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Enantioselective Friedel–Crafts Alkylation Reactions Catalyzed by a Chiral Nonracemic C_2-Symmetric 2,2′-Bipyridyl Copper(II) Complex

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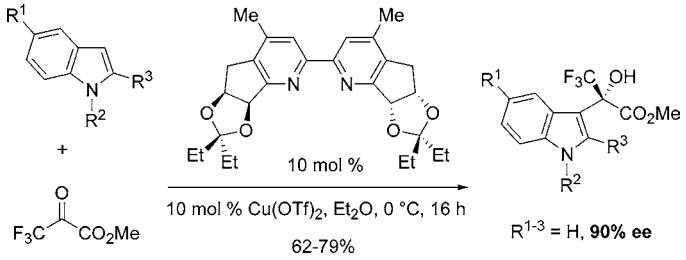
ABSTRACT



Enantioselective Friedel–Crafts alkylation reactions of a series of substituted indoles with methyl trifluoropyruvate, catalyzed by a chiral nonracemic C_2-symmetric 2,2′-bipyridyl copper(II) triflate complex, are described. The corresponding 3,3,3-trifluoro-2-hydroxy-2-indole-3-yl-propionic acid methyl esters were formed in good yield and in high enantiomeric excess (up to 90%). This is the first report of the use of a chiral nonracemic 2,2′-bipyridyl ligand in catalytic and enantioselective Friedel–Crafts alkylation reactions. The structural characterization of a copper(II) chloride complex of the chiral 2,2′-bipyridyl ligand by X-ray crystallography is also presented.

Many different types of chiral ligands have been developed for catalytic asymmetric synthesis and of these, chiral nonracemic 2,2′-bipyridines and 1,10-phenanthrolines have received considerable attention.[1,2] We have recently reported an efficient synthesis of a low molecular weight, chiral nonracemic C_2-symmetric bipyridyl ligand (+)-**1** and demonstrated that it is an outstanding chiral director for use in asymmetric copper(I)-catalyzed cyclopropanation reactions of alkenes and diazoesters (Figure 1).[3] The ligand (+)-**1** was prepared in a convergent manner using a notable and highly enantioselective (90% ee) catalytic asymmetric dihydroxylation reaction of the 2-chloropyrindine **2** as a key step. On conversion to the corresponding 3-pentanone cyclic acetal, a subsequent nickel-mediated homocoupling reaction afforded the desired 2,2′-bipyridyl ligand (+)-**1** in greater than 99% enantiomeric excess. This indicated that a significant

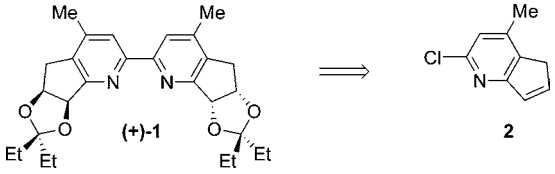


Figure 1. Chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand (+)-**1**.

(1) (a) Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129. (b) Fletcher, N. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1831. (c) Malkov, A. V.; Kočovský, P. *Curr. Org. Chem.* **2003**, *7*, 1737.

(2) For discussions on the coordination chemistry of 2,2′-bipyridines and 1,10-phenanthrolines, see: (a) Reedijk, J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1987; Vol. 2, pp 73−98. (b) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, *100*, 3553.

(3) Lyle, M. P. A.; Wilson, P. D. *Org. Lett.* **2004**, *6*, 855.

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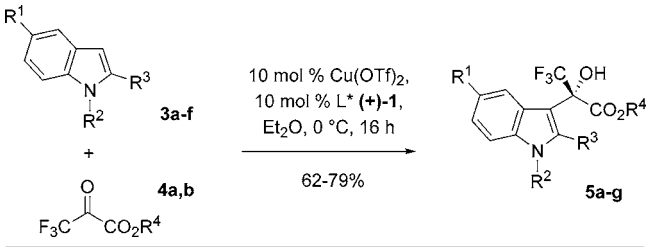
enrichment in the enantiomeric purity of the chiral material had occurred in this coupling reaction.

