Catalytic, Highly Enantioselective Friedel−Crafts Reactions of Aromatic and Heteroaromatic Compounds to Trifluoropyruvate. A Simple Approach for the Formation of Optically Active Aromatic and Heteroaromatic Hydroxy Trifluoromethyl Esters

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A new catalytic enantioselective synthetic method for the formation of optically active aromatic and heteroaromatic hydroxy-trifluoromethyl ethyl esters is presented. This catalytic enantioselective Friedel−Crafts reaction of trifluoromethyl pyruvate with aromatic and heteroaromatic compounds is catalyzed by a chiral bisoxazoline copper(II) complex and proceeds in good yield and with high enantiomeric excess. For a series of substituted indoles, the corresponding 3-substituted hydroxy-trifluoromethyl ethyl esters are formed in up to 93% yield and 94% ee. Pyrrole and 2-substituted pyrroles also react with trifluoromethyl pyruvate in a highly enantioselective aromatic electrophilic reaction and up to 93% ee and good yields are obtained. Furanes and thiophenes give the corresponding 2-hydroxy-trifluoromethyl ethyl esters in high enantiomeric excess; however, the yields of the products are only moderate. Various types of aromatic compounds react in this catalytic reaction with trifluoromethyl pyruvate to give the aromatic electrophilic addition product in good yield. To obtain high enantiomeric excess (>80% ee) it is necessary that aromatic amines are protected with sterically demanding protecting groups such as benzyl or allyl. This prevents coordination of the amine nitrogen atom to the catalyst, as aromatic amines having a *N*,*N*-dimethyl group probably coordinate to the catalyst, leading to a significant reduction of the enantioselective properties of the catalyst. On the basis of the experimental results and the absolute configuration of the formed chiral center, the mechanism for the catalytic enantioselective Friedel−Crafts reaction is discussed.

Introduction

The addition of aromatic and heteroaromatic compounds to carbonyl compounds, the Friedel−Crafts reaction, is one of the fundamental reactions in organic chemistry, as this aromatic electrophilic substitution reaction gives highly valuable products which are widely used in academia and industry. These reactions are normally performed in a nonenantioselective fashion catalyzed by Lewis acids,[1] and, according to our knowledge, only very few catalytic enantioselective addition reactions of aromatic and heteroaromatic compounds to carbonyl compounds have been developed.[2]

Organofluorine compounds play an important role in several science disciplines,[3] and the synthesis of compounds containing fluorine is an important field of chemistry. One of the important fluorine-containing groups is the trifluoromethyl group which has been found to have unique physical and biological properties.[3−5]

This paper presents the first catalytic enantioselective Friedel−Crafts reaction of heteroaromatic and aromatic compounds **1** with ethyl trifluoropyruvate **2** catalyzed by chiral bisoxazoline−copper(II) Lewis acids.[6,7] (eq 1). This new reaction leads to a simple synthetic procedure for the introduction of an optically active hydroxy-trifluoromethyl ethyl ester group in aromatic and heteroaromatic compounds. These novel organofluorine compounds potentially may be important in various fields of science due to the unique physical and biological properties of fluorine.[3−5]

(1) See e.g.: (a) Olah, G. A.; Khrisnamurti, R.; Surya Prakash, G. K. *Comprehensive Organic Synthesis*, 1st ed.; Pergamon: Oxford, 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) (a) Ishii, A.; Soloshonok, V. A., Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597. (b) Toshimitsu, A.; Hirosawa, C.; Tamao, K. *Synlett.* **1996**, 465. (c) Ishii, A.; Mikami, K. *J. Fluorine Chem.* **1999**, *97*, 51. (d) Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Gasparri Fava, G.; Belicchi, M. F. *J. Org. Chem.* **1985**, *50*, 5018.

(3) (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 Symposium Series, 1996. (d) *Fluorine-containing Amino Acids, Synthesis and Properties*; Kukhar', V. P., Soloshonok, V. A., Eds.; John Wiley & Sons Ltd.: New York, 1995.

(4) For a recent review of the synthesis of trifluoromethyl containing compounds see, for example, Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635.

