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Catalytic and Highly Enantioselective Friedel–Crafts Alkylation of Aromatic Ethers with Trifluoropyruvate under Solvent-Free Conditions

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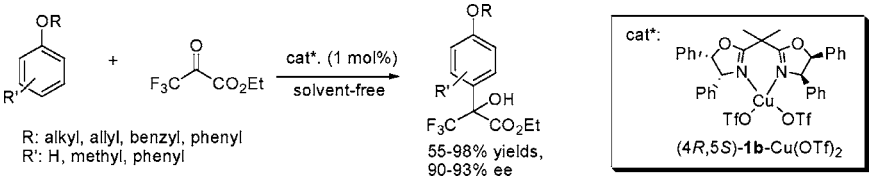
ABSTRACT



Highly enantioselective Friedel–Crafts alkylation of simple and aromatic ethers (4a–l) with 3,3,3-trifluoropyruvate (3) was accomplished by using chiral (4*R*,5*S*)-DiPh-BOX(1b)–Cu(OTf)$_2$ complex (1 mol %) as a catalyst under solvent-free conditions. Excellent yields and enantioselectivities (90–93% ee, after recrystallization up to 99% ee) of the Friedel–Crafts alkylation products were obtained.

Friedel−Crafts reaction of aromatic and heteroaromatic compounds with carbonyl compounds is one of the fundamental reactions for forming carbon−carbon bonds.[1] Recently, there has been considerable interest in developing asymmetric Friedel−Crafts reactions by using various chiral catalysts. Such reactions provide an efficient method to prepare optically active aromatic compounds possessing biological and pharmaceutical activities.[2] Representative examples include the chiral aluminum complexes,[3] titanium complexes,[4] zirconium complexes,[5] and chiral bisoxazoline (BOX)−metal complexes.[6] Jørgensen reported enantioselective Friedel−Crafts alkylation of electron-rich aromatic and heteroaromatic compounds such as aniline and indole derivatives with glyoxylate[7] or trifluoropyruvate[8] catalyzed by chiral BOX−metal complexes. Corma[9] reported the use of chiral silica-anchored catalysts in asymmetric reaction of aromatic compounds with trifluoropyruvate. Török and coworkers[10] successfully used organocatalysts for the enantioselective reaction of indoles with trifluoropyruvate. However, there are very few studies on the catalytic enantioselective Friedel−Crafts alkylation of the less reactive aromatic ethers with carbonyl compounds, except for the more activated dimethoxybenzene.[8b,9] On the other hand, there has been great progress in studying organic reactions under solvent-free

(1) Olah, G. A.; Khrisnamurti, R.; Surya Prakashi, G. K. In *Comprehansive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 3, pp 293−339.

(2) For review on catalytic asymmetric Friedel−Crafts alkylation, see: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

(3) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G. *J. Org. Chem.* **1985**, *50*, 5018.

(4) (a) Ishii, A.; Soloshonok, V. A.; Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597. (b) Yuan, Y.; Wang, X.; Li, X.; Ding, K. *J. Org. Chem.* **2004**, *69*, 146.

(5) Erker, G.; van der Zeijden, A. A. H. *Angew. Chem., Int. Ed.* **1990**, *29*, 512.

(6) For a recent excellent review on chiral bis(oxazoline) ligands in asymmetric catalysis, see: Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

(7) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517.

(8) (a) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009. (b) Jørgensen, K. A. *Synthesis* **2003**, 1117.

(9) Corma, A.; Garcia, H.; Moussaif, A.; Sabater, M. J.; Znibe, R.; Redouane, A. *Chem. Commun*. **2002**, 1058.

(10) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Surya Prakash, G. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086.

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conditions.[11] However, only a limited number of enantioselective solvent-free catalytic reactions have been reported.[12] Recently, we reported a highly efficient reaction of indoles with trifluoropyruvate under solvent- and catalyst-free conditions.[13] As part of our continuous interest in enantioselective solvent-free reactions for generating optically active CF_3-containing compounds for biological applications,[14] herein we report a highly enantioselective Friedel−Crafts alkylation of simple and aromatic ethers with trifluoropyruvate catalyzed by (4*R*,5*S*)-DiPh-BOX-Cu(OTf)$_2$ under solvent-free conditions.

