates were prepared according to procedures published by Manabe and Tsuji.[ref] All other reagents were obtained from commercial sources and were used as obtained unless otherwise noted. The solvents toluene, DMSO, and DMF were degassed with argon prior to use. Triethylamine was purified by distillation from calcium hydride under N_2 prior to use.

^{1}H NMR data were recorded at 400 MHz using a Varian Inova 400 FT-NMR spectrometer. ^{1}H NMR chemical shifts are reported in ppm relative to the internal reference tetramethylsilane (δ 0.00). Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet). ^{13}C NMR data were recorded at 100 MHz using a Varian Inova 400 FT-NMR spectrometer. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). High resolution mass spectrometry measurements were determined at the University of Michigan mass spectrometry facility.

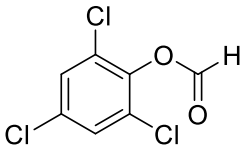
Preparation of substrates.



9a

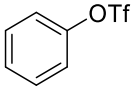
Phenyl formate (9a).[23] Acetic anhydride (150 mL, 1.6 mol, 8 equiv) was added to a 500-mL, round-bottomed flask equipped with a stir bar and cooled to 0 °C. Formic acid (76 mL, 2.0 mol, 10 equiv) was added, and the mixture was stirred at rt for 10 min, then to 60 °C for 1 h. After cooling to rt, phenol (18.8 g, 200 mmol, 1 equiv) and $NaHCO_3$ (33.8 g, 400 mmol, 2 equiv) were added and the resulting mixture stirred at rt for 12 h. The solution was transferred to a separatory funnel, where CH_2Cl_2 (100 mL) and H_2O (100 mL) were added. The aqueous layer was back extracted with CH_2Cl_2 (100 mL x 3), and the combined organic layers were washed first with water (100 mL x 3), and then with brine (100 mL), and dried over anhydrous Na_2SO_4. Removal of the organic solvent by rotary evaporation provided 23.2 g (95 %) of phenyl formate (**9a**) as a pale

yellow oil. TLC R_f = 0.60 (10:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.43-7.39 (m, 2H) 7.28 (dd, *J* = 7.1, 7.5 Hz, 1H), 7.15-7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 149.9, 129.7, 126.4, 121.1.



9b

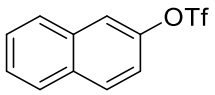
2,4,6-trichlorophenyl formate (9b).[25] Formic acid (18.9 mL, 500 mmol, 5 equiv) and acetic anhydride (37.7 mL, 400 mmol, 4 equiv) were added to a 500 mL round-bottomed flask equipped with a stir bar, and heated under reflux at 60 °C for 1 h. Then, the flask was cooled to 0 °C, and toluene (300 mL), 2,4,6-trichlorophenol (19.7 g, 100 mmol, 1 equiv), and sodium acetate (8.20 g, 100 mmol, 1 equiv) were added to the solution. After 10 min, the mixture was warmed to rt, resulting in the formation of a white precipitate. The mixture was stirred for an additional 30 min at rt. Water (100 mL) was added, which resulted in dissolution of the white precipitate, and the reaction mixture was transferred to a separatory funnel where the layers were separated. The organic layer was washed with H_2O (100 mL x 3) and brine (100 mL x 2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The solid was recrystallized from hexane/EtOAc (50/1 v/v, *ca*. 150 mL) to afford **9b** (20.7 g, 92%) as clear needles. TLC R_f = 0.38 (10:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.41 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 141.9, 132.6, 129.2, 128.7.



12a

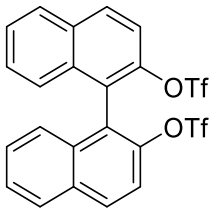
Phenyl trifluoromethanesulfonate (12a).[28] In a 250-mL, round-bottomed flask, phenol (2.4 g, 25 mmol, 1 equiv) and *N*-phenyl-bis(trifluoromethanesulfonimide) (8.9 g, 25 mmol, 1 equiv) were dissolved in CH_2Cl_2 (80 mL). The flask was cooled to -23 °C in a CCl_4 dry-ice bath. Triethylamine (2.53 g, 26.2 mmol, 1.05 equiv) was added slowly, and the reaction was stirred 3 h at rt. The resulting pale green solution was transferred to a separatory funnel, to which 1 M HCl (80 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL).

The organic layers were combined and washed with brine, then dried over anhydrous $MgSO_4$. The filtrate was concentrated, and the crude product was purified by flash chromatography on silica gel (20:1 hexane / ethyl acetate) to afford 5.37 g (95%) of **12a** as a clear liquid. TLC R_f = 0.71 (20:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.39 (m, 3H), 7.29-7.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 130.3, 128.4, 121.3, 118.7 (q, $^1J_{CF}$ = 319 Hz).



