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Catalytic Asymmetric Synthesis of α,α,α-Trifluoromethylamines by the Copper-Catalyzed Nucleophilic Addition of Diorganozinc Reagents to Imines

Caroline Lauzon and André B. Charette*

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

andre.charette@umontreal.ca

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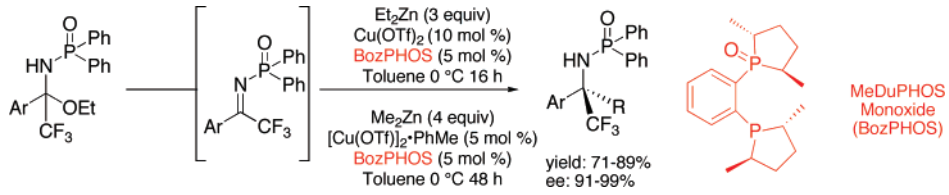
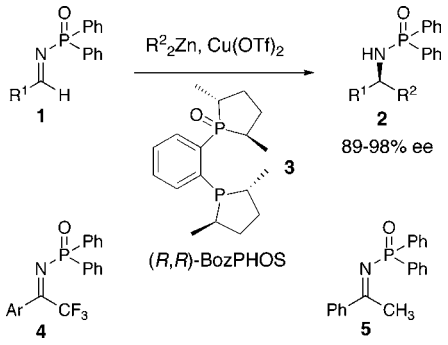
ABSTRACT



A copper-catalyzed asymmetric addition of diorganozinc reagents to *N*-phosphinoylimines has been developed for the synthesis of chiral α,α,α-trifluoromethylamines. The trifluoromethyl ketimines, generated in situ from the corresponding hemiaminals, led to the chiral amides in high yields (71–89%) and excellent enantiocontrol (91–99% ee).

The incorporation of lipophilic trifluoromethyl groups in bioactive compounds is a popular strategy to increase their bioavailabilities by increasing their ability to cross membranes. In addition, the strength of the carbon−fluorine bond generally results in an increased metabolic stability relative to that of the parent C−H analogue.[1] Although there are many known methods for the enantioselective synthesis of tertiary chiral amines bearing a trifluoromethyl group, the majority rely on the use of chiral auxiliaires.[2,3] Even though there are a number of catalytic asymmetric additions of diorganozinc reagents to aldimines,[4] extension of these approaches to ketimines has not been reported so far. We have recently reported a copper-catalyzed asymmetric addition of diorganozinc reagents to *N*-phosphinoylimines involving bis(phosphine) monoxide ligand **3** (Scheme 1).[5] Herein, we report a new method for the preparation of α-trifluoromethyl-substituted amines based on this asymmetric transformation and the use of a new precursor to imine **4**.

Scheme 1. Synthesis of α-Chiral Amines



Although *N*-phosphinoylimines derived from ketones are significantly less reactive than those synthesized from aldehydes, it was anticipated that trifluoromethyl-substituted imines **4** should display reactivities similar to those of the corresponding aldimines. No addition to imine **5** was observed upon treatment with diethylzinc (3 equiv), $Cu(OTf)_2$ (5 mol %), and BozPHOS (**3**, 5 mol %) and quenching experiments with deuterium oxide indicated that deprotona-

(1) (a) *Organofluorine Compounds: Chemistry and Applications*; Hiyama, T., Ed.; Springer: New York, 2000. (b) *Fluorine-Containing Molecules. Structure, Reactivity, Synthesis, and Applications*; Liebman, J. F., Greenberg, A., Dolbier, W. R., Eds.; VCH: Weinheim, 1988.

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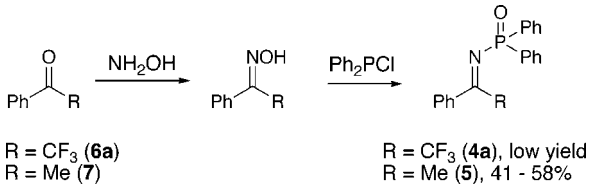
tion to generate the α-metalloimine was the main reaction pathway instead of nucleophilic addition.

