Catalytic Enantioselective Friedel−Crafts Reactions of Aromatic Compounds with Glyoxylate: A Simple Procedure for the Synthesis of Optically Active Aromatic Mandelic Acid Esters

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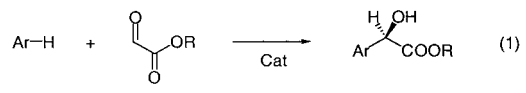
Received July 14, 2000

Abstract: The first catalytic highly enantioselective Friedel−Crafts reaction of aromatic compounds with glyoxylate catalyzed by chiral Lewis acids is presented. The reaction has been developed for mainly aromatic amines reacting with ethyl glyoxylate in the presence of chiral bisoxazoline−copper(II) complexes as the catalyst. A series of chiral bisoxazoline−copper(II) complexes have been tested as catalysts for the reaction with *N*,*N*-dimethylaniline and it has been found that a highly regio- and enantioselective Friedel−Crafts reaction takes place in the presence of especially *tert*-butyl bisoxazoline−copper(II). This reaction proceeds with the formation of exclusively the para-substituted isomer in up to 95% yield and 94% ee. The reaction has been investigated for *N*,*N*-dimethylaniline under different reaction conditions and has been developed to be a catalytic highly enantioselective reaction for meta-substituted *N*,*N*-dimethylanilines, containing either electron-withdrawing or electron-donating substituents. The catalytic enantioselective Friedel−Crafts reaction also proceeds well for cyclic aromatic amines such as *N*-methylindoline, *N*-methyltetrahydroquinoline, and julolidine, where up to 91% yield and 93% ee are obtained. For polyaromatic amines high yields, but moderate ee values, of the Friedel−Crafts products are obtained. To enhance the potential of the reaction the *N*,*N*-dimethyl- and *N*-methyl substituents can be removed successfully leading to either the mono-*N*-methyl product or the free amine. The latter class of products allow for the introduction of a variety of other substituents on the aromatic nucleus. The catalytic enantioselective reaction also proceeds for heteroaromatic compounds such as 2-substituted furans which react with glyoxylate as well as trifluoropyruvates, giving up to 89% ee of the Friedel−Crafts products. Furthermore, ethyl trifluoropyruvate reacts in a highly enantioselective reaction with *m*-methoxyanisole to give the corresponding Friedel−Crafts product in good yield. On the basis of the experimental results and the absolute configuration of the products, the mechanism for this catalytic highly enantioselective Friedel−Crafts reaction is presented.

Introduction

The Friedel−Crafts reaction of aromatic compounds with carbonyl compounds is one of the most fundamental reactions in organic chemistry.[1] There are numerous examples of the development and use of this reaction in chemistry; however, the catalytic enantioselective version of the Friedel−Crafts reaction is still an unexplored field, although the aromatic optically active products formed are highly valuable.

This paper presents the catalytic enantioselective Friedel−Crafts reaction of aromatic compounds **1** to α-dicarbonyl compounds of the glyoxylate type **2** catalyzed by chiral Lewis acids (eq 1).



Numerous examples of addition reactions of aromatic compounds to activated carbonyl[2,3] and α-dicarbonyl compounds[4,5] in the presence of Lewis acids such as $AlCl_3$ are known. For diastereoselective reactions it has been found that glyoxylate derivatives having a chiral auxiliary,[6] chiral ketoesters,[7] and aldehydes[8] can react with, e.g., phenolic substrates. There are also few examples of Friedel−Crafts reactions with α-dicarbonyl

(1) (a) Olah, G. A.; Khrisnamurti, R.; Surya Prakash, G. K. *Comprehensive Organic Synthesis*, 1st ed.; Pergamon: New York, 1991; Vol. 3, pp 293−339. (b) Roberts, R. M.; Khalaf A. A. *Friedel−Crafts Alkylation Chemistry. A Century of Discovery*, Marcel Dekker: New York, 1984.

(2) Reactions for benzaldehyde see e.g.: (a) Adams, S. R.; Kao, J. P. Y.; Grynkeiwicz, G.; Minta, A.; Tsien, R. Y. *J. Am. Chem. Soc.* **1988**, *110*, 3212. (b) Sasakura, K.; Terui, Y.; Sugasawa, T. *Chem. Pharm. Bull.* **1985**, *33*, 1836. (c) Albrecht, K. *Chem. Ber.* **1888**, *21*, 3292.

(3) Reactions for chloral see e.g.: (a) Menegheli, P.; Rezende, M. C.; Zucco, C. *Synth. Commun.* **1987**, *17*, 457. (b) Hebert, P. *Bull. Soc. Chim. Fr.* **1920**, *27*, 52. (c) Casiraghi, G.; Casnati, G.; Sartori, G.; Catellani, M. *Synthesis* **1979**, 824. (d) Fritsch, P. *Lieb. Ann. Chem.* **1897**, *296*, 344. (e) Menegheli, P.; Rezende, M. C.; Zucco, C. *Synth. Commun.* **1987**, *17*, 457. (f) Dinesmann, A. *C. R. Hebd. Seances Acad. Sci.* **1905**, *141*, 201.

