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Direct Transformation of Amides into α-Amino Phosphonates *via* a Reductive Phosphination Process

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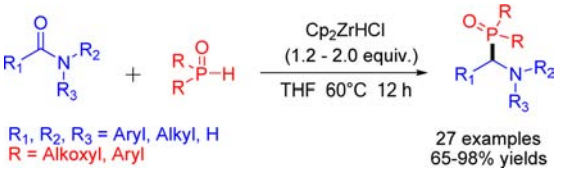
ABSTRACT



The first general method for the reductive phosphination of amides in one pot has been developed. The reactions described provide a novel access to α-amino phosphonates in good to excellent yields, cover a broad scope of substrates such as secondary and tertiary amides, and do not require a low temperature.

α-Amino phosphonates have played an increasingly important role in a variety of areas such as medical chemistry and biologicals,[1] herbicides,[2] and fungicides.[3] Despite more than 60 years of effort and the development of numerous methods, organic chemists continue to search for more straightforward ways to make α-amino phosphonates. Among them, the Pudovik reaction[4] and the Kabachnik–Fields reaction[5] emerged as the most widely adopted protocols (Scheme 1). The nucleophilic addition reaction of phosphites with imines is an important general method for the formation of the N–C–P bonds, which is usually promoted by Lewis bases and acids following the pioneering work of Pudovik.[4] However, these generate good yields of α-amino phosphonates only if an imine is employed as a conjugated system.[6] The Kabachnik–Fields reaction is a three-component reaction of an amine, an aldehyde, and a dialkyl phosphite, leading to the formation of α-aminophosphonic acid esters.

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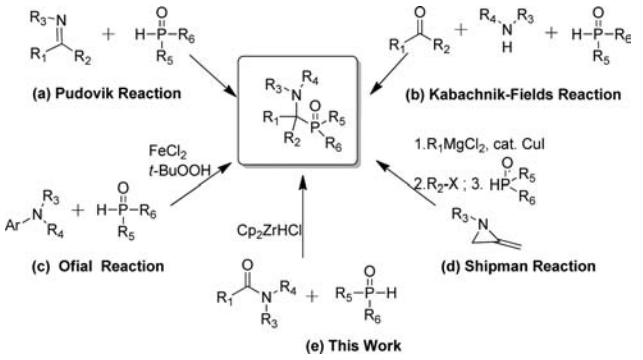
Scheme 1. Synthetic Routes to α-Amino Phosphonates



The important advantages of the method include the fact that it is a single-stage process and the availability of the starting compounds. Recently, great efforts have been made to develop the Lewis acid catalytic,[7] catalyst-free,[8] and asymmetric[9] synthesis of α-amino phosphonates involving the condensation of *H*-phosphonates with aldehydes or imines, along with the use of microwave techniques.[10] Although these methods are very mature, the range of starting materials is limited to aldehydes or imines. In 2009, Shipman and co-workers developed a "one-pot" synthesis of α-amino phosphonates from methyleneaziridines.[11] In addition, in 2010 Ofial et al. discovered that C(sp^3)−H bonds in the α-position to nitrogen of *N,N*-dialkylanilines could be activated for a subsequent C−P bond formation.[12] α-Amino phosphonate could be also obtained by the oxidation of benzyl alcohol in the presence of aniline and dimethyl phosphite, but only one example was reported by the Fan group.[13] Unfortunately, only the special starting materials such as aromatic amines and methyleneaziridines were investigated in recent years. Consequently, the development of a general and direct method for the transformation of other functional groups such as amides into α-amino phosphonates is highly desirable in synthetic organic chemistry.

Amides as a class of readily available compounds are pervasive in nature. Owing to their resonance stabilization, the amide group is relatively inert to reduction and direct nucleophilic addition.[14] Traditionally, before nucleophilic addition, preactivation of amides is required.[15] The most popular reductant is lithium aluminum hydride which has poor selectivity, and many more groups may be reduced. Recently, the research groups of Belanger[16] and Huang[15e] reported the triflic anhydride activated reductive alkylation of amides into amines respectively. Moreover, Gunda I. Georg et al. reported the use of Schwartz's reagent (Cp_2ZrHCl) to reduce amides to the corresponding aldehydes and its mechanism was discussed.[18] Additionally, Noritaka Chida et al. demonstrated the use of reactive nucleophile DIBAL[17] and Cp_2ZrHCl[19] to directly transform amides into amines by reductive alkylation using organic metallic reagents as the nucleophiles. However, the reaction conditions were harsh. Based on these considerations, it would be particularly interesting and valuable to develop the reductive phosphorus nucleophilic addition reaction of amides under mild conditions, which has not been reported so far. We envisioned that reduction of the amide carbonyl using the Schwartz reagent might help us to achieve this goal.

Our continued interest in P−C formations recently[20] prompted us to explore the possibility of the phosphination of inert amide carbonyls promoted by Cp_2ZrHCl for the preparation of α-amino phosphonates (Scheme 1). Compared with the aldehydes and imines, the amides are readily available, highly stable, and less toxic. Direct condensation of simple *H*-phosphonates with amides is found to be a more interesting and valuble route than those reactions using aldehydes and imines as the reagents.