12b

Naphthalen-2-yl trifluoromethanesulfonate (12b).[28] The procedure for preparing phenyl triflate above was applied with 2-naphthol (3.63 g, 25 mmol, 1 equiv), and *N*-phenyl-bis(trifluoromethanesulfonimide) (8.9 g, 25 mmol, 1 equiv), and trimethylamine (2.53 g, 26.2 mmol, 1.05 equiv) in 80 mL CH_2Cl_2 and purified by silica gel flash chromatography (10:1 hexane / ethyl acetate) to afford 6.42 g (93%) of **12b** as a white solid. TLC R_f = 0.56 (10:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.78 (6 H, m), 7.77 (s, 2 H), 7.61-7.55 (m, 4H), 7.39 (dd, J= 6.4 Hz, 2.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 133.5, 132.5, 130.7, 128.1, 128.0, 127.8, 127.7, 127.3, 123.8, 119.6, 119.3, 119.0 (q, $^1J_{CF}$ = 319 Hz).



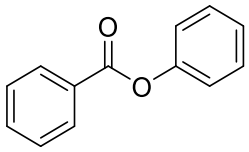
6

1,1'-Binaphthalene-2,2'-diyl bis(trifluoromethanesulfonate) (6).[28] In a 250-mL, round-bottomed flask, 1,1'-binaphthalene-2,2'-diol (4.3 g, 15 mmol, 1 equiv), *N*-phenyl-bis(trifluoromethanesulfonimide) (10.7 g, 30 mmol, 2 equiv), and DMAP (0.92 g, 4.3 mmol, 0.3 equiv) were dissolved in CH_2Cl_2 (90 mL). The flask was cooled to 0 °C. Triethylamine (3.0 g, 30 mmol, 2 equiv) was added slowly, and the reaction was stirred overnight (16 h) at rt. The resulting pale yellow solution was transferred to a separatory funnel, to which 1 M HCl (90 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The organic

layers were combined and washed with brine, then dried over anhydrous $MgSO_4$. The filtrate was concentrated, and the crude product was purified by silica gel flash chromatography (20:1 hexane / ethyl acetate) to afford 8.25 g (94 %) of **6** as a white solid. TLC R_f = 0.47 (10:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) 8.12 (d, *J* = 8.8 Hz, 2H) 7.99 (d, *J* = 8.4 Hz, 2H), 7.62-7.55 (m, 4H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 6 Hz, 2H); ^{13}C NMR 145.3, 133.1, 132.3, 132.0, 128.3, 128.0, 127.3, 126.7, 119.3, 118.0, (q, $^1J_{CF}$ = 320 Hz).

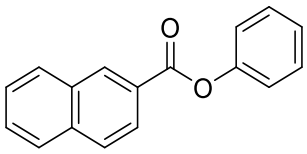
General Procedure A: Synthesis of Esters from Triflates.[23-24]

The appropriate triflate (1 equiv) was added to a reaction vessel equipped with a stir bar and capped with a septum with palladium catalyst (5-15 mol %), ligand (5-20 mol %) under an argon atmosphere. Solvent was added by a syringe, followed by base (1.2-4 equiv) and aryl formate (1.2-4 equiv). Thre reaction mixture was stirred at 80-100 °C for 24 h. The reaction mixture was then left to cool to rt, after which Et_2O (10 mL for 1 mmol) and H_2O (10 mL for 1 mmol) were added and the mixture was separated in a separatory funnel. The organic layer was washed with H_2O and brine, and dried (Na_2SO_4). The organic solvent was removed under reduced pressure.



13a

Phenyl benzoate (13a). General Procedure A was used with the following reagents: phenyl triflate (405 µL, 2.5 mmol, 1 equiv), $PdCl_2(PhCN)_2$ (48 mg, 0.125 mmol, 5 mol %), Xantphos (72 mg, 0.125 mmol, 5 mol %), triethylamine (0.70 mL, 5.0 mmol, 2 equiv), and phenyl formate (0.55 mL, 5.0 mmol, 2 equiv) in DMF at 80 °C. After flash chromatography (hexane), the reaction sequence afforded 480 mg (97%) of **13a** as a white solid. TLC R_f = 0.31 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.2 Hz, 2 H), 7.67-7.63 (m, 1 H), 7.55-7.50 (m, 2 H), 7.47-7.42 (m, 2 H), 7.31-7.22 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 151.1, 133.6, 130.2, 129.6, 129.5, 128.6, 125.9, 121.7.