(4) Reactions for phenylglyoxyal derivatives see e.g.: (a)Fuson, R. C.; Weinstock, H. H.; Ullyot, G. E. *J. Am. Chem. Soc.* **1935**, *57*, 1803. (b) Arnold, R. T.; Fuson, R. C. *J. Am. Chem. Soc.* **1936**, *58*, 1295. (c) Fuson, R. C.; Emerson, W. S.; Weinstock, H. H. *J. Am. Chem. Soc.* **1939**, *61*, 412. (d) Fuson, R. C.; Armstrong, M. D.; Wallace, W. E.; Kneisley, J. W. *J. Am. Chem. Soc.* **1944**, *66*, 1274. (e) Gualtieri, F.; Riccieri, F. M. *Boll. Chim. Farm.* **1965**, *104*, 149. (f) Coan, S. B.; Trucker, D. E.; Becker, E. I. *J. Am. Chem. Soc.* **1955**, *77*, 60. (g) Christy, M. E.; Colton, C. D.; MacKay, M.; Staas, W. H.; Wong, J. B.; Engelhardt, E. L.; Torchiana, M. L.; Stone, C. A. *J. Med. Chem.* **1977**, *20*, 421. (h) Bridge, A. W.; Fenton, G.; Halley, F.; Hursthouse, M. B.; Lehmann, C. W.; Lythgoe, D. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, *22*, 2761. (i) Sohda, D. J.; Mizuno, K.; Imamiya, E.; Tawada, H.; Meguro, K.; Kawamatsu, Y.; Yamamoto, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3601.

(5) Reaction for *tert*-butyl glyoxal see e.g.: Hahn, B.; Kopke, B.; Voss, J. *Liebigs Ann. Chem.* **1981**, *1*, 10.

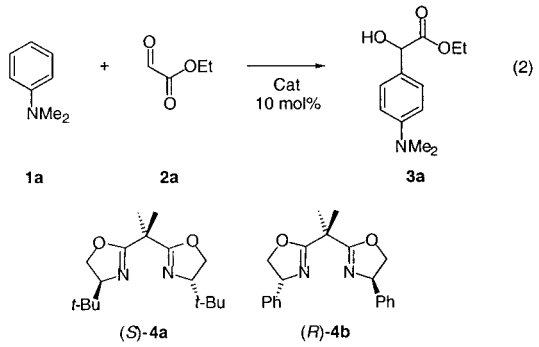
10.1021/ja002593j CCC: $19.00
Published on Web 11/30/2000

compounds attached to a chiral auxiliary giving chiral products.[9] Catalytic enantioselective Friedel−Crafts reactions have been found for chloral reacting with anisole derivatives catalyzed by chiral alkoxyaluminum chlorides,[10] and very recently the reaction of fluoral with anisole using BINOL-TiX_2 catalysts yielding products with up to 90% ee.[11] This group also reported the enantioselective Friedel−Crafts-type reaction of aromatic methyl vinyl ethers with fluoral catalyzed by BINOL-TiX_2 catalysts.[12]

The Friedel−Crafts products formed in this paper are potential starting materials for many biologicaly active compounds, e.g., *p*-aminomandelic acid derivatives.[13] Antibacterial properties have been shown in several mandelic amide compounds,[14] and many substituted mandelic acid compounds show pharmacological activity.[15]

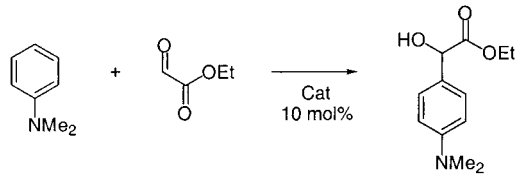
Results and Discussion

Several different chiral bisoxazoline metal(II) complexes[16,17] can catalyze the catalytic enantioselective Friedel−Crafts reaction of *N*,*N*-dimethylaniline **1a** with ethyl glyoxylate **2a** (eq 2).



Some representative examples for the reaction using the *t*-Bu-BOX (*S*)-**4a** and Ph-BOX (*R*)-**4b** (BOX = bisoxazoline) and Lewis acids catalysts are presented in Table 1.