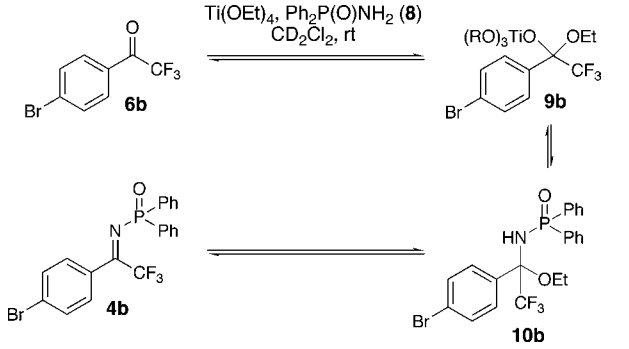
The synthesis of an *N*-phosphinoylketimine using the Stec reaction[6] was accomplished in moderate to good yields from acetophenone (Scheme 2).[7]

Scheme 2. Synthesis of *N*-Phosphinoylketimines



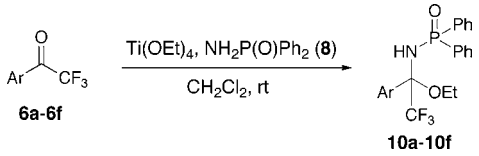
However, when these conditions were applied to trifluoroacetophenone, only low yields of imine **4a** were observed.[8] A screening of several Lewis acids to mediate the condensation between α,α,α-trifluoro-4-bromoacetophenone (**6b**) and *P*,*P*-diphenyl phosphinamide (**8**) did not lead to any improvement in the yield of **4b**. However, hemiaminal **10b** was obtained when $Ti(OEt)_4$ was used as the Lewis acid (Scheme 3). ^{19}F NMR monitoring of the reaction indicated that when **6b** (−72.3 ppm) was mixed with **8** and $Ti(OEt)_4$, **9b** was rapidly formed (broad singlet between −80.5 and −81.5 ppm) along with residual ketone. The integration of this species (**9b**) slowly decreased over time, forming in its place hemiaminal **10b** (−78.2 ppm) and a small amount of imine **4b** (−70.8 ppm). Although this transformation was extremely slow and the various compounds were in equilibrium, only a small amount of imine **4b** was formed (after 4 days and using 3 equiv of ketone). Although we could detect significant quantities (up to 10%) of imine **4b** by NMR monitoring of the reaction, all of our attempts to isolate it from this reaction mixture were unsuccessful, since it underwent rapid hydrolysis back to ketone **6b** upon workup. However, the latter was recycled in all of the reactions. Hemiaminal **10b** was a convenient starting material and surrogate for imine **4b** because it could be isolated as a colorless, air-stable and easy to manipulate solid. Furthemore, previous results from our laboratory established that ethylzinc ethoxide (the possible byproduct resulting from the hemiaminal decomposition into the imine) was a compatible additive in the copper-catalyzed nucleophilic addition chemistry.[9]

Scheme 3. NMR Monitoring of Hemiaminal Formation



The isolated yield of hemiaminals **10a**−**10f** from various trifluoromethyl ketones ranged between 47% and 63% (Table 1).[10] We envisioned that hemiaminals **10** could be used to generate the corresponding imines in situ. This was confirmed by spectroscopically observing the formation of the imine when diethylzinc was added to a solution of the pure hemiaminal in CD_2Cl_2. Several other titanium-based Lewis

Table 1. Synthesis of Hemiaminals **10a**−**10f**[13]



entry	Ar (ketone)	yield (%)	product
1	Ph (**6a**)	47	**10a**
2	4-BrC_6H_4 (**6b**)	56	**10b**
3	3-MeC_6H_4 (**6c**)	53	**10c**
4	4- MeC_6H_4 (**6d**)	46	**10d**
5	2-naphthyl (**6e**)	51	**10e**
6	4-ClC_6H_4 (**6f**)	63	**10f**