(5) Soloshonok, V. A. *Enantiocontrolled Synthesis of Fluoro-organic Compounds, Stereochemical Challenges and Biomedical Targets*; John Wiley & Sons Ltd.: New York, 1999.

(6) For reviews of C_2-bisoxazoline-Lewis acid complexes as catalysts, see, for example, (a) Ghosh, A. K.; Mathivanen, 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.

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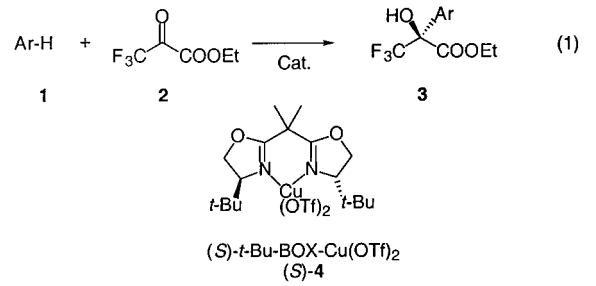
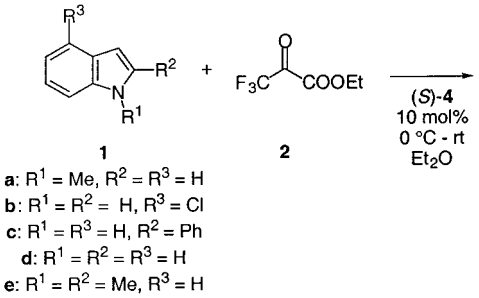
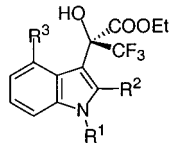


Results and Discussion

The reaction of *N*-methylindole **1a** with ethyl trifluoropyruvate **2** was studied for different chiral catalysts under various reaction conditions.[8] It was found that chiral bisoxazoline−copper(II) complexes, which have been found to be very efficient catalysts for addition reactions to, for example, α-dicarbonyl compounds,[6,7] gave the best results. The results for reaction of the indoles **1a**−**e** with **2** catalyzed by (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ (*S*)-**4** (10 mol %) in Et_2O leading to the introduction of a chiral hydroxy-trifluoromethyl ethyl ester substituent in the 3-position of the indole ring are shown in eq 2. The reactions were performed under the same general conditions, and both the yield and enantioselectivity for each reaction might be improved by further optimization. It appears from the results in eq 2 that the reaction proceeds with high yield (88−94%) and high enantioselectivity (83−94%) for sterically unhindered indole substrates. The reaction also proceeds with good yields and high enantioselectivity for unprotected indoles and *N*-methyl-protected indoles. Different sterically demanding substituents such as methyl and phenyl can be present in the heteroaromatic nucleus without affecting the enantioselectivity of the product (e.g., **3c** and **3e**). When substrates containing more bulky substituents underwent the (*S*)-**4** catalyzed Friedel−Crafts reaction, the high degree of enantioinduction was maintained, but the yield decreased to 70 and 61% for **3b** and **3c**, respectively. The phenyl substituent in **1c** is sterically repulsed by the copper complex, while the chloro substutuent in **1b** intereacts adversly with **2** bound to the catalyst.



a: R^1 = Me, R^2 = R^3 = H
b: R^1 = R^2 = H, R^3 = Cl
c: R^1 = R^3 = H, R^2 = Ph
d: R^1 = R^2 = R^3 = H
e: R^1 = R^2 = Me, R^3 = H



a: R^1 = Me, R^2 = R^3 = H, 94% yield, 89% ee
b: R^1 = R^2 = H, R^3 = Cl, 70% yield, 89% ee
c: R^1 = R^3 = H, R^2 = Ph, 61% yield, 87% ee
d: R^1 = R^2 = R^3 = H, 93% yield, 83% ee
e: R^1 = R^2 = Me, R^3 = H, 88% yield, 94% ee

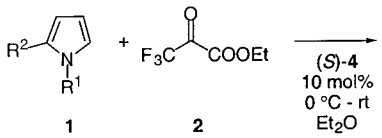
To assign the absolute configuration of the chiral center generated in the reaction 4-chloro-indole **1b** was chosen as the substrate, and the X-ray structure of **3b** was solved (Supporting Information). On the basis of the X-ray structure, the absolute configuration of the chiral center in **3b** was assigned as (*S*).

