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Novel Enantiocomplementary C_2-Symmetric Chiral Bis(imidazoline) Ligands: Highly Enantioselective Friedel–Crafts Alkylation of Indoles with Ethyl 3,3,3-Trifluoropyruvate

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Dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

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Abstract: Enantioselective Friedel–Crafts alkylations of a variety of indoles with ethyl 3,3,3-trifluoropyruvate catalyzed by novel chiral *m*-phenylenebis(imidazoline)-copper(II) complexes or the bis(imidazoline)-achiral acid combination afforded products with high enantioselectivity. Both enantiomers of indole derivatives can be prepared with high enantioselectivities by tuning the N-substituents of the imidazoline.

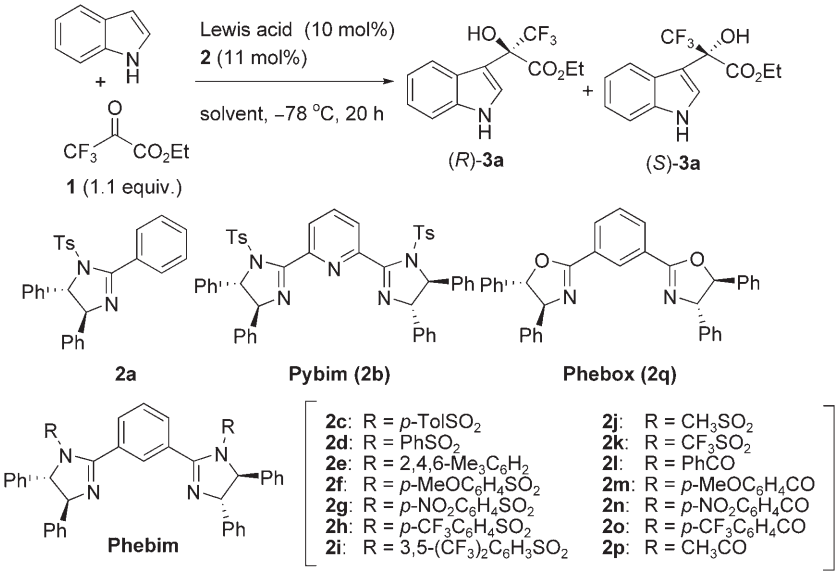
Keywords: asymmetric catalysis; Friedel–Crafts reaction; imidazolines; Lewis acids

The development of asymmetric catalysts has been extensively studied over the last decade. Certainly, one of the privileged classes of chiral ligands is the bis(oxazoline) framework, which consists of two *N*,*O*-containing five-membered rings coordinating to a metal cation.[1] Fine tuning of the electron density and the steric bulkiness of the oxazoline ring remain to be solved. The highly tuneable construction of bis(imidazoline) ligands would overcome this limitation and realize better matching of chiral ligands, metal ions, and substrates other than bis(oxazoline)s, and thus achieve excellent catalytic performance. We started to explore bis(imidazoline) catalytic reactions several years ago. During our study, a number of studies of asymmetric synthesis using Lewis acid-bis(imidazoline) catalysts have appeared.[2,3] Herein we report new excellent bis(imidazoline) ligands, "phebims", having various substituents, in the asymmetric Friedel–Crafts (F-C) alkylation of indole derivatives with ethyl 3,3,3-trifluoropyruvate (**1**). Outstanding aspects of these ligands are also described: (i) a new dual activation mechanism for the chiral induction is proposed, (ii) both enantiomers can be obtained with phebim by changing the substituents on the nitrogen atom and the counter ion of the cupric salt, and (iii) phebim acts as a chiral Brønsted acid by the action of an achiral acid without using a Lewis acid. The F-C alkylation of indole derivatives was chosen as a benchmark reaction for using phebim, since the synthesis of indole derivatives has captured much attention in organic chemistry for many decades.[4,5] Catalytic enantioselective F-C alkylation reactions of indole derivatives using chiral Lewis acids[6] and organocatalysts[7] have been reported.