The Friedel−Crafts (F−C) alkylation reaction is one of the oldest known organic transformations to employ Lewis acid catalysts, and it is a particularly versatile carbon−carbon bond formation reaction.[4,5] Recently, Jørgensen and co-workers have pioneered the catalytic enantioselective F−C alkylation reaction of activated aromatic compounds with electron-deficient carbonyl compounds and alkenes using chiral bisoxazoline copper(II) complexes as catalysts.[6] In this paper, in regard to the exploration of the versatility of our new chiral nonracemic 2,2′-bipyridyl ligand (+)-**1**, we report a study of the application of this ligand in copper(II)-catalyzed asymmetric F−C alkylation reactions.

The 2,2′-bipyridine (+)-**1** was evaluated in the copper(II)-catalyzed F−C reaction of a series of commercially available indoles **3a**−**f** with the ethyl and methyl esters of 3,3,3-trifluoropyruvic acid **4a**,**b** (Table 1). To the best of our knowledge, this is the first report of the application of a 2,2′-bipyridyl ligand in catalytic enantioselective F−C reactions. The active copper(II) catalyst was generated in situ on reaction of 10 mol % copper(II) triflate with 10 mol % 2,2′-bipyridyl ligand (+)-**1**. Typically, the F−C reactions were carried out in ether at 0 °C. These reaction conditions were established on performing a series of optimization experiments.[7] Under the optimized reaction conditions, the $Cu(OTf)_2$·ligand (+)-**1** complex displayed excellent catalytic activity and the F−C reactions reached completion within 16 h in all instances. The F−C reaction of indole **3a** with ethyl 3,3,3-trifluoropyruvate **4a** afforded the known product **5a** in good yield (68%) and in good enantiomeric excess (74%) (entry 1). The absolute stereochemistry of product **5a** was assigned as *S* on comparison of the optical rotation with a literature value.[8] The F−C reaction of indole **3a** with methyl 3,3,3-trifluoropyruvate **4b** afforded product **5b** in similar yield (77%) but in significantly higher enantiomeric excess (90%) (entry 2). This result compares favorably with the $Cu(OTf)_2$·(*S*)-*t*-BuBox-catalyzed reactions reported by Jørgensen and co-workers for a range of substrates (83−94% ee).[6b] Of note, we assume that the absolute stereochemistry of the reaction product **5b** is *S* in that it is reasonable to expect that the alternative use of the methyl ester of 3,3,3-trifluoropyruvic acid **4b** will not effect the stereochemical outcome of the reaction. No further improvement in the enantioselectivity of the reaction was achieved by repeating the above experiment at a lower temperature (entry 3). Thus, methyl 3,3,3-trifluoropyruvate **4b** was used exclusively in subsequent experiments, and the reactions were performed at 0 °C.

Table 1. Asymmetric Friedel−Crafts Alkylation Reactions of Indoles **3a**−**f**



entry	R^1	R^2	R^3	R^4	product	yield (%)[a]	ee (%)[b]
1	H	H	H	Et	**5a**	68	74
2	H	H	H	Me	**5b**	77	90
3	H	H	H	Me	**5b**	62	90[c]
4	H	H	Me	Me	**5c**	79	86
5	OMe	H	H	Me	**5d**	69	72
6	NO_2	H	H	Me	**5e**	75	60[d]
7	H	Me	H	Me	**5f**	74	18
8	H	Me	Ph	Me	**5g**	65	18

[a] Isolated yield after purification by flash chromatography. [b] Determined by analytical chiral HPLC (Daicel Chiracel OD column). [c] The reaction was performed at −10 °C. [d] The enantiomeric excess, in this instance, was determined by ^{1}H NMR analysis using the chiral shift reagent $Eu(hfc)_3$.

