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Wittig-Type Reactions

Carbonylation of Csp^3–H Bonds through Oxidative Wittig-Type Reaction: An Unprecedented Version of Wittig Reaction

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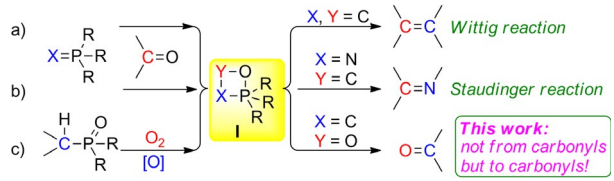
Abstract: A Wittig-type reaction was achieved by radical cation salt induced aerobic oxidation of Csp^3–H bonds. Different from the "standard" version of the Wittig reaction, in which a carbon-carbon double bond is formed from a carbonyl, carbonyl groups can be installed by similar process.

First reported in 1953,[1] the Wittig olefination reaction is one of the most powerful synthetic tools for selective construction of carbon-carbon double bonds.[2] Due to the broad applications of this method, the development of novel transformations which utilize new classes of Wittig reagents has attracted much attention in organic synthesis.[3,4] In these elegant modifications and improvements, only two versions of Wittig-type reactions were fully investigated: the classic Wittig reaction, which can install carbon-carbon double bonds from aldehydes or ketones (Scheme 1, eq. (a)), and the aza-Wittig reaction



Scheme 1. Different versions of Wittig reactions.

(Staudinger reaction), which can construct carbon-nitrogen double bonds from phosphazenes (Scheme 1, eq. (b)), nitrogen based phosphorus ylides. The formation of the four-membered oxaphosphetane intermediate (Scheme 1, intermediate I) is the key step from which the product alkene or Schiff base are released accompanied by the triphenylphosphine oxide byproduct. However, the separation of the product alkene from the byproduct triphenylphosphine oxide is a classical problem and typically requires tedious chromatography or recrystallization. To overcome this problem, the Horner–Wadsworth–Emmons olefination was developed,[5] in which the byproduct dialkyl phosphates are water-soluble and more easily separable from the alkene products than triphenylphosphine oxide.

Recently, C–H activation mediated by radical intermediates has attracted considerable attention, and a variety of methods have been established.[6] As part of our ongoing research project on radical cation initiated C–H bond functionalization,[7] we are particularly interested in developing a new process for these phosphorus substrates. We hypothesized that oxidizing Csp^3–H bonds alpha to phosphorus could produce a free radical that could be captured by dioxygen resulting in the formation of an oxo-four-membered intermediate (Scheme 1, intermediate I, X = carbon and Y = oxygen). After dialkyl phosphate leaves, a carbonyl compound arising from a formal N-formylation would be afforded (Scheme 1, eq. (c)). If feasible, this transformation would be an interesting variant of Wittig reaction, where instead of forming olefins from carbonyls, carbonyl groups could be installed through Wittig-type process.

We chose α-anilino phosphonate **1a**, which can be easily synthesized from the corresponding aniline, formaldehyde and trimethyl phosphite (see the supporting information), as the model substrate to test the possibility of this oxidative Wittig reaction. Our study began with oxidation of **1a** initiated by $TBPA^{+\cdot}$ (tris(4-bromophenyl)aminium hexachloroantimonate) in the presence of dioxygen (Table 1). To our delight, the carbonylation occurred smoothly in the presence of 10 mol% of $TBPA^{+\cdot}$ under O_2 (1 atm), yielding the expected product **2a** in 76% yield (entry 1). Although formamides can be obtained from the corresponding amines, using carboxylic acid derivatives as an acylation reagent under strongly acidic conditions by a mild and environmentally friendly method for synthesizing these compounds is still desirable and has practical benefits. Therefore, a solvent screening was then performed (entries 1–5). $CHCl_3$ was found to be the best solvent and the yield of the formylation product increased to 98% (entry 3). Evaluation of the catalyst loading (entries 5–7) showed that even 2 mol% of $TBPA^{+\cdot}$ can efficiently induce this Csp^3–H oxidation, giving the desired product in 87% yield (entry 7), although the reaction time was longer at 46 h. In view of reaction time and reaction yield, 5 mol% of $TBPA^{+\cdot}$ and $CHCl_3$ as reaction solvent were chosen as the best reaction conditions. Other single electron oxidants, such as $Mn(OAc)_3$ and oxone were also tested, but the yield of the reaction decreased dramatically, providing the desired product in trace and 31%

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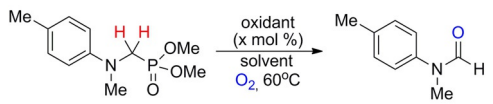
Table 1. Optimization of reaction conditions.