Table 1. Results for the Catalytic Enantioselective Friedel−Crafts Reaction of *N*,*N*-Dimethylaniline **1a** with Ethyl Glyoxylate **2a** Catalyzed by Chiral Bisoxazoline−Metal(II) Complexes as the Catalysts in Various Solvents[a]



entry	catalyst	solvent	temp (°C)	**2a** (equiv)	yield[b] (%)	ee[a] (%)
1	(*S*)-**4a**-Cu(OTf)$_2$	CH_2Cl_2	rt	1.5	81	80
2	(*S*)-**4a**-Cu(OTf)$_2$	Et_2O	rt	1.5	78	89
3	(*S*)-**4a**-Cu(OTf)$_2$	THF	rt	1.5	72	90
4	(*S*)-**4a**-Cu(OTf)$_2$	CH_2Cl_2	rt	10	90	82
5	(*S*)-**4a**-Cu(OTf)$_2$	THF	−30	5	71	74
6	(*S*)-**4a**-Cu(OTf)$_2$	$MeNO_2$	0	5	32	18
7	(*S*)-**4a**-Cu(SbF_6)$_2$	THF	rt	5	36	0
8	(*R*)-**4b**-Cu(OTf)$_2$	CH_2Cl_2	rt	1.5	70	54
9	(*R*)-**4b**-Cu(OTf)$_2$	Et_2O	rt	1.5	76	42
10	(*R*)-**4b**-Cu(OTf)$_2$	THF	rt	1.5	81	22
11	(*R*)-**4b**-Zn(OTf)$_2$	CH_2Cl_2	rt	1.5	41	12

[a] For experimental details see Supporting Information. [b] Isolated yield.

The results in Table 1 show that the combination of the *t*-Bu-BOX (*S*)-**4a** ligand and copper(II) gives the best results,

(6) (a) Bigi, F.; Bocelli, G.; Maggi, R.; Satori, G. *J. Org. Chem.* **1999**, *64*, 5004. (b) Bigi, F.; Sartori, G.; Maggi, R.; Cantarelli, E.; Galaverna, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2411. (c) Bigi, F.; Casnati, G.; Sartori, G.; Dalprato, C.; Bortolini, R. *Tetrahedron: Asymmetry* **1990**, *1*, 861.

(7) Casiraghi, G.; Bigi, F.; Casnati, G.; Sartori, G.; Soncini, P.; Gasparri, G.; Fava, G.; Belicchi, M. F. *J. Org. Chem.* **1988**, *53*, 1779.

(8) (a) Bigi, F.; Casnati, G.; Sartori, G.; Araldi, G. *Gazz. Chim. Ital.* **1990**, *120*, 413. (b) Bigi, F.; Casnati, G.; Sartori, G.; Araldi, G.; Bocelli, G. *Tetrahedron Lett.* **1989**, *30*, 1211.

(9) (a) Costa, P. R. R.; Cabral, L. M.; Alencar, K. G.; Schmidt, L. L.; Vasconcellos, M. L. A. A. *Tetrahedron Lett.* **1997**, *38*, 7021. (b) El Kaim, L.; Guyoton, S.; Meyer, C. *Tetrahedron Lett.* **1996**, *37*, 375.

(10) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Gasparri Fava, G.; Belicchi, M. F. *J. Org. Chem.* **1985**, *50*, 5018.

(11) Ishii, A.; Soloshohonok, V. A.; Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597.

(12) Ishii, A.; Mikami, K. *J. Fluorine Chem.* **1999**, *97*, 51.

(13) (a) Nakamura, K.; Tsuji, K.; Kiyoshi, K.; Nobukiyo, M.; Matsuo, M. *Chem. Pharm. Bull.* **1993**, *41*, 2050. (b) Kato, H.; Nakayama, K.; Takata, Y.; Kurihara, J.; Sakai, T. *Arzneim Forsch.* **1985**, *35*, 1037. (c) *Chem. Abstr.* **1970**, *74*, 53563. (d) *Chem. Abstr.* **1976**, *86*, 5665. (e) *Chem. Abstr*. **1970**, *74*, 88185.

(14) Khalaj, A.; Shadnia, H.; Sharifzadeh, M. *Pharm. Pharmacol. Commun.* **1998**, *4*, 373.

(15) (a) Miersch, O.; Kramell, R.; Parthier, B.; Wasternack, C. *Phytochemistry* **1999**, *50*, 353. (b) El-Nimr, A. E.; Salama, H. A.; Khalil, R. M.; Kassem, M. A. *Pharmazie* **1983**, *38*, 728. (c) Nishihata, T.; Takahagi, H.; Yamamoto, M.; Tomida, H.; Rytting, J. H.; Higuchi T. *J. Pharm. Sci*. **1984**, *73*, 109. (d) Yoshioka, M.; Yoshida, A.; Ichihashi, Y.; Saito, H. *Chem. Pharm. Bull.* **1985**, *33*, 2145.

(16) For recent reviews dealing with the use of chiral bisoxazoline−Lewis acids as catalysts see: (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605. (c) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (d) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558.

