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Catalytic Enantioselective Addition of Diethylzinc to Trifluoromethyl Ketones

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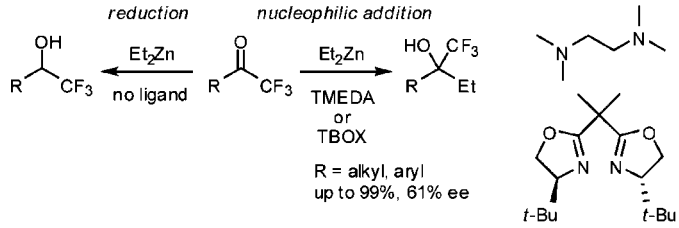
ABSTRACT



A procedure for nucleophilic addition of diethylzinc to trifluoromethyl ketones was developed. The TMEDA-catalyzed method converts aromatic substrates to the corresponding 2-aryl-1,1,1-trifluorobutan-2-ols in up to 99% yield, and it is also applicable to less reactive aliphatic ketones if stoichiometric ligand amounts are employed. The first asymmetric variant producing tertiary alcohols with up to 61% ee when TBOX is used as catalyst is described.

Numerous examples of asymmetric additions of diethylzinc to aldehydes, ketones, and imine analogues have been reported to date, but to the best of our knowledge, this otherwise extensively studied reaction has not been successfully applied to trifluoromethyl ketones.[1] Despite the significance of trifluoromethyl-substituted tertiary alcohols, which exhibit an important subunit in several pharmaceuticals including anticonvulsants, anesthetics, and Merck's anti-HIV agent efavirenz,[2] enantioselective carbon−carbon bond formation with trifluoromethyl ketones and organometallic reagents has been barely developed and is restricted to nucleophiles devoid of a β-hydrogen.[3] As a result, the synthesis of chiral trifluoromethyl-derived tertiary alcohols mostly relies on the asymmetric cinchona alkaloid-catalyzed addition of (trifluoromethyl)trimethylsilane, CF_3TMS, to aryl ketones followed by TBAF-promoted cleavage of the intermediate silyl ethers (Scheme 1).[4] Noteworthy, catalytic

(1) Selected examples of asymmetric 1,2-additions of diethylzinc to aldehydes: (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072. (b) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111–7115. (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036. (d) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321–1323. (e) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800–9809. (f) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824. (g) Wolf, C.; Francis, C. J.; Hawes, P. A.; Shah, M. *Tetrahedron: Asymmetry* **2002**, *13*, 1733–1741. (h) Wolf, C.; Hawes, P. A. *J. Org. Chem.* **2002**, *67*, 2727–2729. (i) Kozlowski, M. C.; Dixon, S. L.; Panda, M.; Lauri, G. *J. Am. Chem. Soc.* **2003**, *125*, 6614–6615. (j) Liu, S.; Wolf, C. *Org. Lett.* **2007**, *9*, 2965–2968. Selected examples of asymmetric 1,2-additions of diethylzinc to ketones: (k) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781–3784. (l) Garcia, C.; Larochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970–10971. (m) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669. (n) Ramon, D.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284–287. (o) Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416–16425. (p) Hui, A.; Zhang, J.; Fan, J.; Wang, Z. *Tetrahedron: Asymmetry* **2006**, *17*, 2101–2107. (q) Forrat, V. J.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2054–2058. (r) Forrat, V. J.; Prieto, O.; Ramon, D. J.; Yus, M. *Chem.−Eur. J.* **2006**, *12*, 4431–4445. Recent reviews on nucleophilic additions to imines, see: (s) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873–888. (t) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541–2569. (u) Ferraris, D. *Tetrahedron* **2007**, *63*, 9581–9597.