Various novel bis(imidazoline) ligands **2c–p** were prepared by the reaction of benzene-1,3-dicarbaldehyde, chiral 1,2-diphenylethylenediamine, and NBS as an oxidant[8] giving phenylenebis(imidazoline), followed by sulfonylation and acylation.[9,10]

The results of the F-C alkylation of indole with **1** using imidazoline catalysts are shown in Table 1. The reaction using chiral Lewis acids prepared from $Cu(OTf)_2$[11] and mono-imidazoline **2a** or pyridine-bis(imidazoline) (pybim) **2b**[2d,f,j] in CH_2Cl_2 at −78 °C afforded the product (*R*)-**3a** with low enantioselectivity (entries 1 and 2). On the other hand, the reaction using *N*-*p*-toluenesulfonyl-substituted phebim **2c** gave (*R*)-**3a** in high yield with 94% *ee* (entry 3). As we expected, the enantioselectivity of **3a** depended on the substituents on the imidazolyl nitrogen atoms. The reaction using various *N*-arenesulfonyl- or *N*-alkanesulfonyl-substituted phebims **2d–k** with $Cu(OTf)_2$ afforded (*R*)-**3a** with good enantioselectivity albeit lower

Table 1. Enantioselective reaction of indole with **1** using various chiral imidazoline ligands with $Cu(OTf)_2$ or CF_3SO_2H in CH_2Cl_2.



Run	Ligand	Lewis Acid	Solvent	Yield [%] of **3a**	*ee* [%][a]
1	**2a**	$Cu(OTf)_2$	CH_2Cl_2	81	0
2	**2b**	$Cu(OTf)_2$	CH_2Cl_2	88	1
3	**2c**	$Cu(OTf)_2$	CH_2Cl_2	93	94 (*R*)
4	**2d**	$Cu(OTf)_2$	CH_2Cl_2	86	93 (*R*)
5	**2e**	$Cu(OTf)_2$	CH_2Cl_2	53	74 (*R*)
6	**2f**	$Cu(OTf)_2$	CH_2Cl_2	78	84 (*R*)
7	**2g**	$Cu(OTf)_2$	CH_2Cl_2	42	80 (*R*)
8	**2h**	$Cu(OTf)_2$	CH_2Cl_2	75	88 (*R*)
9	**2i**	$Cu(OTf)_2$	CH_2Cl_2	58	46 (*R*)
10	**2j**	$Cu(OTf)_2$	CH_2Cl_2	77	6 (*R*)
11	**2k**	$Cu(OTf)_2$	CH_2Cl_2	84	20 (*R*)
12	**2l**	$Cu(OTf)_2$	CH_2Cl_2	47	23 (*R*)
13	**2n**	$Cu(OTf)_2$	CH_2Cl_2	79	18 (*R*)
14	**2q**	$Cu(OTf)_2$	CH_2Cl_2	87	77 (*R*)
15[b]	**2c**	$Cu(OTf)_2$	CH_2Cl_2	95	95 (*R*)
16[c]	**2c**	$Cu(OTf)_2$	CH_2Cl_2	97	93 (*R*)
17[d]	**2c**	$Cu(OTf)_2$	CH_2Cl_2	91	87 (*R*)
18	**2c**	TfOH	CH_2Cl_2	83	82 (*R*)
19	**2q**	TfOH	CH_2Cl_2	96	48 (*R*)

[a] Determined by chiral HPLC analysis.
[b] Catalyst loading is 5 mol%.
[c] Catalyst loading is 0.5 mol%.
[d] Catalyst loading is 0.2 mol%.

than that from the reaction using **2c** (entries 4–11). *N,N'*-Dibenzolylbis(imidazoline) **2l** also afforded (*R*)-**3a** but with low enantioselectivity (entry 12). On the other hand, the reaction using the phebox ligand **2q** as a bis(oxazoline)-type ligand gave (*R*)-**3a** with lower enantioselectivity than when using **2c** (entry 14). We next attempted to decrease the catalyst loading. Even 0.5 mol% of **2c** worked efficiently, and the reaction using 0.2 mol% of **2c** showed slightly lower enantioselectivity (entries 16 and 17). Thus, the turnover numbers (TONs) reached to almost 200 together with high enantioselectivity. Phebim **2c** was found to work as a chiral Brønsted acid catalyst in combination with CF_3SO_3H to give (*R*)-**3a** with a good level of enantioselectivity (entry 18), whereas the combination of phebox **2q** with CF_3SO_3H activated the reaction to give (*R*)-**3a** with lower enantioselectivity than that obtained by the **2c**-CF_3SO_3H combination. The absolute

Table 2. Enantioselective reaction of indole with **1** using various chiral bis(imidazoline) ligands with $Cu(NTf_2)_2$ or Tf_2NH.