To begin our study, we chose the six chiral BOX-ligands shown in Figure 1. Although the reaction of 3-methoxyanisole **2** with ethyl 3,3,3-trifluoropyruvate **3** in the presence of chiral catalyst (4*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ [(4*S*)-**1f**, 10 mol %] in ether gave the product **5** in 56% yield with 86% ee,[8a] unfortunately, a simple and less activated aromatic ether, anisole **4a**, did not react with **3** at all under the reported conditions (Scheme 1). We speculated that the employment of solvent-free conditions would overcome the low reactivity of aromatic ethers. Furthermore, the acceleration of the reaction under solvent-free conditions may, at the same time, also be accompanied by high enantioselectivity of the reaction. Thus, **4a** was reacted with **3** under solvent-free conditions together with various chiral catalysts (Scheme 1). The results are summarized in Table 1. To our delight, Cu(OTf)$_2$ and Cu(ClO$_4$)$_2$ provided both excellent catalytic abilities and high enantioselectivities (entries 1 and 4). Among the chiral ligands examined, [(4*R*,5*S*)-**1b**] gave the most promising results with 90% yield and 88% ee (Table 1, entry 1).

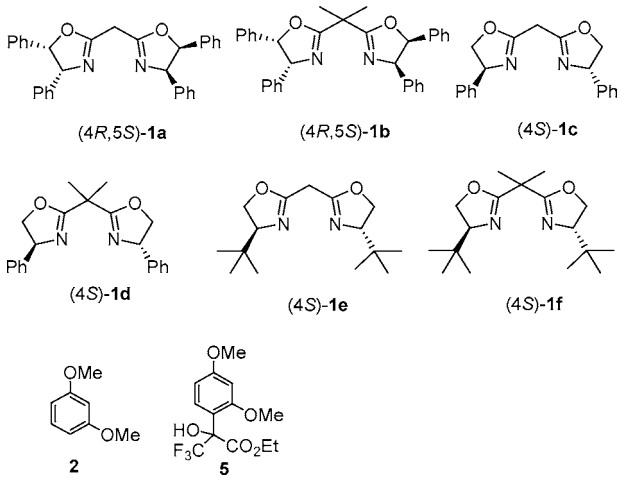


Figure 1. Chiral BOX ligands and compounds **2** and **5**.

Scheme 1

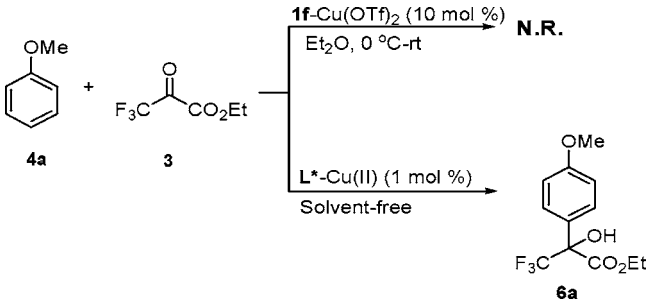


Table 1. Screening Ligands and MXn by Reaction of **3** with **4a**[a]

entry	L*[b]	MX$_n$[b]	time (h)	yield[c] (%)	ee[d] (%)
1	**1b**	Cu(OTf)$_2$	10	90	88
2	**1b**	Cu(OTf)$_2$[e]	20	85	86
3	**1b**	Cu(OTf)$_2$[f]	20	70	85
4	**1b**	Cu(ClO$_4$)$_2$	18	95	81
5	**1b**	Cu(OAc)$_2$	24	trace	
6	**1b**	CuCl$_2$	24	trace	
7	**1b**	CuOTf	24	trace	
8	**1b**	Zn(OTf)$_2$	24	45	81
9	**1b**	Mg(OTf)$_2$	24	trace	
10	**1b**	Sc(OTf)$_3$	24	trace	
11	**1b**	FeCl$_3$	24	<5	
12	**1a**	Cu(OTf)$_2$	15	80	80
13	**1c**	Cu(OTf)$_2$	20	78	22
14	**1d**	Cu(OTf)$_2$	17	85	79
15	**1e**	Cu(OT)$_2$	24	trace	
16	**1f**	Cu(OTf)$_2$	24	trace	
17		Cu(OTf)$_2$	24	7	

[a] Under solvent-free conditions at room temperature. [b] L*/MX$_n$ = 1:1.2, catalyst loading: 1 mol %. [c] Isolated yield. [d] Determined by chiral HPLC. [e] cat.: 0.1 mol %. [f] cat.: 0.01 mol %.

The reaction requires only 1 mol % of catalyst to achieve 90% yield and 88% ee. The amount of catalysts can be further reduced to 0.1 mol % to give nearly the same yield (85%) and enantiomeric excess (86%) of **6a** with a prolonged reaction time (Table 1, entry 2). *Remarkably, even when the catalyst loading was further reduced to 0.01 mol %, the reaction still gave* ***6a*** *in 70% yield with 85% ee* (Table 1, entry 3). In contrast, if Cu(OTf)$_2$ (1 mol %) alone was used as the catalyst, the reaction of **4a** with **3** gave only 7% yield of **6a** after 24 h (Table 1, entry 17).