(17) For the use of C_2-symmetric BOX complexes to Mukaiyama-aldol reactions see e.g.: Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669 and references therein. Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686 and references therein. Diels−Alder reactions see e.g.: Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582 and references therein. Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559 and references therein. 1,3-Dipolar cycloaddition reactions see e.g.: Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346. Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353. Cyclopropanation reactions see e.g.: Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373. Evans, D. A.; Worpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430. Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745. Allylic substituton reactions see e.g.: von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuburger, M.; Zehnder, M.; Rüegger, H.; Pregogin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265. Allylation and addition reactions see e.g.: Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029. Sibi, M. P.; Ji, J.; Wu, J.-H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. Aziridination reactions see e.g.: Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676. Carbonyl-ene reactions see e.g.: Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824. Reichel, F.; Fang, X.; Yao, S.; Ricci, M.; Jørgensen, K. A. *Chem. Commun.* **1999**, 1505. Gathergood, N.; Jørgensen, K. A. *Chem. Commun.* **1999**, 1869. Hetero-Diels−Alder reactions see e.g.: Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757. Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, *52*, 7321. Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1183. Johannsen, M.; Yao, S.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1997**, 2169. Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 118. Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599. Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2165. Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2404. Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3372. Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. Audrian, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487. Zhuang, W.; Thorhauge, J.; Jørgensen, K. A. *Chem. Commun.* **2000**, 459.

Table 2. The Catalytic Enantioselective Friedel−Crafts Reaction of *N*,*N*-Dimethylaniline **1a** with Ethyl Glyoxylate **2a** Catalyzed by (*S*)-**4a**-Cu(OTf)$_2$ at 0 °C under Various Reaction Conditions[a]

entry	catalyst loading (mol %)	solvent	**2a** (equiv)	yield[b] (%)	ee[a] (%)
1	10	CH_2Cl_2	1.5	85	61
2	10	Et_2O	1.5	92	90
3	10	THF	1.5	82	94
4	10	Et_2O	5	94	86
5	10	THF	5	91	82
6	5	THF[c]	5	74	88
7	1	THF[c]	5	45	87

[a] For experimental details see Supporting Information. [b] Isolated yield. [c] Reaction performed at room temperature.

compared with the Ph-BOX (*R*)-**4b** ligand and copper(II) and zinc(II) as the Lewis acid. For (*S*)-**4a**-Cu(OTf)$_2$, the Friedel−Crafts product **3a** is obtained in high yield and up to 90% ee at room temperature in various solvents (entries 1−4). It is notable that lowering the reaction temperature to −30 °C and increasing the amount of **2a** to 5 equiv leads to a reduction in both yield and ee of **3a** (entries 3 and 5). The reaction using (*S*)-**4a**-Cu(OTf)$_2$ as the catalyst is dependent on the solvent and counterion; in THF, CH_2Cl_2, and Et_2O high yield and ee are obtained of **3a**, whereas in $MeNO_2$ only 32% yield of **3a** with low ee is found (entry 6). To study the effect of the counterion (*S*)-**4a**-Cu(SbF$_6$)$_2$ was used as the catalyst; this shows the importance of the triflate as the counterion, as hexafluoroantimonate gives a racemic product in low yield (entry 7). The Ph-BOX ligand (*R*)-**4b** and copper(II) and zinc(II) as the Lewis acid also catalyze the reaction. The yield of **3a** for these catalysts is good; however, at room temperature only low ee is observed. Changing the metal from copper(II) to zinc(II) (entries 8 and 11) gave poor results with low yield and ee. It is notable that the same enantiomer of **3a** is formed using either (*S*)-**4a**-Cu(OTf)$_2$ or (*R*)-**4b**-Cu(OTf)$_2$ as the catalyst.[18] To further refine the catalytic reaction, it was decided to focus on the (*S*)-**4a**-Cu(OTf)$_2$ catalyst at 0 °C. Some representative results are presented in Table 2.

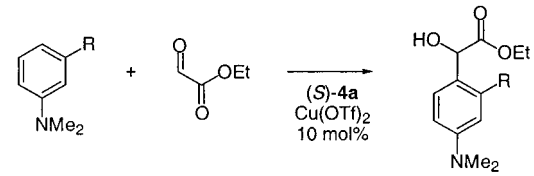
Table 2 shows the effect of temperature and amount of **2a** on the catalytic enantioselective reaction of **1a**. On comparison of entries 1−3 in Table 2 with entries 1−3 in Table 1, a lowering of the reaction temperature to 0 °C leads to an increase in the ee of the reaction in THF and Et_2O to 94% and 90%, respectively. Studying entries 2 and 3 with entries 4 and 5 leads to the conclusion that an increase in the yield of **3a** is observed in THF and Et_2O when the amount of **2a** is increased from 1.5 to 5 equiv. The ee unfortunately decreases slightly. Lowering the catalyst loading did not affect the ee of the reaction, but a reduction in yield to 74% and 45%, at 5 mol % and 1 mol % catalyst, respectively, was observed. It is notable that the reaction can be performed in gram scale giving the same high yield and ee of product.

The catalytic enantioselective Friedel−Crafts reaction proceeds well for various meta-substituted *N*,*N*-dimethylanilines (eq 3) in CH_2Cl_2 or THF and the results are presented in Table 3.