Run	Ligand	Acid	Solvent	Yield [%] of **3a**	*ee* [%][a]
1	**2l**	$Cu(NTf_2)_2$	toluene	93	62 (*S*)
2	**2m**	$Cu(NTf_2)_2$	toluene	27	56 (*S*)
3[b]	**2n**	$Cu(NTf_2)_2$	toluene	99	90 (*S*)
4[b]	**2o**	$Cu(NTf_2)_2$	toluene	53	83 (*S*)
5[b]	**2p**	$Cu(NTf_2)_2$	toluene	61	12 (*S*)
6[b,c]	**2n**	$Cu(NTf_2)_2$	toluene	95	88 (*S*)
7[b,d]	**2n**	$Cu(NTf_2)_2$	toluene	95	80 (*S*)
8	**2n**	Tf_2NH	toluene	90	73 (*S*)

[a] Determined by chiral HPLC analysis.
[b] Molecular sieves 4 Å were added.
[c] Catalyst loading is 5 mol%.
[d] Catalyst loading is 0.5 mol%.

stereochemistry of product **3a** was assigned to be *R* in comparison with the value of the specific rotation reported in the literature.[6c]

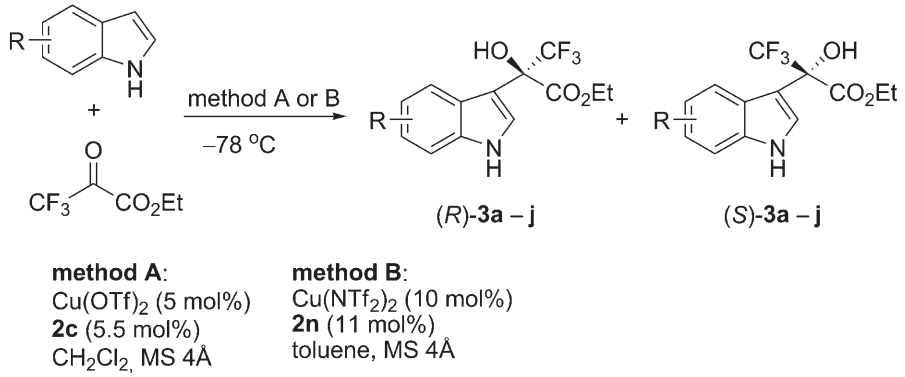
Interestingly, the reaction using *N*-benzoyl-substituted phebim **2l** and $Cu(NTf_2)_2$ in toluene afforded (*S*)-**3a** having a stereochemistry opposite to that obtained in the reaction using phebims and $Cu(OTf)_2$ (Table 2, entry 1).[12,13] Optimization experiments for the fine tuning of the substitution of phebim **2** were carried out to improve the enantioselectivity of (*S*)-**3a**. Electron-withdrawing substituents on the bis(imidazoline) showed high enantioselectivity, i.e., *N*-*p*-nitrobenzoyl-substituted phebim **2n** was found to be very efficient (entry 3). The catalyst loading of **2n** can be reduced to 5 mol% without loss of enantioselectivity, although the reaction using 0.5 mol% of **2n** resulted in slightly lower enantioselectivity (entries 6 and 7). It should be noted that the **2n**-Tf_2NH combination gave (*S*)-**3a** with good enantioselectivity (entry 8), showing that phebim **2n** acts as a chiral Brønsted acid in combination with Tf_2NH.

