COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Enantioselective Friedel–Crafts reaction of indoles with arylidene malonates catalyzed by ^{i}Pr-bisoxazoline–Cu(OTf)$_2$†

Jian Zhou and Yong Tang*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China. E-mail: tangy@mail.sioc.ac.cn; Fax: (+86) 21-64166128

Received (in Cambridge, UK) 20th October 2003, Accepted 15th December 2003
First published as an Advance Article on the web 19th January 2004

The cheap and simple ^{i}Pr-bisoxazoline–Cu(OTf)$_2$ proves to be an efficient catalyst in the asymmetric Friedel–Crafts reaction of indole with arylidene malonates. In ^{i}BuOH, the *S*-enantiomer was obtained in up to 97% ee, while the opposite enantiomer was obtained in up to 78% ee in CH_2Cl_2 or TTCE.

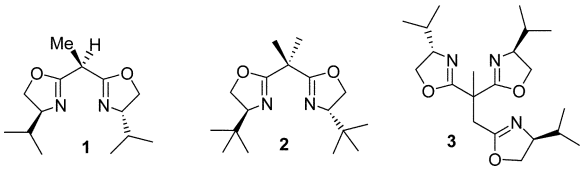
One of the challenges in asymmetric catalysis is to develop a highly enantioselective reaction under convenient conditions using a simple catalyst system which is as cheap as possible.[1] Generally, conformationally rigid chiral ligands with increased steric hindrance are regarded as being able to provide better enantiofacial control than conformationally flexible ligands with small steric bias. For example, *t*-Bu-bisoxazoline (Box) **2** gives better enantiomeric excess than ^{i}Pr-Box in most cases.[2] In our efforts to develop new strategies for achieving highly enantioselective reactions using a simple and cheap catalytic system, we found recently that pseudo-C_3 symmetric trisoxazoline **3** (Scheme 1) derived $Cu(ClO_4)_2{\cdot}6H_2O$ complex[3a] could promote the asymmetric Friedel–Crafts reaction of indole with arylidene malonates[4] smoothly and up to 93% ee was achieved. The enantioselectivity enhancement (compared with the use of the *t*-Bu-bisoxazoline) was proposed to be due to the effective chiral environment resulting from the coordination of the sidearmed oxazoline to the copper center (Scheme 2).[2a] Based on this mechanistic insight, we envisaged that high enantioselectivity might also be achieved using the cheap and simple bisoxazoline **1**–Cu(OTf)$_2$ as the chiral catalyst, if an appropriate coordinating-additive was introduced instead of the pendant oxazoline. By this strategy, we found that the cheap and simple bisoxazoline **1** was a powerful ligand in the asymmetric Friedel–Crafts reaction of indoles with arylidene malonates. In this communication, we wish to report the preliminary results.

Considering that the addition of hexafluoro-^{i}PrOH (HFIP) could greatly improve the reactivity of the indole alkylation without loss of ee as we reported previously,[3a] we first tried to use alcohols as the additives. As shown in Table 1, in the mixed solvent of acetone and ether (1 : 3, v/v), only 6% ee was obtained using chiral catalyst bisoxazoline **1**–Cu(OTf)$_2$ (entry 1, Table 1). Gratifyingly, the addition of two equivalents of ^{i}PrOH improved the enantioselectivity markedly, to 52% (entry 2). Moreover, if ^{i}PrOH was used as the solvent, the ee was further improved to 79% (entry 5). This result encouraged us to test other alcohols as the solvent. Noticeably, it was found that the enantioselectivity depended on the size of the alcohol (entries 3–6). As the size of the alcohol (MeOH < EtOH < ^{i}PrOH < ^{i}BuOH) increased, the enantiomeric excess improved from 60% to 82% at 15 °C. These data suggested that the alcohol might coordinate to the copper center, and thus the size of the alcohol significantly influenced the enantioselectivity.[5] When the reaction was carried out in ^{i}BuOH, further lowering the temperature to −25 °C increased the enantioselectivity to 93% (entry 7), the same as that obtained by using trisoxazoline **3**–$Cu(ClO_4)_2{\cdot}6H_2O$ in the mixed solvent of acetone and ether with the aid of HFIP at the same temperature.

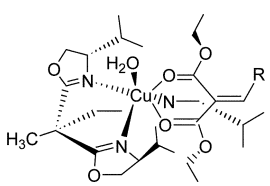
To further probe if the enantioselectivity enhancement resulted from the coordination of isobutanol to the copper center to relay chiral information, we next examined the performance of bisoxazoline **1**–Cu(OTf)$_2$ in weak coordinating solvents. Astonishingly, the reversal of enantioselectivity was observed. When reaction was carried out in CH_2Cl_2, 78% ee was achieved for the opposite enantiomer (entry 8).[6] Thus, either one of the enantiomers could be obtained at will with high selectivity (> 99% ee could be obtained after recrystallization).