Both electron-donating and electron-withdrawing substituents are tolerated in the meta-position in the catalytic enantioselective reaction of *N*,*N*-dimethylanilines **1a**−**e** with **2a**. For the fluoro-, chloro-, and bromo-substituted *N*,*N*-dimethylanilines **1b**−**d**, the Friedel−Crafts products **3b**−**d** are obtained in good yield and high ee, and with up to 95% ee for **1c** (entry 3). Changing the

(18) For a discussion of this observation in previous reactions see e.g. ref 16.

Table 3. The Catalytic Enantioselective Friedel−Crafts Reaction of Meta-Substituted *N*,*N*-Dimethylanilines **1a**−**f** Catalyzed by (*S*)-**4a**-Cu(OTf)$_2$ (10 mol %) at Room Temperature with Ethyl Glyoxylate **2a** (5 equiv)[a]



1
a: R = H
b: R = F
c: R = Cl
d: R = Br
e: R = Me
f: R = OMe

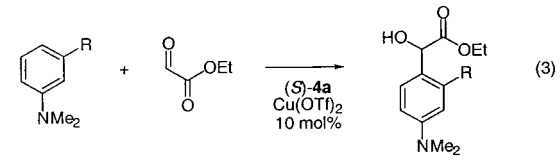
2a

3
a: R = H
b: R = F
c: R = Cl
d: R = Br
e: R = Me
f: R = OMe

entry	subst	reaction time (d)	product	yield[b] CH_2Cl_2/THF (%)	ee[a] CH_2Cl_2/THF (%)
1[c]	**1a**	1	(+)-(*S*)-**3a**	81/72	80/90
2	**1b**	1	(+)-**3b**	80/58	85/81
3	**1c**	2	(+)-**3c**	84/41	93/95
4	**1d**	4	(+)-**3d**	68/36	88/89
5	**1e**	1	(+)-**3e**	77/76	80/92
6	**1f**	1	(+)-**3f**	21/19	77/86

[a] For experimental details see Supporting Information. [b] Isolated yield. [c] 1.5 equiv of ethyl glyoxylate.

meta-substituent from hydrogen (90% ee, entry 1) to fluoro (81% ee, entry 2), chloro (95% ee, entry 3), and then bromo (89% ee, entry 3) led to a stepwise increase in the reaction time



(3)

1
a: R = H
b: R = F
c: R = Cl
d: R = Br
e: R = Me
f: R = OMe

2a

3
a: R = H
b: R = F
c: R = Cl
d: R = Br
e: R = Me
f: R = OMe

to maintain the high yield of product. This effect is probably attributed to the increasing steric interaction of the meta-substituent and the catalyst. The yield and ee of the halogen-containing products were found to be independent of the halogen substituent. *m*-Methyl-*N*,*N*-dimethylaniline **1e** reacts with **2a** in the presence of (*S*)-**4a**-Cu(OTf)$_2$ as the catalyst and in THF **3e** is obtained in high yield and with 92% ee (entry 5). For the reaction of *m*-methoxy-*N*,*N*-dimethylaniline **1f**, product **3f** is formed with good ee, but a low yield was obtained in both solvents (entry 6). It is proposed that **3f**, containing an alcohol and methyl ether, binds to the catalyst, forming a favorable six-member ring which inhibits the catalytic effect.

N-Methylindoline **1g** and *N*-methyltetrahydroquinoline **1h** react smoothly with **2a** in the presence of (*S*)-**4a**-Cu(OTf)$_2$ (10 mol %) as the catalyst (eq 4). The reaction of **1g** with **2a** in

(4)

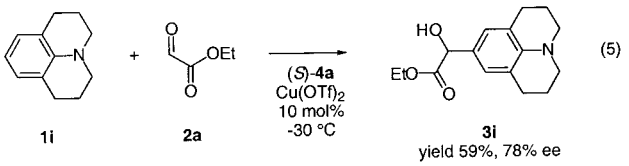
1
g: n = 1
h: n = 2

2a

3
g: n = 1; yield 76%, 83% ee (0 °C)
h: n = 2; yield 76%, 90% ee (rt)
h: n = 2; yield 56%, 93% ee (0 °C)

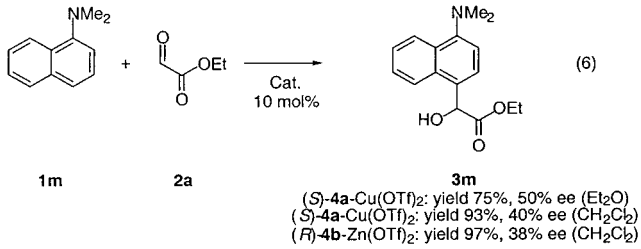
THF at 0 °C leads to the formation of **3g** as the only isomer in 76% yield and 83% ee. The result for this reaction is notable as **3g** can easily be converted to optically active 5-indolyl-α-hydroxy acids by oxidation of the indoline moiety.[19] *N*-Methyltetrahydroquinoline **1h** also reacts in a highly selective Friedel−Crafts reaction, with 76% isolated yield of **3h** and an excellent ee of 90%, while a slightly lower yield and an increase to 93% ee was found at 0 °C (eq 4).