Pyrroles **1f**−**h** react with ethyl trifluoropyruvate **2** in the presence of (*S*)-**4** as the catalyst in highly enantioselective reactions for the introduction of a chiral hydroxy-trifluoromethyl ethyl ester group. Substitution occurred into the 2-position on the pyrrole ring as shown in eq 3. The assignment of the regiochemistry of the Friedel−Crafts product as the 2-isomer is based on an X-ray structure of **3f** (Supporting Information). The reactions proceed in good yields and high enantioselectivities for pyrroles **1f** and **1h**, giving **3f** and **3h** in 80% and 69% yield, with 83% ee and 89% ee, respectively. *N*-Methylpyrrole **1g** reacts with **2** to give product **3g** with 93% ee; however, **3g** was isolated in only 42% yield.

The enantioselective Friedel−Crafts addition reactions also proceed for furans **1i**−**k** and 2-methylthiophene **1l** which react with ethyl trifluoropyruvate **2** catalyzed by

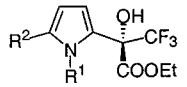
(7) For the use of C_2-symmetric bisoxazoline Leiws acid complexes in various catalytic reactions: (a) Mukaiyama-aldol reactions, see, for example, Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669 and references therein. Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686 and references therein. (b) 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. (c) 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. (d) Cyclopropanation reactions see, for example, 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. (e) Allylic substituton reactions see, for example, 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. (f) Allylation and addition reactions see, for example, 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. (g) Aziridination reactions see, for example, 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. (h) Carbonyl-ene reactions see, for example, 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. (i) Hetero-Diels−Alder reactions see, for example, 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.* **1998**, *37*, 2404. Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **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. (j) Homoaldol reaction of pyruvate: Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Chem. Commun.* **2000**, 2211. (k) Optically active δ- lactones: Audrain, H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 11543.

(8) Other reaction conditions and catalysts tested for the reaction of **1a** with **2**: (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ at room temperature in CH_2Cl_2: **3a** 89% yield and 76% ee; (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ at room temperature in THF: **3a** 89% yield and 85% ee; (*S*)-Ph-BOX-Cu(OTf)$_2$ at room temperature in Et_2O: **3a** 83% yield and 40% ee; (*S*)-Ph-BOX-Zn(OTf)$_2$ at room temperature in Et_2O: **3a** 85% yield and 0% ee.



1 **2**

f: $R^1 = R^2 = H$
g: $R^1 =$ Me, $R^2 = H$
h: $R^1 =$ Me, $R^2 =$ C(O)Me

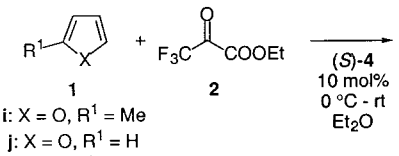


(3)

3

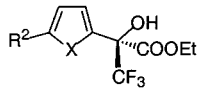
f: $R^1 = R^2 = H$, 80% yield, 83% ee
g: $R^1 =$ Me, $R^2 = H$, 42% yield, 93% ee
h: $R^1 =$ Me, $R^2 =$ C(O)Me, 69% yield, 89% ee

(*S*)-**4**. The results are presented in eq 4, and it is observed for these substrates that the chiral hydroxy-trifluoromethyl ethyl ester substituent is also introduced in the 2-position of the heteroaromatic nucleus. For the furans **1j**,**k** and thiophene **1l** the isolated yields of the reactions are low (15−32%), but the enantioselectivities are good (76−81% ee). Methyl-substituted furan **1i** reacts with **2** to give **3i** in good yield (65%) and very high enantioselectivity (93%).