(2) (a) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Vittanen, S. K. *J. Med. Chem.* **2000**, *43*, 2019–2030. (b) Choudhury-Mukherjee, I.; Schenck, H. A.; Cechova, S.; Pajewski, T. N.; Kapur, J.; Ellena, J.; Cafiso, D. S.; Brown, M. L. *J. Med. Chem.* **2003**, *46*, 2494–2501. (c) Schenck, H. A.; Lenkowski, P. W.; Choudhury-Mukherjee, I.; Ko, S.-H.; Stables, J. P.; Patel, M. K.; Brown, M. L. *Bioorg. Med. Chem.* **2004**, *12*, 979–993. (d) Xue, Y.; Chao, E.; Zuercher, W. J.; Willson, T. M.; Collins, J. L.; Redinbo, M. R. *Bioorg. Med. Chem.* **2007**, *15*, 2156–2166.

(3) (a) Martina, S. L. X.; Jagt, R. B. C.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2006**, 4093–4095. (b) Motoki, R.; Tomita, D.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 8083–8086. (c) Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2997–3000. For a catalytic enantioselective nitroaldol reaction of trifluoromethyl ketones, see: (d) Tur, F.; Saa, J. M. *Org. Lett.* **2007**, *9*, 5079–5082.

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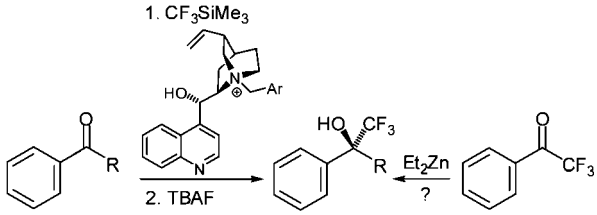
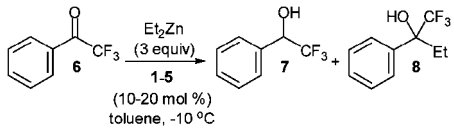
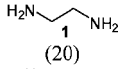
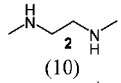
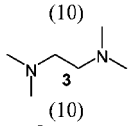
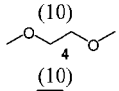
Scheme 1. Asymmetric Addition of CF_3TMS to Aromatic Ketones and Alternative Approach to Trifluoromethyl-Derived Tertiary Alcohols Using Trifluoromethyl Ketones and Diethylzinc



enantioselective synthesis of tertiary trifluoromethyl alcohols has also been accomplished via Sharpless dihydroxylation,[5] Friedel−Crafts acylation,[6] ene reaction,[7] and aldol reaction.[8]

Table 1. Screening of the Ligand-Catalyzed Nucleophilic Addition of Et_2Zn to 2,2,2-Trifluoroacetophenone, **6**

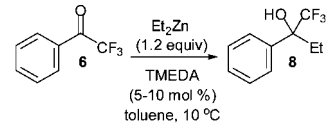


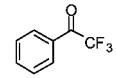
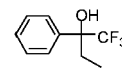
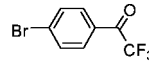
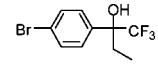
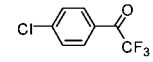
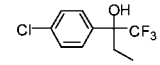
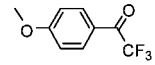
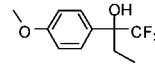
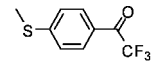
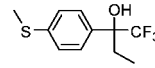
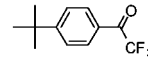
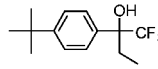
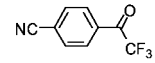
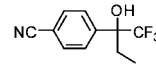
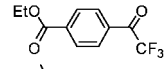
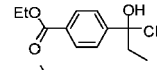
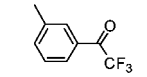
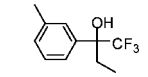
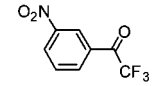
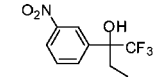
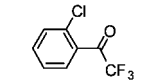
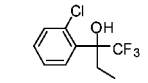
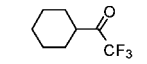
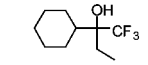
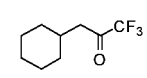
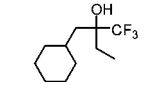
entry	ligand (mol %)	time (h)	yield (%) 6	7	8
1	/	24	7	93	/
2	 1 (20)	4	77	22	1
3	 2 (10)	20	63	28	9
4	 3 (10)	24	36	3	61
5	 4 (10)	4	66	31	3
6	 5 (10)	4	62	27	11