The C_2-symmetric substrate julolidine **1i** reacts with **2a** catalyzed by (*S*)-**4a**-Cu(OTf)$_2$ in THF to give **3i** in good yield and ee (eq 5). The reaction of **1i** is dependent on the temperature as only 56% yield with 21% ee of **3i** are obtained in THF at room temperature.



The catalytic enantioselective Friedel−Crafts reactions have also been performed for *N*,*N*-diethyl-, *N*,*N*-dibutyl-, and *N*,*N*-diisopropylaniline **1j**−**l**. Compound **1j** reacts with **2a** to give the expected product in 53% yield and 80% ee in THF using (*S*)-**4a**-Cu(OTf)$_2$ as the catalyst. For the reaction of **1k** and **1l**, a significant reduction in the yield and ee of the Friedel−Crafts products **3k** and **3l** are found. The former compound is only formed in 34% yield as a racemic product, while for the latter no reaction occurred. We postulate that the inactivity of **1l** in the Friedel−Crafts reaction is due to the geometry of the lone pair electrons on the nitrogen atom. The bulky *i*-Pr groups clash with the *o*-hydrogen atoms, rotating the aryl−nitrogen bond so that the nitrogen lone pair electrons contribution into the π-system of the aromatic ring is diminished. This deactivates **1l** to an aromatic electrophilic substitution reaction. Comparison of the pK_a values of **1a** and **1l** (5.16 and 8.25, respectively)[20] shows that **1l** is the stronger base, thus contributing less electron density to the aromatic ring. Further evidence for the relationship between reactivity and the geometry of the nitrogen lone pair electrons was gained by studying ortho-substituted *N*,*N*-dimethylanilines. *o*-Fluoro-, *o*-chloro-, *o*-bromo-, and *o*-methyl-substituted *N*,*N*-dimethylaniline derivatives failed to react with **2a** using (*S*)-**4a**-Cu(OTf)$_2$ as the catalyst. The lack of reactivity of ortho-substituted *N*,*N*-dimethylanilines in aromatic electrophilic substitution reactions has been observed before.[21]

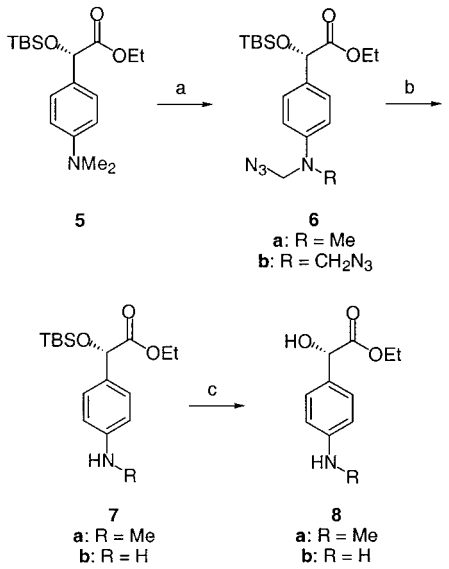
The reaction of *N*,*N*-(dimethylamino)-1-naphthalene **1m** with **2a** can proceed with several chiral bisoxazoline catalysts (eq 6).



(19) See e.g.: (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1676. (b) Takami, H.; Koshimura, H.; Kishibayashi, N.; Ishii, A.; Nonaka, H.; Aoyama, S.; Kase, H.; Kumazawa, T. *J. Med. Chem.* **1996**, *39*, 5047.

(20) Graaf, B. van de; Hoefnagel, A. J.; Wepster, B. M. *J. Org. Chem.* **1981**, *46*, 653.

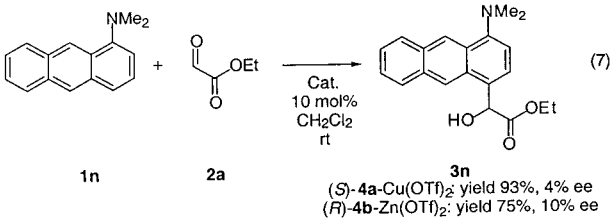
Scheme 1[a]



[a] Conditions: (a) PHIO, $TMSN_3$, CH_2Cl_2, −78 °C, 2 h; (b) saturated $NaHCO_3$(aq), THF (1:1), room temperature, 48 h, **7a** 85%,**7b** 90% from **5**; (c) 10% HCl/EtOH, 12 h, **8a** 92%, **8b** 95%.