(2) (a) Bravo, P.; Capelli, S.; Meille, S. V.; Viani, F.; Zanda, M.*Tetrahedron: Asymmetry* **1994**, *5*, 2009. (b) Bravo, P.; Capelli, S.; Meille, S. V.; Seresini, P.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2321. (c) Bravo, P.; Crucianelli, M.; Vergani, B.; Zanda, M. *Tetrahedron Lett.* **1998**, *39*, 7771. (d) Ishii, I.; Miyamoto, F.; Higashiyama, K.; Mikami, K. *Tetrahedron Lett.* **1998**, *39*, 1199. (e) Bravo, P.; Fustero, S.; Guidetti, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1999**, *64*, 8731. (f) Crucianelli, M.; Bravo, P.; Arnone, A.; Corradi, E.; Meille, S. V.; Zanda, M. *J. Org. Chem.* **2000**, *65*, 2965. (g) Asensio, A.; Bravo, P.; Crucianelli, M.; Farina, A.; Fustero, S.; Soler, J. G.; Meille, S. V.; Panzeri, W.; Viani, F.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **2001**, 1449. (h) Enders, D.; Funabiki, K. *Org. Lett.* **2001**, *3*, 1575. (i) Surya Prakash, G. K.; Mandal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589. (j) Surya Prakash, G. K.; Mandal, M.; Olah, G. A. *Org. Lett.* **2001**, *3*, 2847. (k) Crucianelli, M.; De Angelis, F.; Lazzaro, F.; Malpezzi, L.; Volonterio, A.; Zanda, M. *J. Fluorine Chem.* **2004**, *125*, 573. (l) Gosselin, F.; Roy, A.; O'Shea, P. D.; Chen, C.; Volante, R. P. *Org. Lett.* **2004**, *6*, 641. (m) Wang, H.; Zhao, X.; Li, Y.; Lu, L. *Org. Lett.* **2006**, *8*, 1379.

(3) For a catalytic asymmetric reduction of trifluoroketimines: Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen C.; Volante R. P. *Org. Lett.* **2005**, *7*, 355.

(4) (a) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055. (b) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (c) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (d) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940.

(5) (a) Boezio, A. A.; Pytkowicz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260. (b) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692.

(6) Krzyzanowska, B.; Stec, W. J. *Synthesis* **1982**, 270.

(7) (a) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634. (b) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228.

(8) See also: Jennings, W. B.; O'Shea, J. H.; Schweppe, A. *Tetrahedron Lett.* **2001**, *42*, 101.

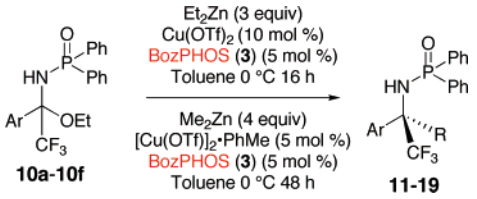
(9) Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405.

(10) Trifluoromethyl ketones **6c** and **6e** were prepared according to literature procedures: (a) Creary, X. *J. Org. Chem.* **1987**, *52*, 5026. (b) Chong, J. M.; Mar, E. K. *J. Org. Chem.* **1991**, *56*, 893. Other ketones were commercially available.

acids were tested, but lower yields of the hemiaminal adduct and/or of the imine were observed.[11,12]

With the trifluoromethylimines in hand, the nucleophilic addition chemistry was tested using our optimized set of reaction conditions.[14] When hemiaminal **10a** was treated with 3.0 equiv of Et_2Zn, $Cu(OTf)_2$ (10 mol %) and (*R*,*R*)-BozPHOS (5 mol %), the desired product was obtained in high yield and high enantioselectivity (Table 2, entry 1). The

Table 2. Nucleophilic Addition to Hemiaminal **10a**−**10f**



entry	starting material	R (product)	yield (%)	ee (%)
1	Ph (**10a**)	Et (**11**)	83	91
2	Ph (**10a**)	Me (**12**)	85	99
3	4-BrC_6H_4 (**10b**)	Et (**13**)	71	95
4	4-BrC_6H_4 (**10b**)	Me (**14**)	89	97
5	3-MeC_6H_4 (**10c**)	Et (**15**)	78	95
6	3-MeC_6H_4 (**10c**)	Me (**16**)	84	99
7	4-MeC_6H_4 (**10d**)	Et (**17**)	77	97
8	2-naphthyl (**10e**)	Et (**18**)	73	94
9	4-ClC_6H_4 (**10f**)	Et (**19**)	71	93

enantiomeric excesses ranged from 91% to 97% for the ethyl group transfer to the various substrates. The addition of less reactive dimethylzinc proceeded well. For the three substrates that were tested, the enantiomeric excesses were higher for methyl group transfer than for ethyl (Table 2, entry 1 vs 2; 3 vs 4; and 5 vs 6). This is in contrast with our previous report for the addition to aldimines.

Although the absolute stereochemistry for most entries was not unambiguously established, an X-ray crystal structure of the product in entry 4 was obtained with a suitable value for the Flack parameter (−0.047(18)), confirming that the absolute chemistry was consistent with that observed for the addition to aldimines (Figure 1).