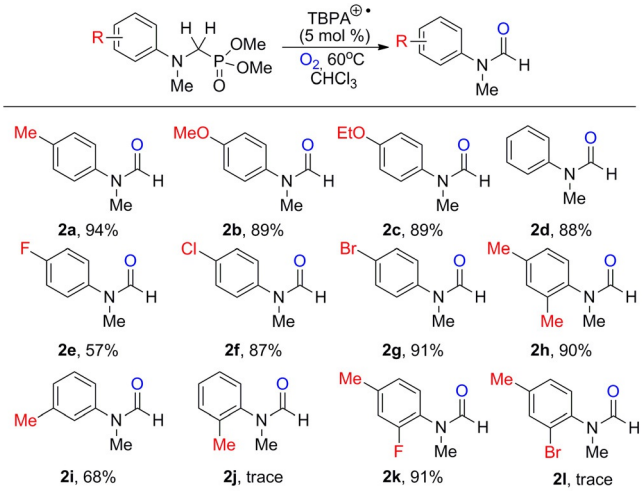
1a **2a**

Entry	Oxidant (mol%)	solvent	T [°C]	t [h]	Yield [%][a]
1	$TBPA^{+\cdot}$ (10)	MeCN	60	24	76
2	$TBPA^{+\cdot}$ (10)	DCM	60	72	trace
3	$TBPA^{+\cdot}$ (10)	$CHCl_3$	60	23	98
4	$TBPA^{+\cdot}$ (10)	$ClCH_2CH_2Cl$	60	27	84
5	$TBPA^{+\cdot}$ (10)	MeOPh	60	24	67
6	**$TBPA^{+\cdot}$ (5)**	**$CHCl_3$**	**60**	**33**	**92 (94)[b]**
7	$TBPA^{+\cdot}$ (2)	$CHCl_3$	60	46	87
8	$Mn(OAc)_3$ (10)	$CHCl_3$	60	72	trace
9	Oxone (10)	$CHCl_3$	60	72	31

[a] Yield of crude product by ^1H NMR spectroscopy using 1,3,5-trimethoxylbenzene as internal standard. [b] Yield in the parentheses is isolated yield.

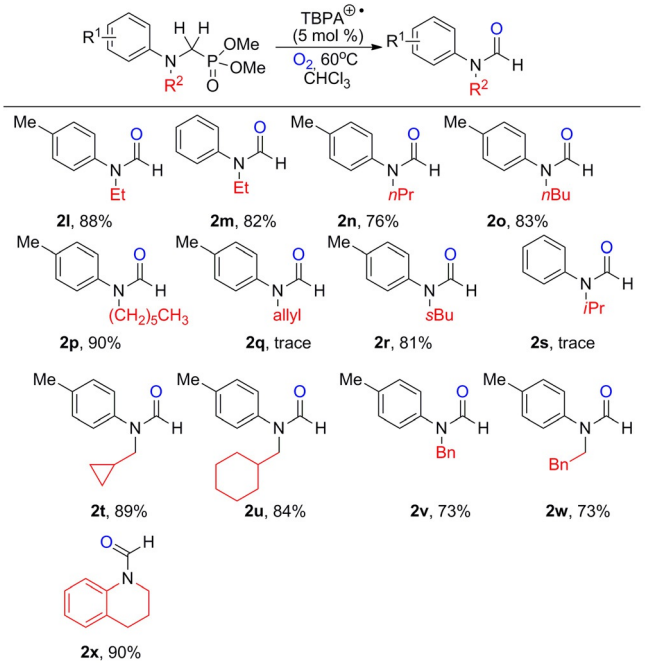
yields, respectively (entries 8 and 9), which showed that $TBPA^{+\cdot}$ can efficiently promote aerobic oxidation.