1 **2**

i: X = O, R^1 = Me
j: X = O, R^1 = H
k: X = O, R^1 = TMS
l: X = S, R^1 = Me

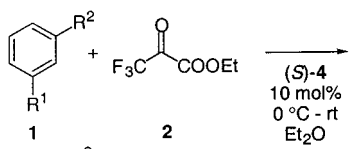


(4)

3

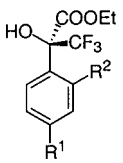
i: X = O, R^1 = Me, yield 65%, 93% ee
j: X = O, R^1 = H, yield 15%, 81% ee
k: X = O, R^1 = TMS yield 32%, 76% ee
l: X = S, R^1 = Me yield 16%, 79% ee

Aromatic compounds react also with ethyl trifluoropyruvate **2** in the presence of (*S*)-**4** as the catalyst. For these substrates electron-donating substituents are necessary for the reaction to proceed. The results for the reaction of *N*,*N*-dimethylaniline **1m** and *m*-methoxyanisole **1n** with **2** are shown in eq 5. The aromatic hydroxy-trifluoromethyl ethyl esters **3m** and **3n** were prepared in moderate yields with 24% ee and 86% ee, respectively. The low ee of **3m** was unexpected; however, this value was consistent with the result obtained using *m*-methoxy-*N*,*N*-dimethylaniline **1o** as the substrate which gave **3o** with only 10% ee (vide infra).



1 **2**

m: $R^1 = NMe_2$, $R^2 = H$
n: $R^1 =$ OMe, $R^2 =$ OMe
o: $R^1 = NMe_2$, $R^2 =$ OMe

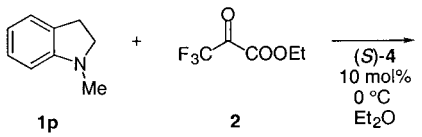


(5)

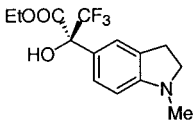
3

m: $R^1 = NMe_2$, $R^2 = H$, yield 60%, 24% ee
n: $R^1 =$ OMe, $R^2 =$ OMe, yield 56%, 86% ee
o: $R^1 = NMe_2$, $R^2 =$ OMe, yield 80%, 10% ee

The low ee obtained for products **3m** and **3o** required further investigation. *N*-Methylindoline **1p** reacted with ethyl trifluoropyruvate **2** in the presence of (*S*)-**4** as the catalyst (eq 6) to give **3p** in good yield; however, the enantioselectivity was also low (22% ee) for this reaction.



1p **2**



(6)

3p
yield 71%, 22% ee

The low enantioselectivity of the Friedel−Crafts products in the reactions where a *N*-methyl substituent is present in the aromatic compounds lead us to postulate that the low enantioselectivity conferred to the aniline products **3m**,**o**,**p** using the (*S*)-**4** catalyst is due to competitive coordination of the "soft" nitrogen atom of the amine to the "soft" copper atom. This can effectively block the open reactive quadrant of the catalyst, decreasing the excellent enantioinduction of this catalyst system to the low level observed (10−24% ee). The indole and pyrrole compounds do not have an available lone pair of electrons, due to their presence in the aromatic ring, so coordination to the copper is not a strong interaction. The "hard" oxygen atom in *m*-methoxy-*N*,*N*-dimethylaniline **1o** also has less affinity for copper than nitrogen, thus unhindered attack on **2** bound to the catalyst leads to high ee.

On the basis of the absolute configuration of compound **3b** obtained in the reaction of 4-chloro-indole **1b** with ethyl trifluoropyruvate **2** catalyzed by (*S*)-**4** it is postulated that **2** binds to the catalyst in a bidentate fashion leading to an intermediate having a distorted square-planar geometry.[9] This intermediate has the *re*-face of the carbonyl functionality of **2** available for approach of the heteroaromatic and aromatic compounds giving the observed absolute configuration observed. The postulated intermediate is shown in Figure 1.

Inspection of the intermediate in Figure 1 reveals that an open reactive quadrant, a "pocket-like" site, is available for coordination of the aromatic compounds having a *N*-methyl substituent at the "lower left-part of the intermediate". Coordination of, for example, *N*,*N*-dimethylaniline at this site should thus be expected to reduce the enantioselective properties of the catalyst. In Figure 2 is shown a model of a square-pyrimidal intermediate,[10] consisting of ethyl trifluoropyruvate **2** and

(9) For a discussion of the intermediate in C_2-bisoxazoline−copper(II) catalyzed reactions see, for example, refs 7, 8h,i.

