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Controllable Enantioselective Friedel−Crafts Reaction[1] between Indoles and Alkylidene Malonates Catalyzed by Pseudo-C_3-Symmetric Trisoxazoline Copper(II) Complexes

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Pseudo-C_3-symmetric trisoxazoline copper(II) complexes prove to be excellent catalysts in the Friedel−Crafts alkylation of indoles with alkylidene malonates. The absolute stereochemistry of this reaction is shown to be dependent on the solvent. Reactions in isobutyl alcohol afford the Friedel−Crafts alkylation adducts in excellent yields and with up to +98% ee. In 1,1,2,2-tetrachloroethane (TTCE), however, the opposite enantiomers of the products are obtained in good yields with up to −89% ee. Water tolerance of chiral catalyst trisoxazoline **2a**/Cu(OTf)$_2$ is examined, and it is found that the addition of up to 200 equiv of water relative to catalyst in isobutyl alcohol has almost no effect on enantioselectivity but slows down the reaction. The reaction scope is studied as well. The roles of alcohol as the solvent to accelerate the reaction are discussed. The stereochemical models of asymmetric induction for reactions both in isobutyl alcohol and in TTCE are also developed.

Introduction

C_2-symmetric chiral bisoxazoline−metal complexes are widely used in asymmetric catalysis.[2] For example, bisoxazoline **1**-derived copper complexes have been established as versatile catalysts for a series of asymmetric reactions such as aziridination,[3] aldol,[4] cycloaddition,[5] carbonyl-ene,[5e,6] Michael,[7] cyclopropanation,[8] δ-lactone formation,[9] amination,[10] Friedel−Crafts,[11] Henry,[12] Mannich,[13] and allylic oxidation reactions.[14] Because of the wide applications of bisoxazolines, much effort has been devoted to the modification of bisoxazoline framework to create superior ligands by varying amino alcohols[15] or bridging substituents.[16] In sharp contrast to the great success of bisoxazolines, the development and applications of trisoxazolines are very limited.[17] In our efforts to develop superior catalysts which are cheap, easy to

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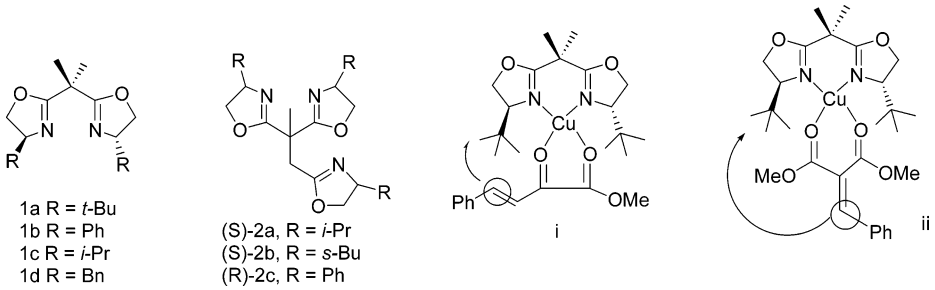
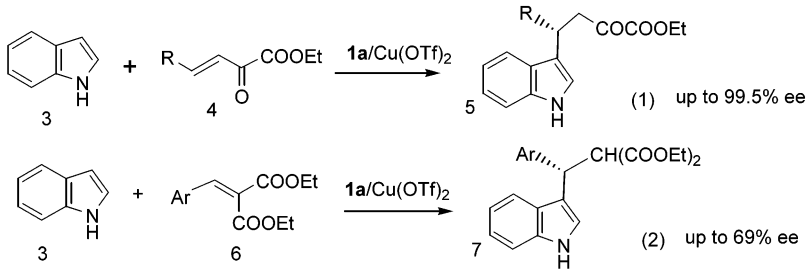
SCHEME 1



SCHEME 2



access, air-stable, and water-tolerant, we focused on pseudo-C_3-symmetric trisoxazoline **2** (Scheme 1), for the following reasons: (1) compared with C_2-symmetric bisoxazolines **1**, the coordination of three nitrogen atoms of trisoxazoline **2** to metallic center induces a more tunable pseudo-C_3-symmetric chiral space, to shield distant reactive sites and (2) tridentate ligand **2** is expected to increase the stability of active intermediates with respect to ordinary bidentate bisoxazolines[18] and the sidearmed oxazoline may be able to modulate the Lewis acidity of the metal center. Thus, the metal complex may be tolerable to moisture and hopefully improve the catalytic activity.