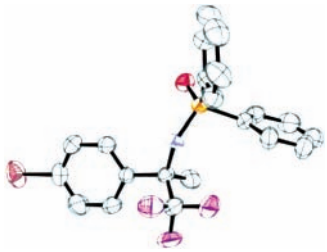
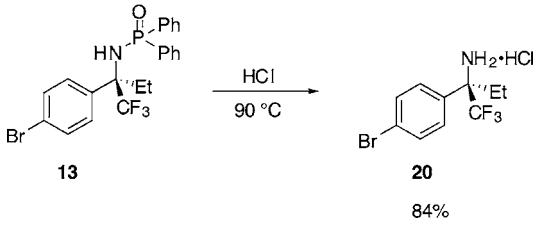


Figure 1. ORTEP Representation of protected amine **14**.

The cleavage of the *N*-phosphinoyl group is usually quite facile. However, in this case, the free amine was obtained obtained by heating the phosphinamide **13** in concentrated hydrochloric acid at 90 °C for 9 h (Scheme 4).[15]

Scheme 4. Cleavage of the *N*-Phosphinoyl Group



In summary, we have developed the first catalytic asymmetric synthesis of α-alkyl-α-aryl-α-trifluoromethylamines. The reaction proceeds with high stereocontrol from a novel stable imine precursor.

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Supporting Information Available: Experimental procedures and data for each reaction, characterization spectra for new compounds, and a CIF file for compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) $TiCl(OEt)_3$: 22% yield of ethanol adduct. $Ti(OMe)_4$: 8% yield of methanol adduct. $TiCl_4$: 23% yield of ketimine.

(12) $Si(OEt)_4$, an efficient reagent for the preparation of *N*-tosylimines led to a 15% yield of the hemiaminal: Love, B. E.; Raje, P. S.; Williams, T. C., II. *Synlett* **1994**, *7*, 493.

(13) **General Procedure for the Synthesis of the Hemiaminal.** To a solution of *P*,*P*-diphenylphosphinic amide (167 mg, 0.77 mmol, 1.1 equiv) in CH_2Cl_2 (7 mL) was added the trifluoromethyl ketone (2.1 mmol, 3.0 equiv) and titanium ethoxide (294 μL, 1.4 mmol, 2.0 equiv). After stirring at room temperature for 96 h, the reaction was quenched with a mixture of Na_2SO_4·$10H_2O$ (2 g) and sand (5 g). Then CH_2Cl_2 (250 mL) was added, and the reaction was stirred at room temperature for 30 min. The suspension was filtered and washed with CH_2Cl_2 (3 × 100 mL). The organic layers were dried over Na_2SO_4. Concentration and purification by flash chromatography gave the hemiaminal as a colorless white solid. The residual ketone could be isolated in the first few fractions of the chromatography.

(14) **General Procedure for the Addition Reaction.** Anhydrous toluene (2 mL) was added to (*R*,*R*)-BozPHOS (6.1 mg, 0.019 mmol, 0.05 equiv) and $Cu(OTf)_2$ (14 mg, 0.038 mmol, 0.10 equiv). The resulting heterogeneous dark green solution was stirred for 1 h at room temperature. Neat diethylzinc (117 μL, 1.14 mmol, 3.0 equiv) was added at room temperature, and the resulting red-brown suspension was stirred for an additional 20 min, before being cooled to 0 °C. After 10 min, a cooled solution (0 °C) of the hemiaminal (0.38 mmol, 1.00 equiv) in toluene (1 mL + 1 mL for washing) was cannulated (using a Teflon cannula) into the catalyst suspension. After stirring 16 h at 0 °C, the reaction was quenched with saturated NH_4Cl (7 mL), and the aqueous phase was washed with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by flash chromatography to give the corresponding addition product as a white solid.

(15) **Representative Procedure for the Cleavage of the Phosphinoyl Group.** Compound **13** (0.446 mmol, 1.0 equiv) was dissolved in 3 mL of concentrated aqueous HCl. The mixture was heated to 90 °C for 9 h. The reaction was cooled to room temperature and neutralized with aqueous NaOH (1 M). The mixture was extracted with CH_2Cl_2 (3 × 7 mL), and the combined organic layers were dried over Na_2SO_4. The mixture was concentrated to give the free amine. The amine was crystallized as its hydrochloride salt from CH_2Cl_2 using a solution of HCl in Et_2O (1 M) (4.46 mmol, 10.0 equiv) to give a white solid.