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Multicomponent One-Pot Procedure for the Synthesis of Free α-Chiral Amines from Aldehydes

Alexandre Côté and André B. Charette*

Département de Chimie, Université de Montréal, P.O. 6128, Station Downtown, Montréal, Québec, Canada H3C 3J7

andre.charette@umontreal.ca

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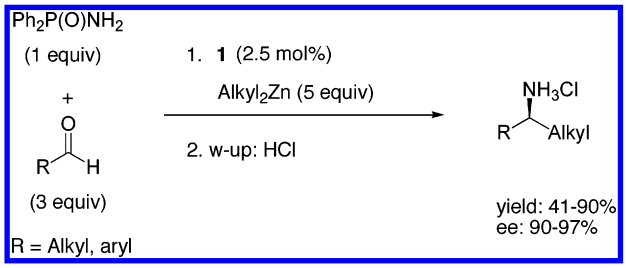

The synthesis of free α-chiral amines by a one-pot multicomponent procedure from commercially available starting materials is described. This enantioselective reaction involves a catalytic asymmetric addition of dialkylzinc reagents to *N*-diphenylphosphinoylimines with use of an air-stable precatalyst complex **1**. The α-chiral amines are prepared with a one-pot procedure from alkyl and aryl aldehydes in good yield (41−90%) and with excellent enantioselectivity (90−97% ee).

The extensive use of enantiopure α-chiral amines in food, agrochemical, biochemical, and pharmaceutical industries has stimulated the development of methodologies to generate them.[1] A one-pot multicomponent[2−4] synthesis would be extremely valuable in high-throughput processes which are amenable to automation, such as combinatorial and parallel synthesis.[5]

Having recently developed a catalytic asymmetric reaction to generate α-chiral amines,[6,7] we have aimed at finding experimental conditions that could be adapted to a parallel synthesis format. Described herein is our approach, which reduces the typical three-step synthesis to a one-pot process (Scheme 1). The dehydrating property of diorganozinc reagents was utilized to generate imines in situ, as previously demonstrated by Hoveyda and Snapper.[3a,b] We have also taken advantage of the facile cleavage of a phosphinoyl activating group[1b,8] from amines under acidic workup conditions.

This is a very effective and general method to gain access to free α-chiral amines directly from commercially available reagents. The Leuckart−Wallach-type conditions developed by Kadyrov and co-workers seem to be limited to acetophenone derivatives.[9] Enzymatic methods possess the disadvantage that enzymes are substrate specific, thus reducing the generality of the protocol.[10]

Optimization experiments were performed with commercially available aldehydes that were not further purified prior to use. Despite the fact that preliminary results have shown that slightly better enantioselectivities could be obtained with neat diorganozinc reagents, we chose to use solutions in toluene for safety (some neat dialkylzinc reagents are pyrophoric), availability, and economical considerations.

An examination of the stoichiometry revealed that 3 equiv of aldehyde and 5 equiv of dialkylzinc reagent, relative to the phosphinoylamide, provided the best compromise between economy of reagents, overall yield, and quantity of side products formed.

The main challenge in transferring the methodology to a parallel synthesis format was to find conditions to effect complexation, since this typically involves mixing

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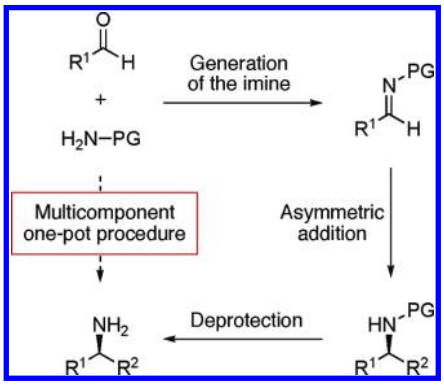
SCHEME 1. Typical Three-Step Sequence for the Synthesis of Free α-Chiral Amines



two heterogeneous solutions under an inert atmosphere. We have not yet isolated a BozPHOS·CuOTf complex, the putative active catalyst. However, we prepared complex **1** (Figure 1) and discovered that the addition of **1** to a solution of aldehyde and phosphinoylamide led to the formation of α-chiral amines with yields and enantioselectivities similar to those obtained from a mixture of BozPHOS and $Cu(OTf)_2$. Complex **1** may be a precursor to the active catalyst, which greatly simplifies the experimental protocol, since **1** is a stable crystalline compound that can be manipulated in air for several weeks.[11] Purification of **1** can be accomplished easily by flash chromatography. As both enantiomeric forms of **1** are accessible, both enantiomers of the product can be synthesized equally well.[12]

Although in our earlier studies we had obtained good enantioselectivities at 0 °C, we found that the yields could be increased by carrying out these multicomponent reactions at ambient temperature without any significant loss of enantioselectivity (Table 1). A study of the precatalyst loading revealed that there was no significant effect on yield and only a small variation in the enantioselectivity within the range between 5 and 1 mol % of **1**. Most notably, similar yields and enantioselectivities were obtained regardless of whether measures were taken to exclude moisture and oxygen (compare entries 1 and 4).