Friedel−Crafts reaction[1c,19] of indoles with electron-deficient olefins has received increasing attention owing to its potential application in the synthesis of molecules with indole framework, which has been widely identified as "privileged " structure or pharmacophore, with representation in over 3000 natural isolates and 40 medicinal agents of diverse therapeutic action.[20] Surprisingly, asymmetric versions of this reaction are less explored and very limited reports appeared in the literature. Recently, Jørgensen et al. pioneered asymmetric Friedel−Crafts alkylation of indoles with α,β-unsatuated ketoesters **4** (eq 1, Scheme 2)[11b] and alkylidene malonates **6** (eq 2)[11c] using ^{t}Bu-bisoxazoline **1a**/Cu(II) complexes as the chiral catalyst. Very recently, MacMillan realized a highly enantioselective organocatalytic indole alkylation[20a] using α,β-unsatuated aldehydes.

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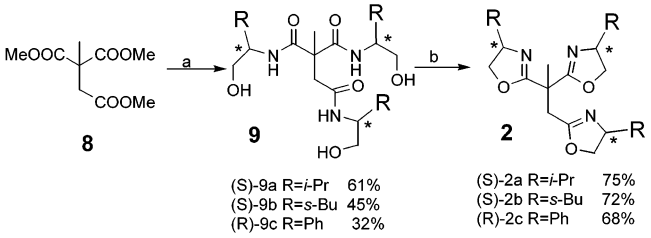
SCHEME 3[a]



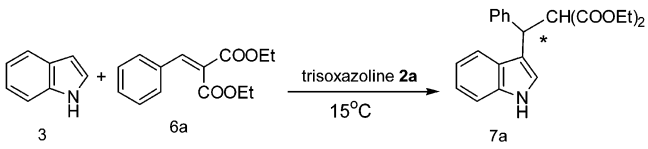
[a] Reagents and conditions: (a) amino alcohol, 70 °C/solvent free; (b) Ph_3P, CCl_4, Et_3N, CH_3CN, 25 °C.

Noticeably, under the catalysis of bisoxazoline **1a**/Cu(OTf)$_2$, as high as 99.5% ee was achieved in the addition of indole to ketoester **4**,[11b] however, only 50−69% ee was obtained[11c] when this reaction is extended to alkylidene malonate **6**[21] (Scheme 2). The difference was probably due to the fact that alkylidene malonate complexation would place the reacting center on the ligand C_2 axis and the prochiral center of the Cu(box)−alkylidene malonate complex would not reside near the ligand chirality (**ii**, Scheme 1), in comparison with the unsaturated α-ketoester−Cu(II) complex (**i**, Scheme 1).[2d] Very recently, we tried the asymmetric Friedel−Crafts reaction between indoles and alkylidene malonates using trisoxazoline **2a**-derived copper(II) as the catalyst, and high enantioselectivity was achieved.[22] In this article, we wish to report the modification of the reaction, the reversal of enantioselectivity by changing solvents, the reaction scope, and the mechanistic elucidation in detail.

Results and Discussion

Ligand Synthesis. Trisoxazolines **2a**−**c** could be easily synthesized from trimethyl 1,2,2-propanetricarboxylate **8**[23] and amino alcohol by two steps. Compound **8** reacted with amino alcohol without solvent at 70 °C to afford highly hydroscopic solid **9a**−**c** in 32−61% yields (Scheme 3).[17b] It should be noted that an excess of amino alcohol was necessary to maintain satisfactory yield in this step, since amino alcohol would gradually be eliminated from the reaction system due to its sublimation when heated at 70 °C in solvent-free conditions. Treatment of compounds **9a**−**c** with PPh_3/CCl_4[24] afforded the desired trisoxazolines **2a**−**c** as a colorless oil in 68−75% yields. Other methods such as using $SOCl_2$/NaOH,[25] TsCl/Et_3N,[26] or 1,2,4-triazole/$POCl_3$[17c] as the cyclization agents gave poor yields.