(10) A square-pyrimidal bisoxazoline−copper(II) intermediate has been postulated. See, for example, Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3373.

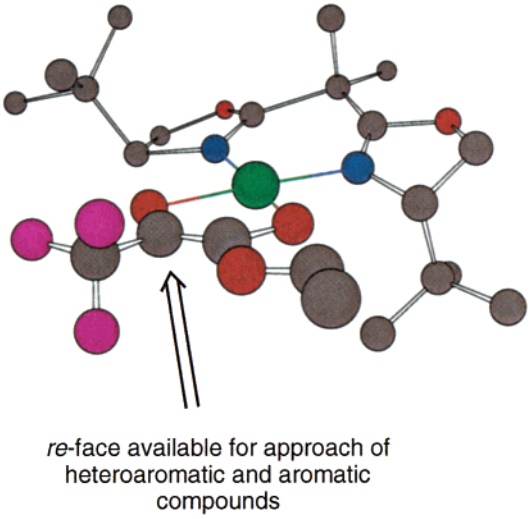


Figure 1. Proposed intermediate in the catalytic enantioselective Friedel–Crafts reaction of aromatic and heteroaromatic compounds to ethyl trifluoropyruvate catalyzed by the *tert*-butyl bisoxazoline–copper(II) complex. The geometry at the copper(II) center is square-planar. Color code: carbon: gray; nitrogen: blue; oxygen: red; fluoro: purple; copper: green. Hydrogen atoms are omitted for clarity.

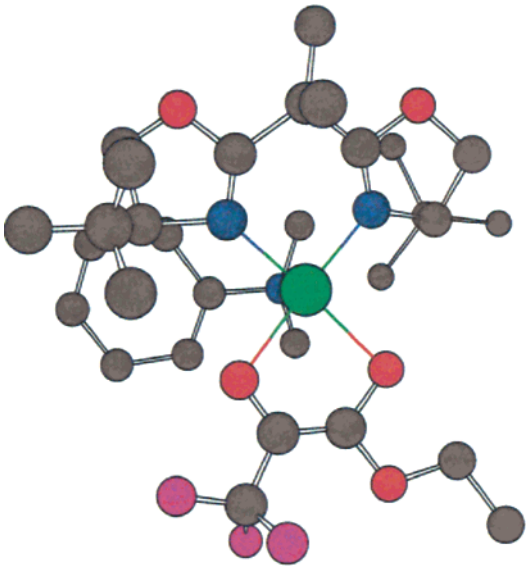
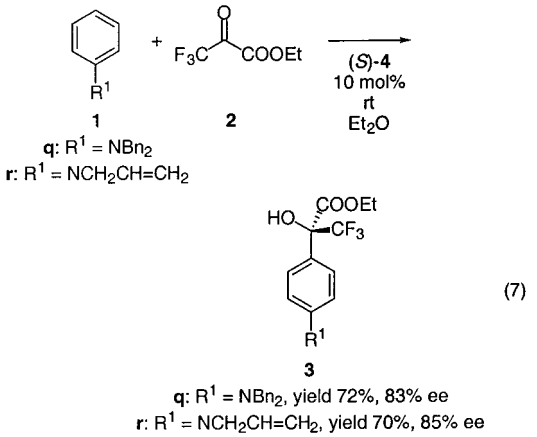


Figure 2. Coordination of *N*,*N*-dimethylaniline at the open reactive quadrant when ethyl trifluoropyruvate is coordinated to *tert*-butyl bisoxazoline–copper(II) which gives a square-pyrimidal intermediate that leads to an intermediate with low enatioselective properties. Color code: carbon: gray; nitrogen: blue; oxygen: red; fluoro: purple; copper: green. Hydrogen atoms are omitted for clarity.