Further experimentation is required to determine the origin of this effect. However, these results do suggest that the indole N−H bond is involved in the reaction transition state or that detrimental steric factors are at play in these particular catalytic reactions.

The F−C reaction of 2-methylindole **3b** again afforded the corresponding product **5c** in good enantiomeric excess (86%) (entry 4). The electron-rich substrate, 5-methoxyindole **3c**, afforded the product **5d** in 72% ee, whereas the electron-poor substrate, 5-nitroindole **3d**, afforded the product **5e** in slightly lower enantiomeric excess (60%). Surprisingly, 1-methylindole **3e** and 1-methyl-2-phenylindole **3f** afforded the corresponding products **5f** and **5g** in low enantiomeric excess (18%) (entries 7 and 8).[9] Thus, it is evident that substitution of the hydrogen atom of the indole nitrogen has a detrimental effect on the enantioselectivity of the F−C reaction.

We have also evaluated the 2,2′-bipyridine (+)-**1** in the conjugate addition reactions of the indole **3a** and 3-methoxyphenol **8** to (3*E*)-2-oxo-4-phenyl-3-butenoic acid methyl ester **6** (Scheme 1).[10,11] In the case of indole **3a**, the conjugate

(4) (a) Friedel, C.; Crafts, J. M. *R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392. (b) Friedel, C.; Crafts, J. M. *R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1450.

(5) Olah, G. A.; Khrisnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*, 1st ed.; Pergamon: New York, 1991; Vol. 3, pp 293−339.

(6) (a) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. (b) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009. (c) Jørgensen, K. A. *Synthesis* **2003**, 1117. (d) For a recent review on the asymmetric F−C alkylation reaction, see: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

(7) The F−C reaction of indole **3a** with methyl 3,3,3-trifluoropyruvate **4b** afforded the product **5b** in good yield in dichloromethane and in tetrahydrofuran. However, the enantioselectivities were lower (28 and 45% ee, respectively) in these instances.

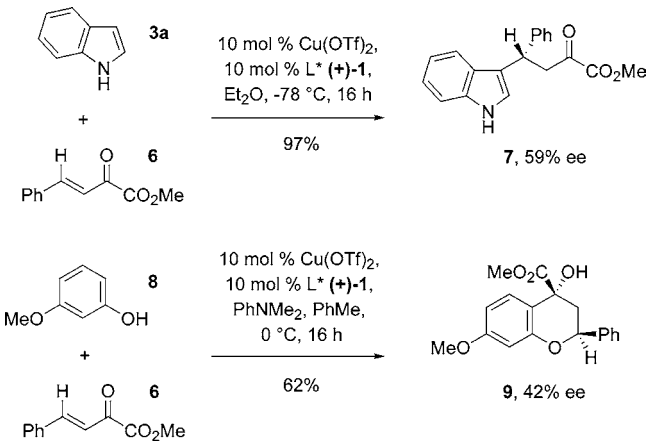
(8) The absolute stereochemistry of (2*S*)-2-(4-chloroindole-3-yl)-3,3,3-trifluoro-2-hydroxy propionic acid ethyl ester has been assigned unambiguously by X-ray crystallography, and the absolute stereochemistry of compound **5a** was assigned by analogy; see ref 6b.

(9) This result is in contrast to the bisoxazoline copper(II) complex-catalyzed reactions in which substitution of the indole nitrogen does not lower the enantioselectivity of the reaction; see ref 6b.

(10) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160.

(11) van Lingen, H. L.; Zhuang, W.; Hansen, T.; Rutjes, F. P. J. T.; Jørgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 1953.