TABLE 1. Evaluation of Copper Salts in Different Solvents[a]



		Cu(ClO$_4$)$_2$·6H$_2$O			Cu(OTf)$_2$		
entry	solvent	time (h)	conv[b] (%)	ee (%)[c]	time (h)	conv[b] (%)	ee (%)[c]
1	THF	64	10	+82	64	5	+81
2	acetone	30	54	+77	30	44	+78
3	Et_2O	20	90	+29	20	84	+10
4	CH_2Cl_2	24	70	−3	24	60	−51
5	CH_2ClCH_2Cl	28	73	+5	28	32	−20

[a] Reactions were run at 15 °C, using 12 mol % of trisoxazoline **2a** and 10 mol % of copper salt under N_2 on a 0.25-mmol scale. [b] Conversion based on malonate **6a**. [c] Determined by chiral HPLC.

Preliminary Results. Since Cu(II) turned out to be an especially effective ion in both binding and activating substrates for a series of reactions,[2d] copper(II) salts were selected as the Lewis acids to start our study. As the perfect matching of ligand structure, copper salts, solvents, and additives was known to be crucial for achieving the maximum chiral discrimination,[27] Cu(OTf)$_2$ and Cu(ClO$_4$)$_2$·6H$_2$O[18b,28] were carefully evaluated in combination with several solvents at 15 °C (Table 1). The reaction between indole and benzylidene malonate proved to be highly solvent-dependent. No reaction took place in CH_3CN and dioxane. As shown in Table 1, in donor solvents such as THF and acetone, Cu(ClO$_4$)$_2$·6H$_2$O and Cu(OTf)$_2$ showed similar enantioselectivity but Cu(ClO$_4$)$_2$·6H$_2$O seemed to be more reactive than Cu(OTf)$_2$. In THF, reaction afforded the best enantioselectivity (82% ee), but only 10% conversion was observed even when the reaction time was prolonged to 64 h (entry 1). In acetone, 54% conversion was obtained with 77% ee after 30 h (entry 2). Reactions in ethyl ether gave higher conversion

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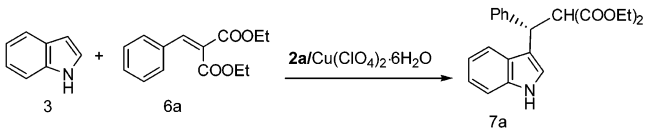
(28) For the use of metal perchlorate hydrates as Lewis acid in asymmetric catalysis, see: (a) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Org. Chem*, **1997**, *62*, 6454. (b) Ghosh, A. K.; Cho, H.; Cappiello, J. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3687. (c) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710. (d) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (e) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (f) Itoh, K.; Oderaotoshi, Y.; Kanemasa, S. *Tetrahedron*: *Asymmetry* **2003**, *14*, 635. (g) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240.

TABLE 2. Effect of Mixed Solvents and Additives[a]



entry	solvent	additive	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	acetone/THF 3:1		15	64	65	+79
2	acetone/^{n}Bu$_2$O 1:1		15	29	78	+74
3	acetone/ether 3:1		15	29	86	+81
4	acetone/ether 1:1		15	29	81	+82
5	acetone/ether 1:3		15	29	88	+82
6	acetone/ether 1:3		0	72	50	+85
7	acetone/ether 1:3	^{i}PrOH	0	20	86	+81
8	acetone/ether 1:3	HFIP	0	20	99	+85
9	acetone/ether 1:3	HFIP	−20	85	84	+89
10	acetone/ether 1:3	HFIP	−25	120	56	+93

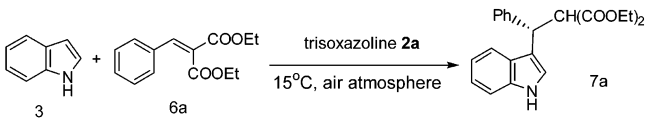
[a] Reactions were run under N_2, using 12 mol % of trisoxazoline **2a** and 10 mol % of $Cu(ClO_4)_2 \cdot 6H_2O$ on a 0.25-mmol scale. [b] Isolated yield. [c] Determined by chiral HPLC.

than that in acetone but low enantioselectivity (entry 3). Interestingly, in dichloromethane and 1,2-dichloroethane, the reversal of enantioselectivity was observed (entries 4 and 5). When this reaction was carried out in dichloromethane with $Cu(OTf)_2$ as Lewis acid, up to 51% ee for the opposite enantiomer was achieved. $Cu(SbF_6)_2$ was also examined in THF and acetone under the same conditions, but was found to be less effective (70% ee in THF and 59% ee in acetone, respectively). On the basis of these results, $Cu(ClO_4)_2 \cdot 6H_2O$ was initially selected as the favored copper salt in this reaction, owing to its higher reactivity, cheapness, and easy-handling.