N,*N*-dimethylaniline coordinated to (*S*)-**4**. It appears that the *si*-face of the carbonyl functionality of **2** (top-face) is still shielded by the *tert*-butyl substituent of the chiral bisoxazoline ligand, while the *re*-face (bottom-face) is shielded by *N*,*N*-dimethylaniline. For **2** coordinated to the catalyst as shown in Figure 2, the Lewis-acid property of the catalyst is still intact, while the enantioselective properties of the catalyst is significantly reduced compared to the intermediate outlined in Figure 1.

To test this hypothesis and to develop catalytic enantioselective Friedel–Crafts reactions of aniline derivatives to ethyl trifluoropyruvate **2**, an increase of the steric-bulk of the substituents on the nitrogen atom was examined. This steric repulsion would prevent the coordination of the nitrogen atom of the amine to the copper center. Increasing the size of the *N*-substituents to, for example, benzyl or allyl will lead to a greater steric repulsion between the *tert*-butyl substituent of the bisoxazoline ligand when **2** is coordinated to the catalyst as shown in Figure 2.

The reactions of *N*,*N*-dibenzylaniline **1q** and *N*,*N*-diallylaniline **1r** with ethyl trifluoropyruvate **2** in the presence of (*S*)-**4** as the catalyst (eq 7) were studied under the same reaction conditions as for the other heteroaromatic and aromatic compounds above. We were pleased to find that both **1q** and **1r** react with **2** catalyzed by (*S*)-**4** to give exclusively the *para*-substituted hydroxy-trifluoromethyl ethyl esters **3q** and **3r** in high yields and enantioselectivity, 83% and 85% ee, respectively. These results are consistent with the hypothesis above that the substrates **1m**,**o**,**p** coordinate to (*S*)-**4** and reduce the enantioselective properties of the catalyst. The results for the *N*-protected anilines **1q**,**r** enhance the potential of the present reaction further, as the *N*-protecting groups in **3q**,**r** can easily be removed by standard chemistry, giving the free amine, which allows for the introduction of a variety of different electron-donating and electron-withdrawing substituents in the aromatic nucleus.



(7)

In summary, a new catalytic enantioselective Friedel–Crafts reaction of trifluoromethyl pyruvate with aromatic and heteroaromatic compounds leading to optically active aromatic and heteroaromatic hydroxy-trifluoromethyl ethyl esters has been presented. This reaction proceeds with substituted indoles giving the corresponding 3-substituted hydroxy-trifluoromethyl ethyl esters in up to 93% yield and 94% ee. For pyrrole and 2-substituted pyrroles, the reactions proceed in up to 93% ee, and good yield of the products are obtained. Furans and thiophenes give the corresponding 2-hydroxy-trifluoromethyl ethyl esters with high enantioselectivity in moderate yield. Aromatic compounds containing an electron-donating substituent react in a catalytic reaction to give Friedel–Crafts products in good yields and >80% ee. This catalytic enantioselective Friedel–Crafts reaction of trifluoromethyl pyruvate leads to a simple synthetic procedure for the introduction of an optically active hydroxy-trifluoromethyl ethyl ester group in aromatic and heteroaromatic compounds.

Experimental Section

General Procedure for the Catalytic Enantioselective Friedel−Crafts Reactions of Ethyl Trifluoropyruvate to Heteroaromatic and Aromatic Compounds. To a flame-dried Schlenk tube were added $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (*S*)-**4** (15.5 mg, 0.053 mmol). The mixture was dried under vacuum for 1−2 h, freshly distilled anhydrous Et_2O (2.0 mL) was added, and the solution was stirred for 0.5−1 h. Subsequently, ethyl trifluoropyruvate **2** (85 mg, 0.5 mmol) and an aromatic or heteroaromatic compound (0.55 mmol) were added. After stirring 1−2 d at room temperature or 0 °C, the reaction mixture was filtered through a pad of silica with Et_2O and concentrated in vacuo, and the product was purified by flash chromatography.

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Supporting Information Available: Complete experimental procedure and characterization; ORTEP of **3b** and **3f**. This material is free of charge via the Internet at http://pubs.acs.org.

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