The reaction of **1m** with **2a** catalyzed by 10 mol % (*S*)-**4a**-Cu(OTf)$_2$ at room temperature in Et_2O leads to 75% yield of **3m** with 50% ee. Excellent yields were also obtained for **3m** when the reaction was performed in CH_2Cl_2; however, the best enantioselectivity was found in ethereal solvents. The (*S*)-**4a** ligand in combination with Cu(OTf)$_2$ or (*R*)-**4b**-Zn(OTf)$_2$ catalyzes this reaction and in CH_2Cl_2 93% and 97% yields are obtained, respectively; however, the ee of **3m** is 40% ee.

N,*N*-Dimethylamino-1-anthracene **1n** reacts with **2a** giving **3n** in excellent yield; however, only 4% ee is obtained (eq 7). An increase in ee was observed when (*R*)-**4b**-Zn(OTf)$_2$ was used as the catalyst.

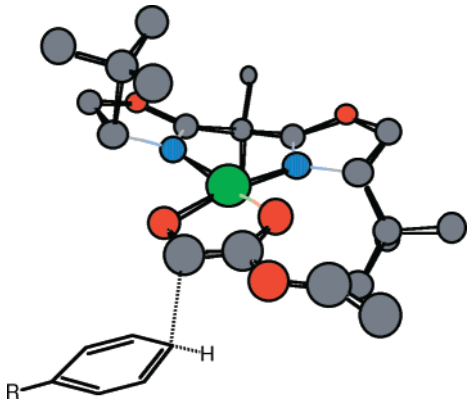


An important synthetically useful aspect of the present reaction is that the corresponding aniline and *N*-methylaniline compounds can be easily prepared from e.g. **3a**. Protection of the alcohol in **3a** as the TBS ether by reaction with TBSOTf gave **5** in 91% yield (Scheme 1). Reaction of **5** with iodosylbenzene and $TMSN_3$ afforded **6a** in good yield,[22] which was converted into the TBS-protected *N*-methyl derivative **7a** by basic hydrolysis at room temperature in 85% overall yield. The TBS group was removed by stirring with 10% HCl/EtOH. The reaction temperature for the *N*,*N*-demethylation of **3a** is critical for the success of the procedure (Scheme 1). At room temperature or 0 °C, the reaction proceeds within a few minutes, but competing side reactions lead to a moderate yield of **6b**. However, when performing the reaction in $CHCl_3$ at −50 °C (45 min) or in CH_2Cl_2 at −78 °C (2 h), a clean quantitative

(21) (a) Tice, B. B. P.; Lee, I.; Kendall, F. H. *J. Am. Chem. Soc.* **1963**, *85*, 329. (b) Brown, W. G.; Widiger, A. H.; Letang, N. J. *J. Am. Chem. Soc.* **1939**, *61*, 2597.

(22) Magnus, P.; Lacour, J.; Weber, W. *Synthesis* **1998**, 547.

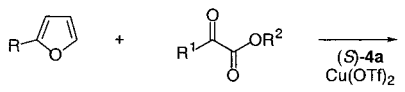
Scheme 2



conversion to the bis azide **6b** was observed. Conversion of **6b** to *p*-aminophenyl-mandelic acid ethyl ester **8b** was accomplished by basic hydrolysis followed by deprotection of the TBS group in 85% overall yield from **5**. The *N*,*N*-demethylation of **3a** leads to the formation of the free amine product **7b** which can be easily converted into the diazonium-BF_4 derivative. This diazonium salt has the potential to be a useful intermediate for the synthesis of e.g. para-substituted mandelic acid derivatives. Thus the amino group in **7b** allows for the introduction of different electron-withdrawing and electron-donating substituents on the aromatic nucleus. Furthermore, the TBS protecting group is stable against a variety of reaction conditions which allows for manipulation of the product without destroying the formed stereogenic center (vide infra).

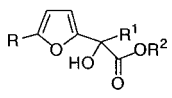
To determine the absolute stereochemistry of **3a**, compound **7b** was transformed into mandelic acid ethyl ester in 86% overall yield via the following three-step sequence: (i) diazotation by $NOBF_4$, (ii) H_3PO_2, and (iii) TBS deprotection. Chiral GC showed no detectable racemization in the synthetically prepared material (94% ee) and the optical rotation [(*S*)] established that the reaction of **1a** with **2a** catalyzed by (*S*)-**4a**-Cu(OTf)$_2$ gave the (*S*)-configuration in the enantioselective step. A model for the approach of **1a** to **2a** coordinated to (*S*)-**4a**-Cu(OTf)$_2$ as a square-planar complex is outlined in Scheme 2.

Other aromatic compounds can also undergo an enantioselective Friedel−Crafts reaction with both ethyl glyoxylate **2a** and trifluoropyruvates, **2b**,**c**, catalyzed by (*S*)-**4a**-Cu(OTf)$_2$. 2-Methylfuran **1o** reacts with ethyl glyoxylate **2a** at room temperature to give **3o** in excellent yield with moderate ee (eq 8).