As shown in Table 2, our methodology can be applied to a wide scope of substrates. Alkyl, aryl, heterocyclic, ether, nitro, and halogen functional groups are compatible with the reaction conditions. This tolerance of functionality, combined with the commercial availability of numerous aldehydes as building blocks, creates the potential for extensive diversification through parallel synthesis. Although there are few dialkylzinc reagents that are commercially available, many efficient methods to generate them are known.[13] In addition, organozinc reagents can support functionalization more readily than organomagnesium and organolithium reagents.[14]

While many aldehydes can be employed under our conditions, they do exhibit differences in reactivity. Benzaldehyde derivatives having electron withdrawing groups (entries 2 and 6) seem to be more prone to side reactions such as reduction and noncatalyzed addition of diethylzinc to aldehyde and imine, which leads to lower yields and enantioselectivities. However, this problem can be circumvented either by decreasing the concentration from 0.2 to 0.1 M or by decreasing the reaction temperature to 0 °C. Typical side products are illustrated in Figure 2.[15] Compounds **3a** and **4a** can be removed by a reverse extraction whereby the ammonium salts are retained in the aqueous phase and the alcohols are retained in the etheral phase. Only very small quantities of compound **5** are produced, which can be separated by either normal phase or reverse phase chromatography.

A low reaction temperature is necessary to achieve high enantioselectivity from the unbranched aliphatic aldehyde **2i** (entry 9). As with other copper-mediated addition to imines, the rate of reaction of dimethylzinc is lower than that of diethylzinc.[3a,7a,16,17] By increasing the reaction time, it is possible to get the desired product with excellent ee in acceptable yields. In the case of the furyl derivative **2g**, improved yields were obtained by isolating the addition product prior to treatment with aqueous HCl to cleave the phosphinoyl group. The neutral form of **2g** is difficult to extract from the aqueous phase, possibly as a result of complexation with excess zinc species in solution.

In conclusion, we have developed a one-pot procedure to gain access to free α-chiral amines using commercially available starting materials and an air-stable chiral precatalyst copper complex. Our methodology is highly suited for automated parallel synthesis.

Experimental Section

Synthesis of Complex (1). $(CuOTf)_2$·toluene (200 mg, 0.39 mmol) and BozPHOS[6] (500 mg, 1.55 mmol) were solubilized in anhydrous MeCN (10 mL) under an atmosphere of argon and the resulting green solution was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel with CH_2Cl_2/MeOH (95:05) as eluent. The title compound was obtained as a light yellow solid (598 mg, 90%). Mp 199.0−200.5 °C; R_f 0.33 (10% MeOH in CH_2Cl_2); $[\alpha]^{23}_D$ +5.47 (*c* 2.53, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.82−7.73 (m, 2H), 7.72−7.61 (m, 4H), 7.55−7.44 (m, 2H), 2.94−2.78 (m, 2H), 2.60−2.09 (m, 14H), 1.81−1.34 (m, 14H), 1.21 (dd, J = 14.9, 6.9 Hz, 6H), 0.94 (dd, J = 6.7, 4.7, 6H), 0.89 (d, J = 7.1 Hz, 6H); ^{13}C NMR (300 MHz, CD_2Cl_2) δ 139.0 (dt, J = 5.0, 5.0 Hz), 135.7 (d, J = 9.8 Hz), 134.5 (dt, J = 77.7, 7.5 Hz), 132.4 (dt, J = 14.1, 3.7 Hz), 131.8, 130.1 (d, J = 12.2 Hz), 121.6 (q, J = 321.6 Hz), 39.3 (d, J

(11) Complex **1** can be stored in a vial under a non-inert atmosphere for several weeks without noticeable decomposition. With time, the complex tends to be hydrated and becomes green. A simple purification by flash chromatography can lead to the initial clean complex.

(12) The absolute configuration was determined by comparison of the optical rotation of compounds **2a**, **2h**, **2i**, and **2j** with the literature and by extrapolation for others.

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(15) The side product ratios for the reactions are dependent on the starting aldehyde. When benzaldehyde was used as the starting material, the ratios were 3/34/40/20/3 (benzaldehyde/**2a/3a/4a/5a**).