The lack of a method that allows direct alkylation of trifluoromethyl ketones with organometallic reagents originates from the unique reactivity of these substrates. Unlike the well-established nucleophilic additions of organozinc reagents to aldehydes or other carbonyl functionalities, trifluoromethyl ketones have been known to undergo predominant reduction upon addition of diethylzinc.[9]

We anticipated that activation of diethylzinc by bidentate ligands **1**−**5** might favor carbon−carbon bond formation over β-hydride elimination and subsequent reduction, thus providing a new entry toward the synthesis of trifluoromethyl-derived tertiary alcohols. Initial screening of catalytic amounts of ethylenediamine, **1**, *N*,*N*′-dimethyl ethylenediamine, **2**, *N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine, **3**, 1,2-dimethoxyethane, **4**, and morpholine, **5**, in toluene at −10 °C indicated that this can be achieved with 3 equiv of Et_2Zn although the alkylation of 2,2,2-trifluoroacetophenone, **6**, appeared to be relatively slow and was accompanied by substantial reduction unless TMEDA was used (Table 1). In particular, ligands **1** and **4** did not favor the alkylation, and more than 20% of 2,2,2-trifluoro-1-phenylethanol, **7**, was formed within 4 h (entries 2 and 5). Employing ligands **2** and **5** in the reaction showed little improvement. The desired 1,1,1-trifluoro-2-phenylbutan-2-ol, **8**, was produced in low yields, and the reduction was still significantly faster (entries 3 and 6). By contrast, the reaction outcome changed dramatically in the presence of 10 mol % of TMEDA: **8**

Table 2. TMEDA-Catalyzed Addition of Et_2Zn to 2,2,2-Trifluoroacetophenone, **6**[a]



entry	ketone	product	yield (%)	time (h)
1			93	1
2			93	1
3			94	1
4			99	1
5			96	1
6[b]			93	2.5
7[c]			81	2
8			89	1
9			87	1
10[d]			92	1
11[e]			84	1
12[f]			82	4
13[f]			84	4

[a] All reactions were performed on a 0.24 mmol scale using 5 mol % of TMEDA and 1.2 equiv of Et_2Zn in toluene at 10 °C unless otherwise noted. [b] 5 °C. [c] −10 °C, 10 mol % of TMEDA. [d] −10 °C. [e] 5 °C, 10 mol % of TMEDA. [f] 1 equiv of TMEDA and 2.4 equiv of Et_2Zn.

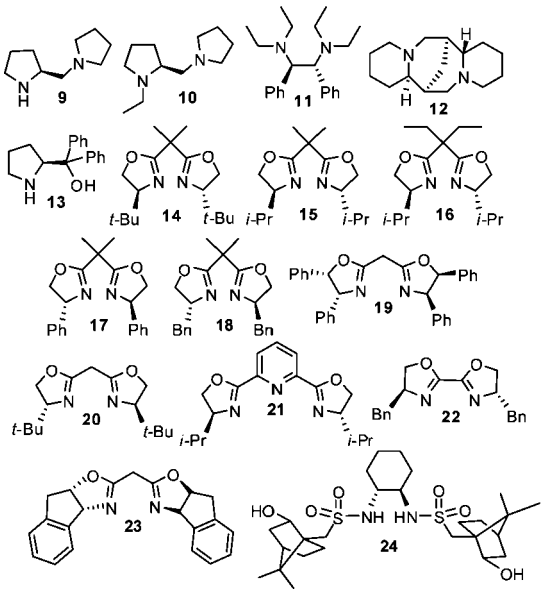
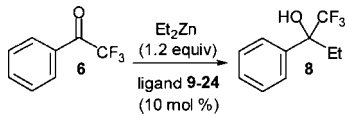


Figure 1. Structures of chiral ligands screened.