With the optimized conditions in hand, we employed various α-anilino phosphonates to test the generality of this reaction. The substituents on aniline were first evaluated and the results are compiled in Scheme 2. These results show that electron-donating substituents (Me, OMe, OEt) and electron-withdrawing groups (F, Cl, Br) do not have any deleterious effects on the reaction, and the desired products were afforded in high yields (**2a**–**2g**). The yield of this reaction was not affected by the use of 2,4-disubstituted α-anilino phosphonates **2h** and **2k** either. In our previous reports, the absence of a *para* substituent at the aniline dramatically decreased the yield of the desired product,[7a–c] but in this case *N*-methyl-*N*-(*m*-tolyl)formamide (**2i**) was obtained in 68% yield. However, only trace amount of the formylation product was detected by TLC, and about 85% of the starting material was recovered, when *o*-tolylanilino phosphonate (**2j**) was used. Although the exact reason remains unknown, we speculate that the *ortho* group hinders the p–π conjugation between nitrogen and aryl ring due to steric hindrance, which weakens the stability of the radical intermediate. A similar result was obtained with 2-bromoanilino phosphonate (compare **2l** with **2k**).



Scheme 2. Reaction of substituted anilino phosphonates.

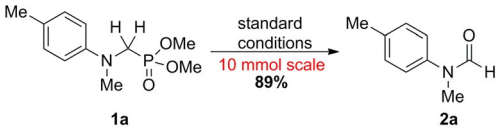
The alkyl groups on nitrogen were then varied to extend the reaction scope. From Scheme 3 we can see that all of the alkyl groups tested did not affect the reaction, and good yields were obtained (**2l**–**2s**). A susceptible cyclopropylmethyl group remained unchanged under the oxidative conditions (**2t**), which shows that the functional group tolerance is good. The existence of another active benzyl Csp^3–H bond, which might disturb the oxidation process, did not exert negative effect on this reaction (**2v** and **2w**), which suggests that the oxidation occurred selectively on the C–H bonds adjacent to phosphorous. This carbonylation of Csp^3–H bonds was also successfully applied to a 1,2,3,4-tetrahydroquinoline-derived phosphorate, and the formylation product was isolated in 90% yield (**2x**).



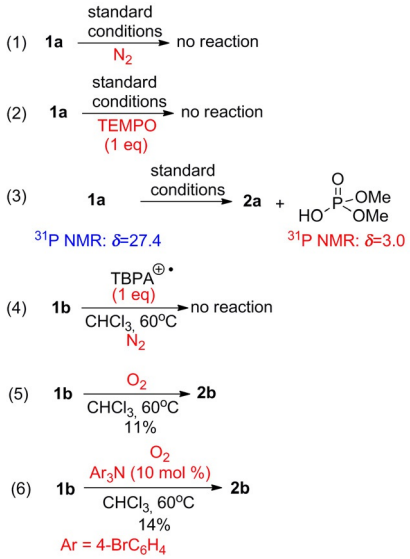
Scheme 3. Reaction of α-anilino phosphonates. Bn = benzyl.

To evaluate the practical application of our method, the reaction of **1a** was performed on large scale. To our delight, in the presence of 2 mol% $TBPA^{+\cdot}$, the desired product was isolated in 89% yield, suggesting potential in industrial applications (Scheme 4).

Various control experiments were conducted to investigate the reaction mechanism (Scheme 5). In the absence of dioxygen, the reaction does not occur, and the starting material was recovered in 95% yield (Eq. (1)), which confirmed the participation of dioxygen. In the presence of radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) the reaction was complete-



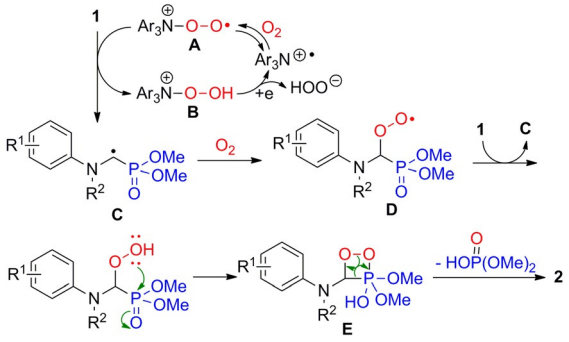
Scheme 4. Oxidative Wittig-type reaction on large scale.