Under these optimized conditions, we next examined the substrate scope (Table 2). Generally, at −25 °C, about 50–94% yields with up to 97% ee were obtained when reactions were carried out in ^{i}BuOH. To obtain the opposite enantiomer, reactions were carried out in 1,1,2,2-tetrachloroethane (TTCE) or CH_2Cl_2 at 0 °C[7] and up to 78% ee for the opposite enantiomer was achieved. It should be noted that reactions in alcohols[8] were carried out in the air. To the best of our knowledge, these results represent the best enantioselective excess achieved for this reaction to date. These results are also among the best for the reversal of the enantioselectivity just by changing solvents.[6]

Interestingly, in halogenated solvents, it was found that triflate played an important role in the switch of enantioselectivity. As

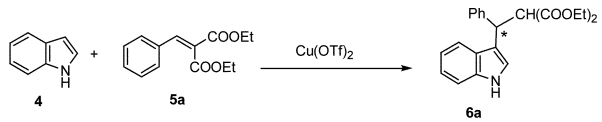


Scheme 1



Scheme 2

Table 1 Friedel–Crafts alkylation of **4** and **5a**[a]



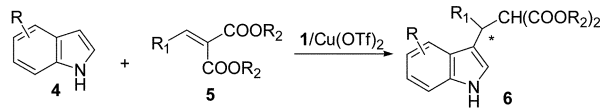
Entry	Solvent	Temp./ °C	Yield[c] (%)	ee[d] (%)	Ab[e]
1	Acetone–ether	15	80	6	*S*
2	Acetone–ether + ^{i}PrOH[b]	15	78	52	*S*
3	MeOH	15	90	60	*S*
4	EtOH	15	94	76	*S*
5	^{i}PrOH	15	99	79	*S*
6	^{i}BuOH	15	99	82	*S*
7	^{i}BuOH	−25	75	93	*S*
8	CH_2Cl_2	0	90	78	*R*

[a] Reactions in alcohols were carried out in the air, and reactions in other solvents were under N_2 using 10–11 mol% of ligand **1** and 10 mol% of Cu(OTf)$_2$. [b] Two equivalents relative to malonate **5a** added. [c] Isolated yield. [d] Determined by chiral HPLC. [e] Ab = absolute configuration.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b313197a/

DOI: 10.1039/b313197a

Table 2 Reactions of indoles **4** with various alkylidene malonates[7]



4a, R = H
4b, R = 5-Methyl
4c, R = 5-Methoxy

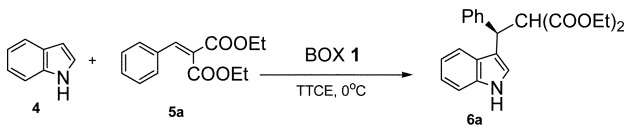
5a, R_1=Ph, R_2=Et; 5b, R_1=Ph, R_2=Me
5c, R_1=Ph, R_2=*i*-Bu; 5d, R_1=*p*-Br-C_6H_4, R_2=Et
5e, R_1=*o*-Cl-C_6H_4, R_2=Et
5f , R_1=*p*-NO_2-C_6H_4, R_2=Et

			Condition A[a,b]		Condition B[a,b]	
Entry	**4**	**5**	Yield[c] (%)	ee[d] (%)	Yield[c] (%)	ee[d] (%)
1	**4a**	**5a**	75	93 (+)	90	78 (−)[f]
2	**4a**	**5b**	80	92 (+)	70	63 (−)[g]
3	**4a**	**5c**	50	96 (+)	30	65 (−)[g]
4	**4a**	**5d**	68	92 (+)	65	78 (−)[f]
5	**4a**	**5e**	56	97 (+)	30	71 (−)[g]
6	**4a**	**5f**	94[e]	83 (+)	88	70 (−)[g]
7	**4b**	**5a**	70	91 (+)	62	75 (−)[g]
8	**4c**	**5a**	70	94 (+)	58	62 (−)[g]

[a] Condition A: under air atmosphere in isobutanol at −25 °C; Condition B: under N_2 atmosphere in anhydrous TTCE or CH_2Cl_2 at 0 °C. [b] Reactions were run using 11 mol% ligand **1** and 10 mol% $Cu(OTf)_2$. [c] Isolated yields. [d] Determined by chiral HPLC. [e] 0 °C. [f] In CH_2Cl_2. [g] In TTCE.

shown in Scheme 3, when **1**–$Cu(ClO_4)_2$·$6H_2O$ was used in TTCE, only 35% ee was obtained for the *R*-enantiomer. However, the addition of one equivalent of KOTf improved the ee to 74% (Scheme 3), the same ee as obtained by using $Cu(OTf)_2$.[9]

Recently, Evans *et al.* described a highly enantioselective Mukaiyama Michael reaction of alkylidene malonates and enolsilanes catalyzed by bis(oxazoline)–Cu(II) complexes.[10] In this paper, they reported that the coordination geometry of the copper center in the dimethyl benzylidene malonate–Cu(II)–Box complexes was ligand-dependent. The crystallographic characterization of Box–Cu(II) complex containing malonate showed that {Cu[(*S*,*S*)-*t*-Bu-Box](malonate)}$(SbF_6)_2$ was a complex with a distorted square-planar geometry at the copper center, while the less sterically demanding complex [Cu(*S*,*S*)-Ph-Box(malonate)]$(SbF_6)_2$ displayed a distorted octahedral geometry with each SbF_6^- counterion in a weak bonding interaction. Based on this mechanistic insight, we propose that the reversal of enantioselectivity just by changing reaction solvents, originates from the change of the coordination pattern of the copper center in different solvents.