1
o: R = Me
p: R = TMS

2
a: R^1 = H, R^2 = Et
b: R^1 = CF_3, R^2 = Me
c: R^1 = CF_3, R^2 = Et

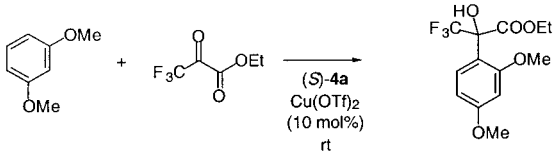


(8)

3
o: R = Me, R^1 = H, R^2 = Et, 95% yield, 45% ee
p: R = Me, R^1 = CF_3, R^2 = Me, 51% yield, 89% ee
q: R = TMS, R^1 = CF_3, R^2 = Et, 32% yield, 76% ee

However, high catalyst loading (40 mol %) was required to obtain good yields, as only 30% yield was formed with 10 mol % (*S*)-**4a**-Cu(OTf)$_2$ catalyst. Higher enantioselectivity was observed when **1o** was reacted with methyl trifluoropyruvate **2b** at 0 °C catalyzed by (*S*)-**4a**-Cu(OTf)$_2$ (10 mol %) to give the corresponding hydroxy trifluoromethyl ester **3p** in 89% ee (eq 8). At room temperature (*S*)-**4a**-Cu(OTf)$_2$ catalyzes the Friedel−Crafts reaction of trimethylsilylfuran **1p** with ethyl trifluoropyruvate **2c** to give the hydroxy trifluoromethyl ester **1q** with good enantioselectivity as 76% ee was obtained at room temperature (eq 8).

m-Methoxyanisole **1q** also undergoes an enantioselective Friedel−Crafts reaction with ethyl trifluoropyruvate **2c** catalyzed by 10 mol % (*S*)-**4a**-Cu(OTf)$_2$. The 4-substituted hydroxy trifluoromethyl ester aromatic product **3r** was the only isomer formed, in good yield and high enantioselectivity (eq 9).



(9)

1q **2c** **3r**
56% yield, 86% ee

The reactions presented in eqs 8 and 9 show that this new catalytic enantioselective Friedel−Crafts reaction of the trifluoropyruvates can be used for the facile introduction of chiral hydroxy trifluoromethyl ester substituent into various aromatic compounds. These reactions lead to a simple synthetic approach for the introduction of the important trifluoromethyl group which has been found to have unique physical and biological properties.[23]

In summary, the first catalytic enantioselective Friedel−Crafts reaction of aromatic amines with glyoxylate catalyzed by chiral bisoxazoline−copper(II) complexes has been developed. The reactions proceed as a regioselective reaction for *N*,*N*-dimethylaniline and meta-substituted *N*,*N*-dimethylanilines in high yield and high enantiomeric excess. Cyclic aromatic amines also react in a highly regio- and enantioselective fashion, while for polyaromatic amines high yields of the Friedel−Crafts products are formed in moderate ee. A synthetic procedure for the removal of the *N*,*N*-dimethyl and *N*-methyl substituents is also presented giving successfully either the mono-*N*-methyl product or the free amine. These derivatives allow the introduction of a variety of other electron-donating or electron-withdrawing substituents on the aromatic nucleus. The reaction has also been shown to proceed for heteroaromatic compounds such as 2-substituted furans, and furthermore, trifluoropuruvates also undergo a highly enantioselective Friedel−Crafts reaction as illustrated by 2-substituted furans and *m*-methoxyanisole. This development is a promising new synthetic procedure for the synthesis of optically active mandelic acid derivatives as well as the introduction of the chiral hydroxy trifluoromethyl ester substituent in various aromatic compounds.

(23) (a) *Organofluorine Chemistry−Principle and Commerical Application*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994. (b) *Fluorine-Containing Molecules, Structure, Reactivity, Synthesis and Applications*; Liebman, J. F., Greenberg, A., Dolbier, W. R., Jr., Eds.; VCH Publishers: Weinheim, 1988. (c) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symp. Ser.; American Chemical Society: Washington, DC, 1996. (d) *Fluorine-containing Amino Acids, Synthesis and Properties*; Kukhar', V. P., Soloshonok, V. A., Eds.; John Wiley & Sons Ltd.: New York, 1995. (e) For a recent review of the synthesis of trifluoromethyl containing compounds see e.g.: Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635. (f) Soloshonok, V. A. *Enantiocontrolled Synthesis of Fluoro-organic Compounds, Stereochemical Challenges and Biomedical Targets*; John Wiley & Sons Ltd.: New York, 1999.

Experimental Section

See Supporting Information.[24]

Acknowledgment. This work was made possible by a grant from the Danish National Research Foundation.

Supporting Information Available: Complete experimental procedure, characterization, and ^{1}H and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA002593J

(24) General Information is provided in the Supporting Information. The following are also included in the Supporting Information: specific reaction conditions, characterization data, absolute stereochemical proofs.