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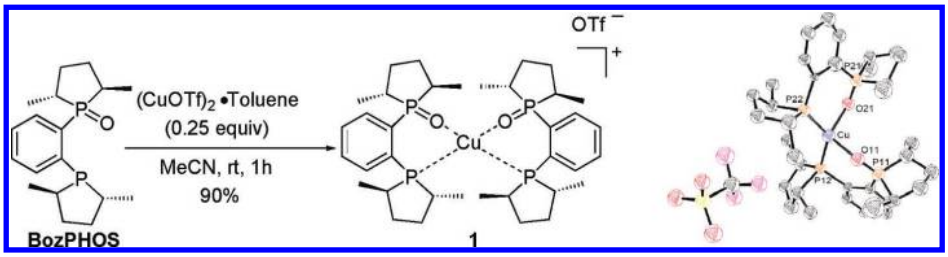
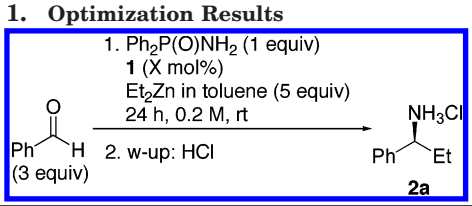


FIGURE 1. Synthesis and ORTEP representation of the organometallic complex **1**.

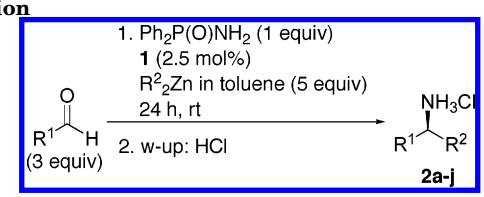
TABLE 1. Optimization Results



entry	**1** (mol %)	yield (%)	ee (%)[a]
1	1	85	93
2	2.5	85	95
3	5	83	96
4[b]	2.5	84	95
5[c]	2.5	88	97
6[d]	2.5	83	98
7[e]	2.5	63	97

[a] Determined by GC on β-Dex column. [b] The reaction was run under non-anhydrous conditions: reaction test tubes were not dried, reagents and complex **1** were weighed under ambient conditions, and the reaction was run in a sealed flask without argon. [c] The reaction was run at 0.1 M. [d] The reaction was run at 0 °C. [e] The reaction was run with 1 equiv of benzaldehyde.

TABLE 2. Scope of the Multicomponent One-Pot Reaction



entry	R^1	R^2	yield (%)	ee (%)[a]
1	Ph (**2a**)	Et	88	97
2[b]	2-ClPh (**2b**)	Et	54	96
3	2-OMePh (**2c**)	Et	90	95
4	2-Me-Ph (**2d**)	Et	68	96
5	1-naphthyl (**2e**)	Et	59	97
6[b]	3-NO_2Ph (**2f**)	Et	79	97
7[b,c]	2-furyl (**2g**)	Et	65	93
8	*i*-Pr (**2h**)	Et	62	93
9[b]	$PhCH_2CH_2-$ (**2i**)	Et	59	90
10[b,d]	Ph (**2j**)	Me	32	92
11[b,e]	Ph (**2j**)	Me	41	90

[a] Determined by GC, HPLC, or SFC on chiral stationary phase. [b] Reaction was run at 0 °C. [c] The addition product was isolated to remove zinc salts prior to the cleavage of the activating group. [d] Reaction was run for 48 h. [e] Reaction was run for 96 h.

= 65.7 Hz), 38.5 (t, J = 8.8 Hz), 37.1 (t, J = 7.8 Hz), 36.7, 36.4, 35.2 (d, J = 69.5 Hz), 32.9 (d, J = 10 Hz), 32.6 (d, J = 8.6 Hz), 20.6 (t, J = 11.5 Hz), 15.0, 14.4, 13.2 (d, J = 3 Hz); ^{19}F NMR (282 MHz, CD_2Cl_2) δ −79.1; ^{31}P NMR (121 MHz, CD_2Cl_2) δ 72.0 (t, J = 5.4 Hz), 5.2 (br); IR (neat) 2929, 2867, 1453, 1262, 1144, 1123, 1030, 740, 667, 635 cm^{-1}; LRMS (APCI+) $[M - OTf]^+$ calcd m/z 707.3, found m/z 707.2. Elemental analysis calcd for $C_{37}H_{56}CuF_3O_5P_4S$: C, 51.83; H, 6.58; S, 3.74. Found: C, 51.74; H, 6.79; S, 3.33.

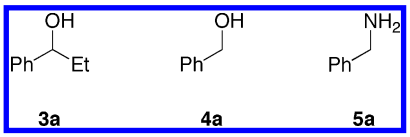


FIGURE 2. Typical side products observed.