Scheme 1. Conjugate Addition Reactions of Indole **3a** and 3-Methoxyphenol **8** to the β,γ-Unsaturated α-Ketoester **6**



addition product **7** was formed in excellent yield (97%) and in good enantiomeric excess (59%). In the case of the reaction of 3-methoxyphenol **8**, the product of the initial conjugate addition reaction undergoes a subsequent intramolecular F−C reaction to afford the novel chromane derivative **9** (as a single diastereoisomer) in moderate enantiomeric excess (42%) and in good yield (62%). The absolute stereochemistry of the major conjugate addition product **7** was assigned as *S* on comparison of the optical rotation with a literature value.[12] The absolute stereochemistry of the chromane derivative **9** is not known. However, we assume that the major product of this reaction has the same absolute stereochemistry (at C2) as that observed for the major conjugate addition product **7**.

To gain insight into the structure of the active catalyst in the above reactions, a copper(II) chloride complex **10** was prepared from the 2,2′-bipyridine (+)-**1** and anhydrous copper(II) chloride. Yellow crystals that were suitable for X-ray crystallography were obtained on recrystallization, by the slow evaporation of the solvent, from a mixture (2:1) of dichloromethane and ethanol. An ORTEP representation of the $CuCl_2$·ligand (+)-**1** complex **10** is provided below (Figure 2). It was found that, in the solid state, the ligands adopt a geometry that lies between square-planar and tetrahedral around the copper atom. In this structure, the chloride ligands are tilted away from the large cyclic acetal moieties of the C_2-symmetric bipyridyl ligand (+)-**1**. Similar structural observations have been recorded for several bisoxazoline copper(II) complexes such as $CuCl_2$·*t*-BuBox, $CuCl_2$·PhBox, and $CuCl_2$·1-NpBox, as well as for other chiral bipyridyl copper(II) complexes.[13,14]

To rationalize the stereochemical outcome of the copper(II)-catalyzed asymmetric F−C reactions of the indoles

(12) See the supporting information for ref 10.

(13) Thorhauge, J.; Roberson, M.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2002**, *8*, 1888 and references therein.

(14) (a) Kwong, H.-L.; Lee, W.-S.; Ng, H.-F.; Chiu, W.-H.; Wong, W.-T. *J. Chem. Soc., Dalton Trans.* **1998**, 1043. (b) Malkov, A. V.; Bella, M.; Langer, V.; Kočovský, P. *Org. Lett.* **2000**, *2*, 3047. (c) Lötscher, D.; Rupprecht, S.; Stoeckli-Evans, H.; von Zelewsky, A. *Tetrahedron*: *Asymmetry* **2000**, *11*, 4341.

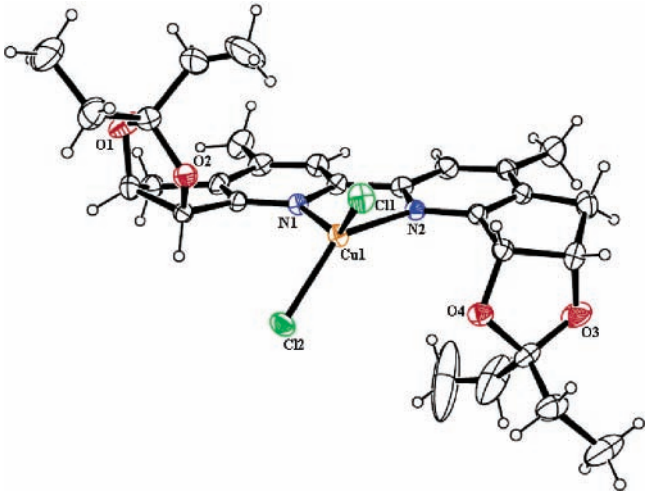


Figure 2. ORTEP representation of the $CuCl_2$·ligand (+)-**1** complex **10**. The thermal ellipsoids are drawn at a 25% probability level for clarity.