(11) For a review on recent advances in solventless organic reactions, see: Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159.

(12) For examples of highly enantioselective solvent-free reactions, see: (a) Kinetic resolution of racemic epoxide: Tokunaga, M.; Larrow, J. F.; Kakuichi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Hetero-Diels−Alder reaction: Long, J.; Hu, J. Y.; Shen, X. Q.; Ji, B. M.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10. (c) Carbonyl ene reaction: Yuan, Y.; Zhang, X.; Ding, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5478. (d) Alkyl addition to ketones: Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416. (e) Aminoalkylation: Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759. (f) Olefin hydroformylation: Shibahara, F.; Nozaki, K.; Hiyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8555. (g) RCM reaction: Dolman, S. J.; Samely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991.

(13) Zhao, J.-L.; Liu, L.; Zhang, H. B.; Wu, Y.-Ch.; Wang, D.; Chen, Y. J. *Tetrahedron Lett.* **2006**, *47*, 2511.

(14) (a) Nelson, D. W.; Owens, J.; Hiraldo, D. *J. Org. Chem.* **2001**, *66*, 2572. (b) Surya Prakash, G. K.; Manadal, M.; Olah, G. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 589. (c) Bravo, P.; Crucianelli, M.; Vergani, B.; Zanda, M. *Tetrahedron Lett.* **1998**, *39*, 7771. (d) Xu, Y.; Dolbier, W. R., Jr. *Tetrahedron Lett.* **1998**, *39*, 9151.

To study the effect of solvent, the reaction of **4a** with **3** was carried out in various polar and nonpolar organic solvents. The experimental results (Table 2) indicated that

Table 2. Solvent Effect on the Reaction of **4a** with **3**[a]

entry	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	none	10	90	88
2	CH_2Cl_2[d]	10	90	88
3	CH_2Cl_2	24	18	89
4	ether	24	21	83
5	toluene	24	12	85
6	THF[d]	24	NR	
7	*i*-PrOH[d]	24	NR	

[a] Catalyst: (4*R*,5*S*)-**1b**/Cu(OTf)$_2$ (1:1.2, 1 mol %). [b] Isolated yield. [c] Determined by chiral HPLC. [d] High concentration: 90 μL of solvent/0.44 mmol of substrate.

the solvent-free condition provided both high yield and high enantioselectivity (entry 1). When ether, toluene, or CH_2Cl_2 was used as a solvent, although no major change in enanatioselectivity occurred, a very low yield of the corresponding product was obtained (12−21%) (entries 3−5). No reaction was observed at all with THF or 2-propanol as solvent (entries 6 and 7). It is interesting to note that in CH_2Cl_2 under a high concentration, the yield and enantioselectivity were similar to the solvent-free conditions (compare entries 1 and 2). Thus, for solid substrates, a small amount of CH_2Cl_2 can dramatically improve the yield while maintaining the same high enantioselectivity.

The reaction temperature also affected the enantioselectivities. At 20 °C, the reaction between **4a** with **3** gave the product **6a** with 88% ee, while the enantioselectivity was increased to 90% at 0 °C and up to 92% at −20 °C, with a prolonged reaction time (24 h) and decreased yield (75%) (Table 3, entries 2−4). Higher reaction temperature (83 °C)

Table 3. Temperature Effect on the Reaction of **4a** with **3**[a]

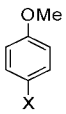
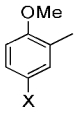
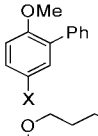
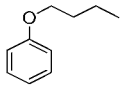
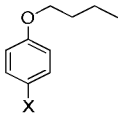
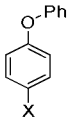
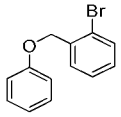
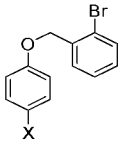
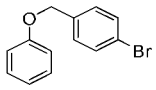
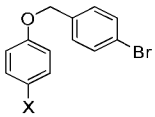
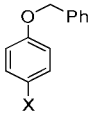
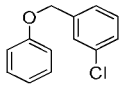
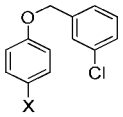
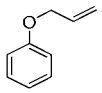
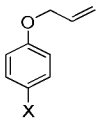
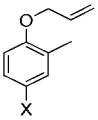
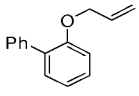
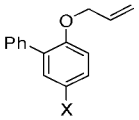
entry	*T* (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	83	10	99	81
2	25	10	90	88
3	0	13	90	90
4	−20	24	75	92