Table 3. Chiral Ligand Screening Results[a]



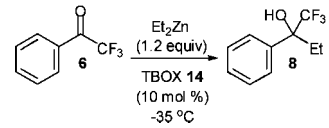
entry	ligand	time (h)	yield (%) 6	7	8	% ee
1	**9**[b]	4	10	10	80	14
2	**10**	0.5	4	1	94	5
3	**11**	0.5	1	2	97	6
4	**12**[b]	4	10	10	80	0
5	**13**	5	23	76	0	n/a
6	**14**	0.5	1	0	99	37
7	**15**	0.1	2	0	98	8
8	**16**	0.2	12	0	88	1
9	**17**	0.5	0	0	99	7
10	**18**	0.5	0	0	99	0
11	**19**[c]	0.5	78	21	0	n/a
12	**20**	5	24	63	13	n.d.
13	**21**[d]	0.6	3	0	97	0
14	**22**[c]	0.4	76	21	3	n/a
15	**23**	0.5	86	13	1	n/a
16	**24**[e]	3	40	60	0	n/a

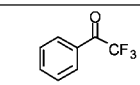
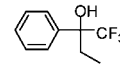
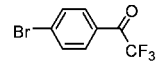
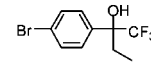
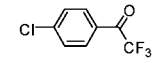
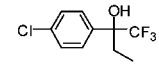
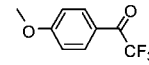
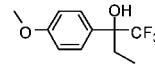
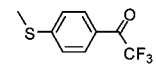
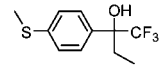
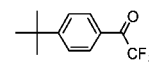
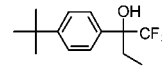
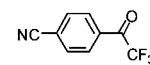
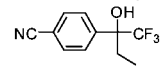
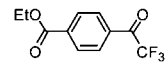
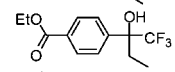
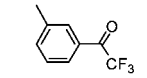
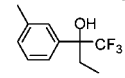
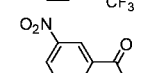
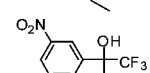
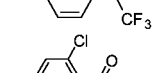
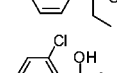
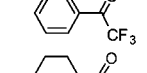
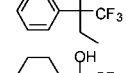
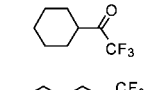
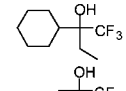
[a] All reactions were performed on a 0.24 mmol scale using 10 mol % of the ligand and 1.2 equiv of Et_2Zn at 5 °C in hexanes/toluene (1/1 v/v) unless otherwise noted. [b] Hexanes. [c] Hexanes/THF (1/1). [d] −35 °C. [e] 25 °C, 1 equiv of Ti(O*i*-Pr)$_4$.

was obtained in 61% yield, while only 3% of the reduction product **7** was isolated and 36% of the starting material was recovered (entry 4, Table 1).

Further optimization of the catalyst loading, reaction temperature, and amount of diethylzinc revealed that aromatic trifluoromethyl ketones undergo fast ethylation in the presence of 5−10 mol % of TMEDA and 1.2 equiv of Et_2Zn at 10 °C

Table 4. TBOX-Catalyzed Addition of Et_2Zn to 2,2,2-Trifluoroacetophenone, **6**[a]



entry	ketone	product	yield (%)	ee (%)	time (h)
1			95 85[b]	51 63	0.5 2
2			99	38	1
3			74	41	6
4			83	56	1.1
5			99	52	0.9
6			75	60	0.5
7			71	16	3
8			92	25	2
9			99	54	0.5
10			83	7	2
11			99	12	1
12[c]			78	2	4
13[c]			76	0	4

[a] All reactions were performed on a 0.24 mmol scale in toluene/hexanes (1/3 v/v) using 10 mol % of TBOX and 1.2 equiv of Et_2Zn at −35 °C unless otherwise noted. [b] −78 °C. [c] 50 mol % of TBOX, 25 °C.