We next examined the reaction of **1** with various indoles using two catalytic systems, method A; **2c**-$Cu(OTf)_2$ and method B; **2n**-$Cu(NTf_2)_2$ (Table 3).[14] The results indicate that (*R*)- and (*S*)-**3a–j** can be obtained in high yield with good to high enantioselectivity by the respective method (entries 5–18) and that enantiocomplementary synthesis is generally quite applicable.[15]

We propose the dual activation transition state for the reaction of indole and trifluoropyruvate in the presence of phebim-$Cu(OTf)_2$ on the basis of the following results. Reactions of indole with **1** in the presence of 5 mol% of **2a**-$Cu(OTf)_2$ or **2c**-$Cu(OTf)_2$ and in the absence of the catalyst were carried out in CD_2Cl_2 at −78 °C for 1 min, and then the mixture was quenched with CD_3OD. The reaction with **2c-**$Cu(OTf)_2$ afforded **3a** in 77% yield, whereas the reactions using **2a**-$Cu(OTf)_2$ and without the catalyst gave **3a** in 13% and 19% yield, respectively. In addition, *N*-methylindole drastically changed the chiral induction giving the racemic **3a** and decreased the reactivity in comparison with the reaction of the unprotected indole (Table 3, entry 1 *vs.* 19). These results suggest that hydrogen bonding of the indole N-H to the imidazoline nitrogen plays an important role in enhancing the reactivity and, hence, enantioselectivity. Avoiding bidentate chelation of phebim with Cu^{2+},[16] phebim **2c** would form a complex with $Cu(OTf)_2$ that in turn activates pyruvate **1** as a chelating Lewis acid (Figure 1),[17] where the triflate is placed at the upward position avoiding the steric interaction with the phenyl group on the imidazoline ring. Through this dual activation transition state, indole approaches the *Si* face of the carbonyl attached to the trifluoromethyl group. It is known that the nitrogen of *N*-sulfonylimidazoline takes the pyramidal structure, while *N*-benzoyl- and *N*-alkylimidazolines have planar nitrogens.[2h] It is possibly due to the drastic change in the nitrogen structure of bis(imidazoline) that the reactions using **2c** and **2n** gave **3** with opposite stereochemistry. Further experiments are needed to prove the above assumed transition state.

In conclusion, we have developed novel *m*-phenylenebis(imidazoline)-Lewis acid systems for the F-C alkylation of indoles. With our new phebim ligands, catalyst loading can be successfully minimized up to 0.5 mol% without a significant decrease in yield and enantioselectivity. The efficient enantioflexible stereocontrol can be achieved by changing the substituents on imidazoline, the counter anion of the Lewis acid, and the solvent. In addition, phebim works as a Brønsted acid in combination with an achiral acid. The above outstanding aspects in the reactivity of phebim are possibly due to the dual activation of indole and pyruvate by two imidazoline rings, thus, effecting the chiral induction. Further experiments are in progress to study the scope of this process and the potential application of phebim to other reactions.

Table 3. Enantioselective reaction of various indoles with **1**.



Entry	R	Method	Time [h]	Product	Yield [%]	*ee* [%]
1	H	**A**	3	(*R*)-**3a**	95	95
2	H	**B**	4	(*S*)-**3a**	99	90
3	2-Me	**A**	2	(*R*)-**3b**	91	60
4	2-Me	**B**	4	(*S*)-**3b**	81	67
5	5-Me	**A**	1	(*R*)-**3c**	85	90
6	5-Me	**B**	4	(*S*)-**3c**	94	93
7[a]	5-F	**A**	4	(*R*)-**3d**	95	86
8	5-F	**B**	4	(*S*)-**3d**	99	91
9	5-Cl	**A**	19	(*R*)-**3e**	95	93
10	5-Cl	**B**	17	(*S*)-**3e**	99	97
11	5-Br	**A**	17	(*R*)-**3f**	99	87
12	5-Br	**B**	17	(*S*)-**3f**	96	93
13	5-I	**A**	17	(*R*)-**3g**	92	87
14	5-I	**B**	17	(*S*)-**3g**	99	96
15[b]	5-CO_2Me	**A**	50	(*R*)-**3h**	75	51
16[b]	5-CO_2Me	**B**	34	(*S*)-**3h**	80	80
17	5-OMe	**A**	2	(*R*)-**3i**	92	57
18	5-OMe	**B**	5	(*S*)-**3i**	99	80
19	*N*-Me	**A**	17	**3j**	79	1

[a] **2c** (10 mol%) and $Cu(OTf)_2$ (11 mo%) were used.
[b] Warmed to −60 °C.