[a] Catalyst: (4*R*,5*S*)-**1b**/Cu(OTf)$_2$ (1:1.2, 1 mol %). [b] Isolated yield. [c] Determined by chiral HPLC.

lowered the ee value down to 81% (Table 3, entry 1). *It should be noted that the reaction is exothermic and must be handled carefully on large scale*. A gram scale reaction of **4a** with **3** was carried out in the presence of **1b**−Cu(II) complex (1 mol %) at 0 °C under solvent-free conditions smoothly, giving the product **6a** with high enantioselectivity (90% ee) and good yield (70%).

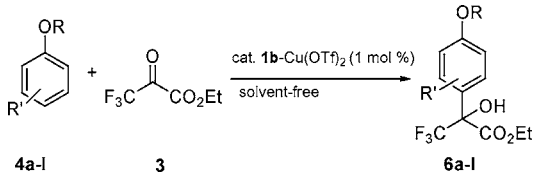
Subsequently, various aromatic ethers (**4a**−**l**) were reacted with **3** in the presence of chiral catalyst (4*R*,5*S*)-**1b**−Cu(OTf)$_2$ (1 mol %) under solvent-free conditions (Scheme 2). Moderate to high yields (55−98%) and high enantioselec-

Table 4. Catalytic and Enantioselective Friedel−Crafts Alkylation of Ar-OR (**4a**−**l**) with **3** under Solvent-Free Conditions[a]

entry	Ar-OR	temp (°C)	time (h)	Product[b]	yield[c] (%)	ee[d] (%)
1	**4a** 	0	10	**6a** 	90	90
2	**4b** 	-20	30	**6b** 	80	90
3	**4c** 	-20	28	**6c** 	55	90
4	**4d** 	-20	40	**6d** 	88	92
5	**4e** 	0	72	**6e** 	62	92
6[e]	**4f** 	15	18	**6f** 	96	92
7	**4g** 	25	36	**6g** 	85	91 (99)[f]
8	**4h** 	0	16	**6h** 	98	90
9	**4i** 	0	28	**6i** 	78	93
10	**4j** 	-20	30	**6j** 	62	93
11	**4k** 	-20	30	**6k** 	75	90
12	**4l** 	-20	48	**6l** 	70	93

[a] Catalyst: **1b**-Cu(OTf)$_2$ (1 mol %). [b] X: $CF_3(OH)(CO_2Et)C$. [c] Isolated yield. [d] Determined by chiral HPLC. [e] High concentration with CH_2Cl_2. [f] After recrystallization.

Scheme 2



4a-l **3** **6a-l**

tivities (90−93% ee, after recrystallization up to 99% ee) were obtained in each case (Table 4). The ^{1}H NMR spectra of the products show that the solvent-free Friedel−Crafts alkylation reactions have excellent para regioselectivity.

The absolute configuration of **6g** was assigned as (*S*) on the basis of the X-ray crystal structural analysis. The stereochemistry outcome can be explained by Figure 2. In general, a four-coordinated Cu(II) complex prefers a square planar geometry. However, when trifluoropyruvate coordinates with the complex of (4*R*,5*S*)-DiPh-BOX-Cu(II), a tetrahedral transition structure is formed, driven by the $\pi-\pi$ stacking interaction of a phenyl group with the ketone carbonyl group of trifluoropyruvate,[15] leading to *Re* face attack of the aromatic ether. Another phenyl group and the methyl groups on the bridge may also play a role in the stereochemical control.

In conclusion, a catalytic and highly enantioselective Friedel−Crafts alkylation of simple aromatic ethers with trifluoropyruvate was achieved under solvent-free conditions. The method provides a practical synthetic approach to optically active CF_3-containing α-hydroxyl-α-arylcarboxylate compounds.

(15) Pandey, M. K.; Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2006**, *47*, 897.

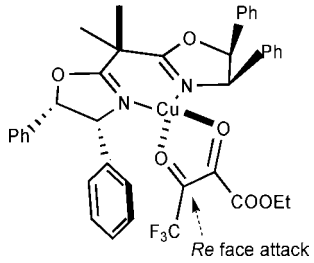


Figure 2. Proposed model for the asymmetric Friedel−Crafts alkylation.

Acknowledgment. We thank the National Natural Science Foundation of China and the Chinese Academy of Sciences for financial support.

Supporting Information Available: Experimental procedures, characterization data of the products, chiral HPLC separations for ee determination, and X-ray structural data of **6g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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