$Cu(ClO_4)_2$ ·$6H_2O$ — 35% ee (R)
$Cu(ClO_4)_2$ ·$6H_2O$ + KOTf (1eq) — 74% ee (R)
$Cu(OTf)_2$ — 74% ee (R)

Scheme 3

A clear mechanistic understanding of the enantio-switch in different solvents awaits further investigation.

In conclusion, we have demonstrated that the cheap bisoxazoline **1**–$Cu(OTf)_2$ is an efficient catalyst in the asymmetric Friedel–Crafts reaction of indole with arylidene malonates. Noticeably, *either one of the enantiomers of the alkylation adducts could be prepared at will using the same catalytic system just by the subtle choice of solvents.* In addition, *using alcohols as solvents for Lewis acid catalyzed reaction is also noted.*[8] Further study to extend this catalytic system to other asymmetric reactions is now in progress in our laboratory.

We are grateful for financial support from the National Natural Sciences Foundation of China and the 'Talented Scientist Program', Chinese Academy of Sciences. This paper is dedicated to Professor Changtao Qian on the occasion of his 70th birthday.

Notes and references

1 H.-U. Blaser, *Chem. Commun.*, 2003, 293.
2 (*a*) J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, 2000, **33**, 325 and references cited therein (*b*) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain and J. Thorhauge, *Acc. Chem. Res.*, 1999, **32**, 605 and references cited therein (*c*) K. A. Jørgensen, *Synthesis*, 2003, 1117.
3 (*a*) J. Zhou and Y. Tang, *J. Am. Chem. Soc.*, 2002, **124**, 9030; (*b*) For the use of trisoxazoline **3** in the Kinugasa reaction, please see: M.-C. Ye, J. Zhou, Z.-Z. Huang and Y. Tang, *Chem. Commun.*, 2003, 2554.
4 The asymmetric indole alkylation with arylidene malonates was pioneered by Jørgensen *et al.* Please see: (*a*) W. Zhuang, T. Hansen and K. A. Jørgensen, *Chem. Commun.*, 2001, 347; (*b*) This reaction could also be regarded as a Michael addition. For a recent review on Michael addition, see: N. Krause and A. Hoffmann Röder, *Synthesis*, 2001, 171.
5 For chiral relay strategy in asymmetric catalysis, please see: (*a*) O. Corminboeuf, L. Quaranta, P. Renaud, M. Liu, C. P. Jasperse and M. P. Sibi, *Chem. Eur. J.*, 2003, **9**, 28; (*b*) For chiral relay by modification of substrates, please see: M. P. Sibi, L. Venkatraman, M. Liu and C. P. Jasperse, *J. Am. Chem. Soc.*, 2001, **123**, 8444; (*c*) M. P. Sibi and M. Liu, *Org. Lett.*, 2001, **3**, 4181; (*d*) L. Quaranta, O. Corminboeuf and P. Renaud, *Org. Lett.*, 2002, **4**, 39; (*e*) For chiral relay by modification of ligands, please see: A. V. Malkov, J. B. Hand and P. Kocovský, *Chem. Commun.*, 2003, 1948.
6 For the reversal of enantioselectivity just by changing solvents in catalysis, please see: (*a*) J. Thorhauge, M. Roberson, R. G. Hazell and K. A. Jørgensen, *Chem. Eur. J.*, 2002, **8**, 1888; (*b*) M. Johannsen and K. A. Jørgensen, *Tetrahedron*, 1996, **52**, 7321; (*c*) In a stoichiometric process: M. Kanai, K. Koga and K. Tomioka, *J. Chem. Soc., Chem. Commun.*, 1993, 1248; (*d*) For a recent review, please see: M. P. Sibi and M. Liu, *Curr. Org. Chem.*, 2001, **5**, 719; (*e*) G. Zanoni, F. Castronovo, M. Franzini, G. Vidari and E. Giannini, *Chem. Soc. Rev.*, 2003, **32**, 115.
7 For the detailed procedure, please see Supporting Information.
8 For the use of alcohols as solvents in chiral Lewis acid catalyzed reactions, please see: (*a*) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692; (*b*) K. R. Knudsen, S. Bachmann and K. A. Jørgensen, *Chem. Commun.*, 2003, 2602.
9 Triflate has been reported to coordinate to the copper center of bisoxazoline **2** derived copper complex, please see: D. A. Evans, S. J. Miller, T. Lectka and P. von Matt, *J. Am. Chem. Soc.*, 1999, **121**, 7559.
10 D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey and J. S. Tedrow, *J. Am. Chem. Soc.*, 2000, **122**, 9134.