3a−**f** with the methyl ester of 3,3,3-trifluoropyruvic acid **4b**, we postulate that the relatively small α-ketoester **4b** coordinates in a bidentate fashion to the copper center of the $Cu(OTf)_2$·ligand (+)-**1** complex in an approximately square-planar geometry (Figure 3). The indoles **3a**−**f** would then

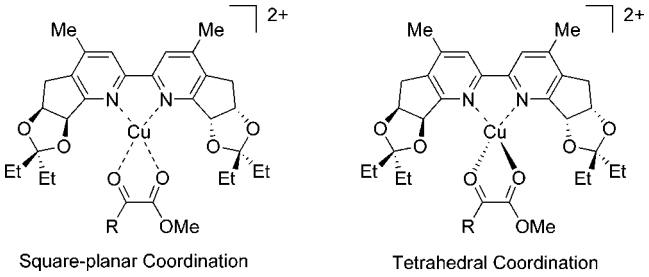


Figure 3. Square-planar and tetrahedral coordination of the α-ketoester reaction substrates **4b** and **6** to the chiral catalyst.

be expected to attack the more sterically accessible *Re*-face of the carbonyl moiety. To rationalize the *opposite* facial selectivity for the reaction of indole **3a** (or the assumed facial selectivity for the reaction of 3-methoxyphenol **8**) with the β,γ-unsaturated α-ketoester **6**, we postulate that this larger β,γ-unsaturated α-ketoester coordinates in a bidentate fashion to the copper center in an approximately tetrahedral geometry and that the β,γ-unsaturated α-ketoester moiety adopts an s-cis conformation. The indole **3a** (or the phenol **8**) would then be expected to attack the β,γ-unsaturated α-ketoester moiety from the more sterically accessible *Si*-face of the complex.[15] The lower enantioselectivity of the latter two reactions can be attributed to the conformational flexibility of β,γ-unsaturated α-ketoester moiety or, more simply, to the fact that reaction center is located further from the chiral pocket of the catalytic entity.

In conclusion, we have evaluated our new low molecular weight, chiral nonracemic C_2-symmetric 2,2′-bipyridyl ligand (+)-**1** in the copper(II)-catalyzed asymmetric F−C alkylation reactions of the substituted indoles **3a**−**f** with the ethyl and methyl esters of 3,3,3-trifluoropyruvic acid **4a**,**b**. This is the first report of the application of a chiral nonracemic 2,2′-bipyridyl ligand in catalytic enantioselective F−C reactions. When indole **3a** and the methyl ester of 3,3,3-trifluoropyruvic acid **4b** were employed as reaction substrates and the reaction was performed in ether at 0 °C, an enantioselectivitiy of 90% ee was recorded. However, it was noted that substitution of the hydrogen atom of the indole nitrogen has a detrimental effect on the enantioselectivity of this $Cu(OTf)_2$·ligand (+)-**1** complex-catalyzed F−C reaction. The copper(II)-catalyzed asymmetric conjugate addition reactions of indole **3a** and 3-methoxyphenol **8** to (3*E*)-2-oxo-4-phenyl-3-butenoic acid methyl ester **6** were also demonstrated. Studies are currently underway to improve the enantioselectivity of these copper(II)-catalyzed F−C reactions by making structural modifications to the cyclic acetal moieties of the 2,2′-bipyridine (+)-**1**.[3] Current investigations are also focused on the use of this notable bipyridyl ligand (+)-**1** in other catalytic asymmetric processes.

(15) The reversal of facial selectivity observed in these reactions is not unusual and has been observed in other closely related reactions that have been catalyzed by C_2-symmetric bisoxazoline copper(II) complexes; see: (a) Jørgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (c) Zhou, J.; Ye, M.-C.; Huang, Z.-Z.; Tang, Y. *J. Org. Chem.* **2004**, *69*, 1309.

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Supporting Information Available: Detailed experimental procedures and full product characterization data for all compounds synthesized, including a procedure for the preparation and crystallization of the $CuCl_2$·ligand (+)-**1** complex **10**, as well as ^1H and ^{13}C NMR spectra for compounds **5b**−**g** (PDF), and X-ray crystallographic data for complex **10** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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