We began our investigations with the examination of the reaction of *N*-benzylbenzamide (**1a**) with diethyl *H*-phosphonate (**2a**) and Cp_2ZrHCl. At the outset, the reaction was carried out in THF. The choice of temperature is critical for the reaction (entries 1−3). At room temperature, product **3a** was detected in only 14% yield (Table 1, entry 1). The reaction also proceeded slowly at 40 °C, giving a 78% yield (entry 2). However, when the temperature was raised to 60 °C for 12 h, the phosphination of amide led to **3a** in 97% yield (entry 3). The choice of

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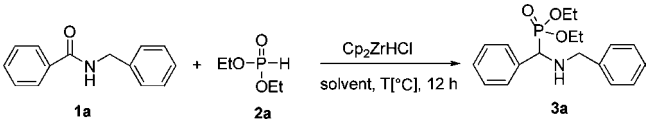
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

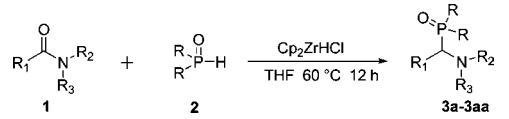
entry	solvent	T (°C)	yield (%)
1	THF	rt	14
2	THF	40	78
3	THF	60	97
4	dioxane	60	62
5	dioxane	100	88
6	toluene	60	21
7	toluene	110	75
8	DCE	60	64
9	DCE	80	91[b]
10	CH_2Cl_2	40	10
11	CH_3CN	80	trace
12	DME	80	75

[a] Reaction conditions: **1a** (0.3 mmol) and **2a** (0.36 mmol), Cp_2ZrHCl (0.66 mmol), solvent (3 mL), under nitrogen for 12 h in a Schlenk tube. Yields were determined by ^{31}P NMR. [b] The reaction time is 24 h.

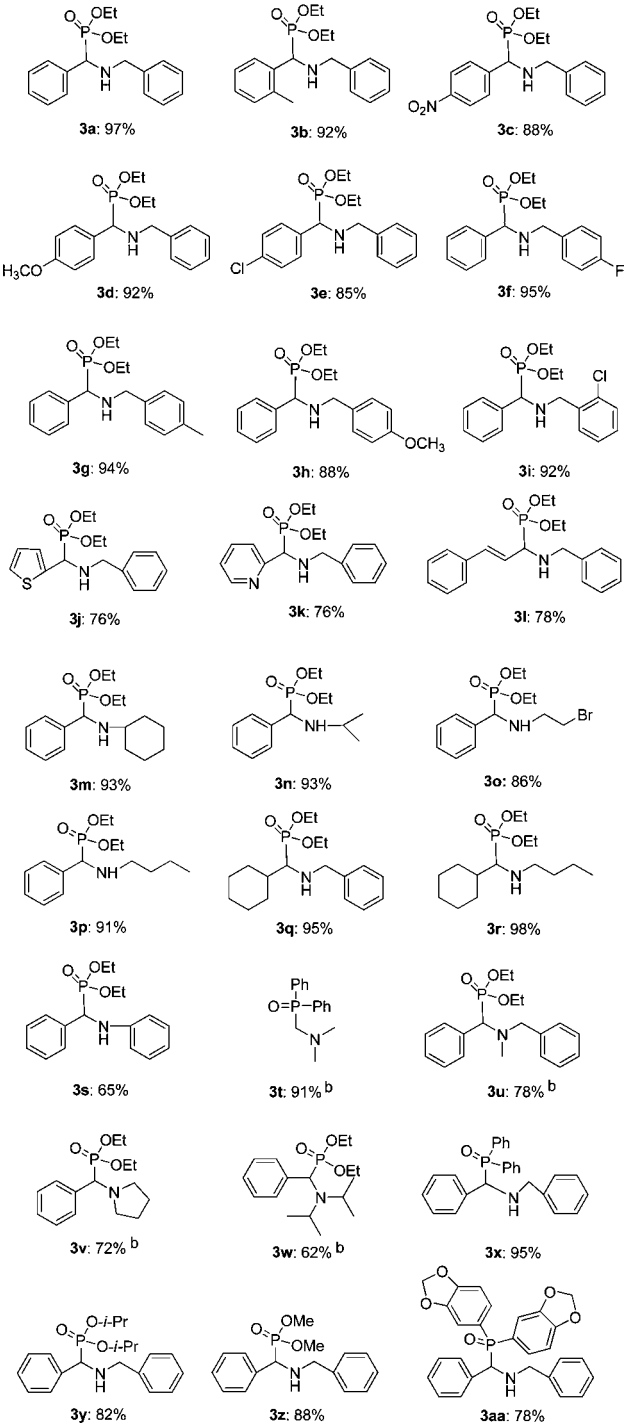
solvent is also very important. Like THF, 1,4-dioxane is also a suitable solvent for this reaction. At 60 °C for 12 h, only a 62% yield was obtained (entry 4). When the temperature was raised to the refluxing temperature, the yield could reach 88% (entry 5). When the reaction was performed in toluene, CH_2Cl_2, or CH_3CN, a much lower yield was obtained at its refluxing temperature. The reaction conducted in 1,2-dichloroethane (DCE) at 60 °C led to a moderate yield. Further screening indicated that raising the temperature to 80 °C and prolonging the time to 24 h resulted in a satisfactory yield (entry 9).