Scheme 5. Control experiments.

ly inhibited, implying the reaction proceeded through a radical intermediate (Eq. (2)). To verify the valence state of phosphorus, the ^{31}P NMR spectra of **1a** and the crude products were compared, and the results show that dimethyl hydrogen phosphate was released (Eq. (3)), which supports the hypothesis that an oxo-four-membered intermediate is formed during the reaction mechanism. As suggested by a reviewer, the roles of TBPA$^{+\cdot}$ and dioxygen were further evaluated. The reaction of **1b** was performed under a nitrogen atmosphere in the presence of one equivalent of TBPA$^{+\cdot}$, but no reaction occurred (Eq. (4)). The starting material was recovered in 95% yield and this result shows that TBPA$^{+\cdot}$ could not oxidize the α-anilino phosphonates directly. Then the aerobic oxidation was conducted in the absence of TBPA$^{+\cdot}$ [Eq. (5)], and the desired product was obtained in 11% yield (the starting material was recovered in 81% yield), suggesting that dioxygen can oxidize the C–H bonds adjacent to nitrogen, but the reaction yield was not good. To rule out other possibilities, we conducted this reaction in the presence of tris(4-bromophenyl)amine, the precursor of TBPA$^{+\cdot}$ (Eq. (6)) and the desired product was isolated in comparable yield (the starting material was recovered in 82% yield). Above results show that this aerobic oxidation was initiated by a combination of dioxygen and TBPA$^{+\cdot}$, which is in accord with our proposed mechanism.[7a–b]

Based on the control experiments, a radical mediated mechanism is proposed (Scheme 6). Initially, TBPA$^{+\cdot}$ couples with dioxygen, generating an active peroxy radical cation **A**, which abstracts a hydrogen from **1** to initiate the C–H oxidation.



Scheme 6. Proposed mechanism of oxidative Wittig-type reaction.

After fragmentation of the peroxide intermediate **B**, TBPA$^{+\cdot}$ is regenerated to participate in the next catalytic cycle. The generated radical **C** is trapped by dioxygen, generating a peroxide radical **D**. After hydrogen abstraction, a peroxide is provided, followed by intramolecular cyclization, and the oxo-four-membered intermediate **E** is formed. Then dialkyl phosphate leaves and the desired carbonylation product of C–H bonds was yielded.

In a conclusion, an oxidative Wittig-type reaction was achieved via radical cation salt promoted aerobic oxidation of sp^3 C–H bonds. Different from the reported versions of Wittig-type reactions, in which a carbonyl group was used to construct C=C bonds, a carbonyl group was installed by similar process. This version of the Wittig reaction is a good complement to the classical Wittig reaction and will inspire new designs of Wittig-type reactions to construct a wider range of functional groups. Further applications of this reaction and other related transformations are still under investigation in our laboratory.

Experimental Section

A solution of **1** (1 mmol) in $CHCl_3$ (5 mL) was mixed fully and flushed with O_2, then TBPA$^{+\cdot}$ (5 mol%) was added dropwise under an oxygen atmosphere. The reaction solution was stirred at 60 °C. After completion, monitored by TLC (by UV visualization), the reaction was quenched by addition of saturated Na_2CO_3 in MeOH (10 mL) solution. The mixture was poured into a separating funnel with the addition of excess $CHCl_3$ (10 mL), and then the crude organic solution was extracted three times with water to remove inorganic salts. The organic phase was then dried over anhydrous magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The products were separated by silica gel column chromatography eluted with petroleum ether/acetone (v/v 10:1) to afford the products.

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Keywords: α-anilino phosphonates · carbonylation · C–H functionalization · oxidative Wittig reaction · radical cations

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