(Table 2). Under these conditions, trifluoroacetophenone gives 1,1,1-trifluoro-2-phenylbutan-2-ol in 93% yield within 1 h (entry 1, Table 2). We found that this reaction furnishes a wide range of tertiary alcohols in 81−99% yield, and ester, nitrile, nitro, halo, and other aryl substituents are tolerated (entries 2−11). Aliphatic substrates proved to be significantly less reactive and required the use of stoichiometric amounts of TMEDA. Nevertheless, 2-cyclohexyl-1,1,1-trifluorobutan-2-ol and 2-(cyclohexylmethyl)-1,1,1-trifluorobutan-2-ol were obtained in 82−84% yield (entries 12 and 13).

With a racemic method in hand, we decided to explore an asymmetric variant. On the basis of the success with TMEDA, chiral diamines and bisoxazolines as well as other ligands that have proved to be very useful in asymmetric

additions of diethylzinc to carbonyl electrophiles were screened (Figure 1).

Diamines **9**−**12** and bisoxazolines **15**−**18** and **21** proved to effectively catalyze the formation of tertiary alcohol **8** which was obtained in 80−99% yield within 4 h albeit in low ee's (entries 1−4, 7−10, and 13, Table 3). The competing reduction of **6** to **7** was favored in the presence of prolinol **13**, bisoxazolines **19**, **20**, **22**, and **23**, and disulfonamide **24**, which was used in conjunction with titanium tetraisopropoxide (entries 5, 11, 12, and 14−16). The most promising results were observed with **14**. Literally quantitative amounts of **8** exhibiting 37% ee were produced when 10 mol % of this bisoxazoline was employed in an apolar solvent system at 5 °C (entry 6).

Variation of reaction parameters showed that the best results are obtained when the asymmetric nucleophilic addition of diethylzinc to aryl trifluoromethyl ketones is conducted in the presence of 10 mol % of ligand **14** in hexanes/toluene (3/1 v/v) at −35 °C (Table 4). Although superior results can be achieved in some cases when pure hexanes are used, we decided to continue with a binary solvent mixture consisting of 25% toluene in hexanes to maintain a homogeneous solution throughout the reaction. Under these conditions, the reaction is generally completed in less than 3 h and the corresponding 2-aryl-1,1,1-trifluorobutan-2-ols are obtained in 77−99% yield. A further decrease in the reaction temperature slightly increased ee's, but yields were usually lower (entry 1, Table 4). We found that the enantioselectivity of this reaction varies considerably. 2,2,2-Trifluoroacetophenone and its methoxy, methylthio, methyl, and *tert*-butyl analogues gave tertiary alcohols in 51−60% ee (entries 1, 4, 5, 6, and 9), but significantly lower ee's were obtained when aryl halides, nitriles, esters, and nitro groups were present (entries 2, 3, 7, 8, 10, and 11). In analogy to the cinchona alkaloid-catalyzed C−C bond formation using CF_3TMS and aliphatic ketones, unsatisfactory yields and ee's were produced with aliphatic substrates (entries 12 and 13).

In conclusion, we have developed the first general procedure for ligand-catalyzed nucleophilic addition of diethylzinc to trifluoromethyl ketones. A range of 2-aryl-1,1,1-trifluorobutan-2-ols have been prepared in up to 99% yield using 10 mol % of TMEDA to favor alkylation over β-hydride elimination. The reaction of aliphatic substrates proved more difficult and was found to require stoichiometric ligand amounts. These findings provide a new route for asymmetric synthesis of trifluoromethyl-derived tertiary alcohols which are important components in many pharmaceuticals. Accordingly, we have introduced the first asymmetric variant of this reaction. Screening of 16 chiral ligands revealed that excellent yields and ee's up to 61% can be obtained with TBOX as catalyst.

Supporting Information Available: Synthetic procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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