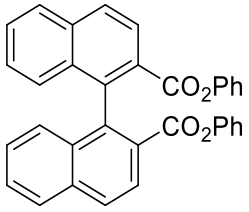


13b

Phenyl 2-naphthoate (13b). General Procedure A was used with the following reagents: naphthyl triflate (0.691 g, 2.5 mmol, 1 equiv), $PdCl_2(PhCN)_2$ (48 mg, 0.125 mmol, 5 mol %), Xantphos (72 mg, 0.125 mmol, 5 mol %), triethylamine (0.70 mL, 5.0 mmol, 2 equiv), and phenyl formate (0.55 mL, 5.0 mmol, 2 equiv) in DMF at 80 °C. After flash column chromatography (10:1 hexane / ethyl acetate), the reaction sequence afforded 590 mg (95%) of **13a** as a white solid. TLC R_f = 0.53 (10:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.22 (d, *J* = 8.4 Hz, 1 H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.97-7.92 (m, 2H), 7.65-7.59 (m, 2H), 7.49-7.45 (m, 2H), 7.33-7.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 151.2, 136.0, 132.6, 132.1, 129.7, 129.6, 128.8, 128.5, 128.0, 127.0, 126.9, 126.0, 125.6, 121.9.

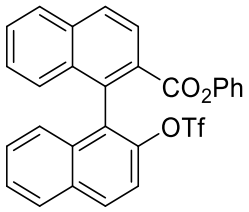
Optimized experimental.

BINOTf (275 mg, 0.50 mmol, 1 equiv), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 10 mol %) and dppp (41 mg, 0.10 mmol, 20 mol %) were added to a test tube capped with a septum and sealed by parafilm. DMSO (2.5 mL) was added through a syringe, and the mixture was stirred for 5 min. Diisopropylamine (0.34 mL, 2.0 mmol, 4 equiv), then phenyl formate (0.22 mL, 2.0 mmol, 4 equiv) was added dropwise with a syringe and the flask was placed in an oil bath at 100 °C for 24 h**.** The reaction mixture was then left to cool, after which EtOAc (40 mL) and H_2O (40 mL) were added and the mixture was separated. The organic layer was washed with H_2O (40 mL x 2) and brine (30 mL), dried (Na_2SO_4), then concentrated under reduced pressure. The products were isolated by silica gel flash column chromatography using 40:1 hexane / ethyl acetate as the eluent.



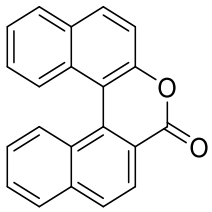
11

Diphenyl [1,1'-binaphthalene]-2,2'-dicarboxylate (11). TLC R_f = 0.52 (6:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2 H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 6.8 Hz, 2H), 7.24-7.17 (m, 8H), 7.08 (t, *J* = 7.2 Hz, 2H), 6.65 (d, *J* = 7.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 150.5, 140.4, 135.2, 132.9, 129.2, 128.3, 128.1, 127.3, 127.0, 127.0, 126.2, 125.5, 121.2; MS (ESI) *m/z* 495.1591 (*m/z* 495.5440 calcd for $C_{34}H_{23}O_4$, M + H^+).



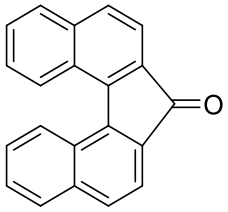
14a

Phenyl 2'-(((trifluoromethyl)sulfonyl)oxy)-[1,1'-binaphthalene]-2-carboxylate (14a). TLC R_f = 0.48 (6:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.8 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 2H), 7.90 (d, *J* = 9.4 Hz, 1H), 7.58-7.46 (m, 3H), 7.34-7.30 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 150.6, 144.3, 135.5, 134.1, 133.8, 132.6, 132.2, 130.5, 129.6, 129.5, 129.2, 128.5, 128.3, 128.2, 128.2, 127.7, 127.4, 127.4, 127.0, 126.4, 126.4, 125.7, 121.3, 119.4, 118.2 (q, $^1J_{CF}$ = 319 Hz); MS (ESI) *m/z* 523.08220 (*m/z* 523.4997 calcd for $C_{28}H_{18}F_3O_5S$, M + H^+).



19

4H-Benzo[f]naphtho[2,1-c]chromen-4-one (19).[29] TLC R_f = 0.60 (6:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.06-8.00 (m, 3H), 7.95-7.90 (m, 2H), 7.69 (t, *J* = 8.0 Hz, 1 H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.43-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 150.7, 136.9, 135.0, 131.9, 131.4, 129.9, 129.6, 129.3, 128.6, 128.6, 128.5, 127.3, 125.9, 125.9, 125.6, 125.6, 124.4, 121.8, 117.4, 113.1; MS (ESI) *m/z* 297.0910 (*m/z* 297.3267 calcd for $C_{21}H_{13}O_2$, M + H^+).



20

7H-Dibenzo[cg]fluoren-7-one [DBcgF] (20).[30] TLC R_f = 0.67 (6:1 hexane / ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37-8.35 (m, 2H), 7.92-7.89 (m, 2H), 7.87 (d, *J* = 8.3 Hz, 2 H), 7.78 (d, *J* = 6.4 Hz, 2 H) 7.59-7.56 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 138.8, 132.9, 130.1, 129.3, 128.1, 127.9, 127.7, 126.4, 119.8. MS (ESI) *m/z* 281.0966 (*m/z* 281.3273 calcd for $C_{21}H_{13}O$, M + H^+).

Chapter 7

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