Having the optimal conditions in hand, we next examined the reactions of various amides with diethyl *H*-phosphonate to understand the scope of the reaction (Table 2). A variety of secondary amides, including aroyl (Table 2, **3a**–**3k**, **3m**–**3p**, **3s**), alkanoyl (Table 2, **3q**, **3r**), and alkenoyl (Table 2, **3l**) amides, were transformed into the corresponding α-amino phosphonates in good to excellent yields. The substituted benzoyl group with electron-withdrawing nitro group and electron-donating methoxyl group also reacted smoothly with *H*-phosphonate resulting in products **3c** and **3d** in 88% and 92% yield, respectively. Although nitro functionalities are easily reduced, they were maintained and the reaction indicated exceptional chemoselectivity (**3c**). Halogen atoms such as fluoro and chloro on the aromatic ring (**3e**, **3f**, **3i**) and alkyl chloride (**3o**) were unaffected under the present reaction conditions. Heteroaromatic compounds can also participate in the α-amino phosphination in a slightly lower yield due to a potential interaction between zirconium and the S, N atoms (**3j**, **3k**). It should be noted that the reaction of α,*β*-unsaturated amides led to a highly selective 1,2-addition and giving a 78% yield (**3l**), whereas amides

Table 2. Direct Transformation of Secondary Amides into α-Amino Phosphonates[a]

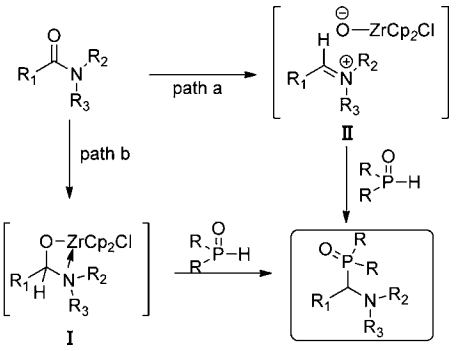


1 2 3a-3aa



[a] Conditions: treatment of **1a** (0.3 mmol) in anhydrous THF (3 mL) with Cp_2ZrHCl (0.66 mmol) under nitrogen which was stirred at rt, and then **2a** (0.36 mmol) was added until the suspension cleared (about 5–15 min); the mixture was stirred at 60 °C for about 12 h in a Schlenk tube. [b] Cp_2ZrHCl (1.2 equiv).

Scheme 2. Possible Mechanism



containing a terminal double bond and terminal triple link did not allow us to isolate the expected product. Similarly, when the amides contain a hydroxyl, no product could be detected, probably because Cp_2ZrHCl could be inactivated by the active hydrogen.

Phosphination of aliphatic amides also gave excellent results (**3n**−**3p**), whereas aliphatic aldimine compounds that react with phosphite often yield α-amino alkylphosphonates in very low yields by the Pudovik reaction. Benzyl (**3a**−**3i**), phenyl (**3t**), *n*-alkyl (**3l**, **3m**), and *sec*-alkyl (**3j**, **3k**) groups on the nitrogen atom of the secondary amides did not influence the reaction efficiency.

Only 1.2 equiv of Cp_2ZrHCl was needed when tertiary amides were used as reactants. The reductive phosphorylation of tertiary amides also resulted in the formation of tertiary α-aminophosphonate in 72−91% yields (**3t**−**3w**). Dimethylformamide (DMF) reacted with *H*-phosphonate to afford **3t** in high yield. Diisopropyl amide reacted for 12 h. providing 62% of the desired product (**3w**). The above results show that steric hindrance on the amine portion of the carboxamide is the cause of the lower yields.

The *H*-phosphonate reaction was also successfully applied to dibenzyl, diisopropyl, and dimethyl *H*-phosphonates and *H*-phosphonates containing acetals in satisfactory yields in addition to diethyl *H*-phosphonate, indicating that the reactivities of these dialkyl phosphonates are almost independent of the alkyl moieties (**3a**, **3x**−**3z**, **3aa**). The acetal group was well tolerated in the reaction (**3aa**), but the yield was affected by the steric hindrance.

Based on the above experiment results and previous reports,[18b,20] a plausible reaction mechanism could be proposed in Scheme 2. By treatment of amide with Cp_2ZrHCl, two possible intermediates I and II were formed and subsequently reacted with *H*-phosphonate to produce the corresponding α-amino phosphonates.

In conclusion, the first general method for the reductive phosphination of amides using the Schwartz reagent in one pot has been developed. The reactions described provide a novel access to α-amino phosphonates in good to excellent yields, cover a broad scope of substrates such as secondary and tertiary amides, and do not require a low temperature. Moreover, the amides are highly stable, easily available, and versatile. Further application of this method toward the synthesis of biologically active molecules is in progress.

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Supporting Information Available. General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.