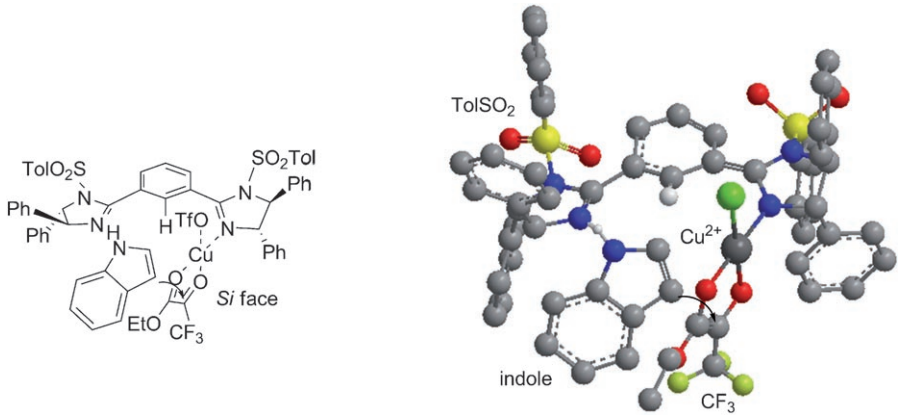


Figure 1. Proposed reaction mechanism of the reaction of indole with **1** using the **2c**-$Cu(OTf)_2$ combination

Experimental Section

Typical Procedure for the Friedel–Crafts Reaction using the Phebim Ligand: (2*R*)-Ethyl 3,3,3-Trifluoro-2-hydroxy-2-(indol-3-yl)propionate [(*R*)-3a]

To a mixture of $Cu(OTf)_2$ (2.5 mg, 6.91 μmol), **2c** (6.3 mg, 7.60 μmol) and molecular sieves 4 Å (24 mg) in CH_2Cl_2 (1.0 mL) was added **1** (20.2 μL, 0.152 mmol) at −78 °C. After stirring for 30 min, a solution of indole (16.2 mg, 0.138 mmol) in CH_2Cl_2 (1.0 mL) was slowly added. After disappearance of indole in the reaction mixture on TLC, the solvent was removed under reduced pressure to give a residue which was purified by column chromatography (hexane/Et_2O = 55:45) giving **3a** as a white solid; yield: 37.6 mg (95%).

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[12] For the reversal of the stereochemistry using the same chiral ligands or similar ones, see review: a) M. P. Sibi, M. Liu, *Curr. Org. Chem.* **2001**, *5*, 719–755; see also: b) M. Kanai, Y. Nakagawa, K. Tomioka, *Tetrahedron* **1999**, *55*, 3831–3842; c) M. P. Sibi, J. Chen, *J. Am. Chem. Soc.* **2001**, *123*, 9472–9473; d) N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett* **2004**, 1703–1706; e) S. Nakamura, N. Sato, M. Sugimoto, T. Toru, *Tetrahedron: Asymmetry* **2004**, *15*, 1513–1516; f) C. P. Casey, S. C. Martins, M. A. Fagan, *J. Am. Chem. Soc.* **2004**, *126*, 5585–5592; g) D. Du, S. Lu, T. Fang, J. Xu, *J. Org. Chem.* **2005**, *70*, 3712–3715; h) N. Kato, T. Mita, M. Kanai, B. Therrien, M. Kawano, K. Yamaguchi, H. Danjo, Y. Sei, A. Sato, S. Furusho, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6768–6769; i) A. Frölander, C. Moberg, *Org. Lett.* **2007**, *9*, 1371–1374.

[13] The reaction using **2c** with $Cu(NTf_2)_2$ afforded (*S*)-**3a** in 53% yield with 3% *ee*.

[14] Molecular sieves 4 Å improved reproducibility of the reaction.

[15] Enantioselective reactions of pyrroles and *N*,*N*-dialkylanilines with trifluoropyruvate in the presence of **2c**-$Cu(OTf)_2$ afforded the products with low enantioselectivity.

[16] Bidentate chelation of phebim with Cu^{2+} could be ruled out because of the significant repulsive effect of the phenyl proton and Cu^{2+}.

[17] A similar dual activation mechanism in the oxidation of tryptophan by human tryptophan dioxygenase has been reported, in which the activations by hydrogen bonding of indole to the imidazole nitrogen in histidine and by coordination of oxygen to Fe^{2+} are involved, see: D. Batabyal, S.-R. Yeh, *J. Am. Chem. Soc.* **2007**, *129*, 15690–15701.