General Multicomponent One-Pot Procedure To Generate α-Chiral Amime (HCl Salt) by Addition of Diethylzinc (2a−i). In a reaction tube equipped with a cross-shaped magnetic stirring bar were added the complex **1** (21 mg, 0.025 mmol), the diphenylphosphinoylamide (217 mg, 1 mmol), and the aldehyde (3 mmol) under argon. Anhydrous toluene (5.5 mL) was added for a 0.1 M concentration and the solution was cooled to the specified temperature (0 or 25 °C). When the temperature was reached, a solution of diethylzinc in toluene (1.1 M, 4.5 mL, 5 mmol) was added over 1 min to control the gas evolution (this is an exothermic step). After 24 h, the reaction tubes were cooled to 0 °C (cooling allows the evolution of gas to be controlled), opened, and quenched by dropwise addition of water (2 mL) (**Caution**: the quench produces a considerable amount of ethane). Finally, concentrated HCl was added (2 mL) and the resulting two-phase solution was stirred for 8 h (for most of the substrates the cleavage was complete in less time). The aqueous phase was separated, washed with Et_2O (4 × 10 mL) to remove side products **3** and **4**, then basified to pH 12 with 4 M NaOH and extracted with Et_2O (4 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and acidified with 2 M HCl in Et_2O to form the corresponding HCl salt, which is less volatile and easier to manipulate than the free amine. The salts were purified by flash chromatography, using CH_2Cl_2/MeOH as eluent, and acidified with gaseous HCl to convert traces of free amine to their salt form. Preparative HPLC with a reverse phase column can also be used.

Specific Multicomponent One-Pot Procedure To Generate (1*S*)-1-(2-Furyl)propan-1-ammonium Chloride (2g). In a reaction tube equipped with a cross-shaped magnetic stirring bar were added the complex **1** (21 mg, 0.025 mmol), the diphenylphosphinoylamide (217 mg, 1 mmol), and the 2-furaldehyde (3 mmol) under argon. The solid mixture was cooled to 0 °C. When the desired temperature was reached, a solution of diethylzinc in toluene (1.1 M, 4.5 mL, 5 mmol) was added over 1 min to control the gas evolution (this is an exothermic step). After 24 h, the reaction tubes were cooled to 0 °C (cooling allows the evolution of gas to be controlled), opened, and quenched by a dropwise addition of a saturated solution of NH_4Cl (10 mL) (**Caution**: the quench produces a considerable amount of ethane). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the organic phases were combined, dried over Na_2SO_4, and evaporated to dryness. The solid residue was suspended in toluene (2 mL), concentrated HCl was added (2 mL), and the resulting two-phase solution was stirred for 8 h. The aqueous phase was separated, washed with Et_2O (4 × 10 mL) to remove side products **3** and **4**, then basified to pH 12 with 4 M NaOH and extracted with Et_2O (4 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and acidified with 2 M HCl in Et_2O to form the corresponding HCl salt, which is less volatile and easier to manipulate than the free amine. The salts were purified by flash chromatography, using CH_2Cl_2/MeOH as eluent, and acidified with gaseous HCl to convert traces of free

amine to their salt form. Preparative HPLC with a reverse phase column can also be used.

General Multicomponent One-Pot Procedure To Generate α-Chiral Amime (HCl Salt) by Addition of Dimethylzinc (2j). In a reaction tube equipped with a cross-shaped magnetic stirring bar were added the complex **1** (21 mg, 0.025 mmol), the diphenylphosphinoylamide (217 mg, 1 mmol), and the aldehyde (3 mmol) under argon. Then a solution of dimethylzinc in toluene (2.0 M, 2.5 mL, 5 mmol) was added over 5 min to control the gas evolution to 25 °C (this is an exothermic step). After 48 or 96 h, the reaction tubes were cooled to 0 °C (cooling allows the evolution of gas to be controlled), opened, and quenched by dropwise addition of water (2 mL) (**Caution**: the quench produces a considerable amount of ethane). Finally, concentrated HCl was added (2 mL) and the resulting two-phase solution was stirred for 8 h (for most of the substrates the cleavage was complete in less time). The aqueous phase was separated, washed with Et_2O (4 × 10 mL) to remove side products **3** and **4**, then basified to pH 12 with 4 M NaOH and extracted with Et_2O (4 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and acidified with 2 M HCl in Et_2O to form the corresponding HCl salt, which is less volatile and easier to manipulate than the free amine. The salts were purified by flash chromatography, using CH_2Cl_2/MeOH as eluent, and acidified with gaseous HCl to convert traces of free amine to their salt form. Preparative HPLC with a reverse phase column can also be used.

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Supporting Information Available: General information, specific experimental conditions, CIF file, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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