Compared with bisoxazoline **1a**/$Cu(OTf)_2$,[11c] trisoxazoline **2a**-derived copper complexes showed obvious improvement in enantioselectivity. Considering the difference of reaction rate and enantioselectivity in different solvents, we examined the effect of mixed solvents using trisoxazoline **2a**/$Cu(ClO_4)_2 \cdot 6H_2O$ as the catalyst (Table 2). In comparison with that in pure acetone, almost no improvement in both reactivity and enantioselectivity was found in the mixed solvent of acetone and THF (3/1, v/v). The mixed solvent of acetone and dibutyl ether was also tested but found to be inferior in enantioselectivity (entry 2). Encouragingly, the mixed solvent of acetone and diethyl ether obviously increased the reactivity and slightly improved enantioselectivity. The ratio of acetone and diethyl ether also influenced both reactivity and enantioselectivity, and the mixed acetone and diethyl ether (1:3, v/v) proved to be the best solvent in the screened conditions (entries 3−5). Lowering reaction temperature to 0 °C improved the ee from 82% to 85% but the alkylation of indole **3** with malonate **6a** proceeded quite slowly. Only 50% yield was examined even when the reaction time was as long as 72 h (entry 6).

A number of publications documented the dramatic impact of alcoholic additives to improve the catalytic efficiency and/or enantioselectivity in some Lewis acid-catalyzed asymmetric reactions.[7b−f,29] Thus, we examined the effect of some alcoholic additives. It was found that the addition of 2 equiv of isopropyl alcohol could improve the reactivity, but slightly decreased the enantioselectivity (entry 7). Gratifyingly, the addition of 2 equiv of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) relative to malonate **6a** could greatly improve the reactivity without obvious loss of enantioselectivity (entry 8).

TABLE 3. Effect of Alcohols as Solvents on Enantioselectivity[a]



		$Cu(ClO_4)_2 \cdot 6H_2O$			$Cu(OTf)_2$		
entry	solvent	time (h)	yield[b] (%)	ee (%)[c]	time (h)	yield[b] (%)	ee (%)[c]
1	MeOH	5.0	88	+50	5.0	90	+48
2	EtOH	3.0	100	+82	3.0	90	+63
3	^{n}PrOH				4.0	90	+85
4	^{i}PrOH	2.0	100	+84	2.0	99	+88
5	^{n}BuOH				3.0	99	+90
6	^{i}BuOH	3.0	100	+87	3.0	99	+90
7	^{i}BuOH[d]	45	99	+89	45	99	+94
8	^{s}BuOH	3.0	99	+88	3.0	99	+91
9	^{n}pentanol	4.5	60	+87	4.5	69	+91
10	^{i}pentanol	7	45	+88	5.0	41	+91

[a] Reactions were carried out at 15 °C under air atmosphere, using 11−12 mol % of trisoxazoline **2a** and 10 mol % of copper salt, [Cu] = 0.005 M. [b] Isolated yield. [c] Determined by chiral HPLC. [d] −25 °C.

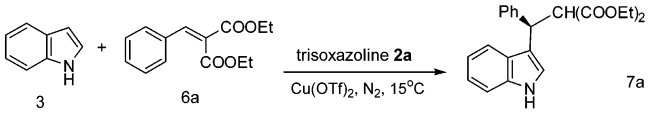
Lowering temperature to −20 °C increased the ee to 89% in 85% yield (entry 9). Although 93% ee was achieved when the temperature was further lowered to −25 °C, the conversion was unsatisfactory and only 56% yield was obtained even when the reaction time was as long as 120 h (entry 10).

Dramatic Solvent Effects (Reversal of Enantioselectivity by Solvents). In view of the above findings that the addition of 2 equiv of *i*-PrOH or HFIP could accelerate this reaction with chiral catalyst trisoxazoline **2a**/$Cu(ClO_4)_2 \cdot 6H_2O$, we tried isopropyl alcohol as the solvent in this reaction. Surprisingly, this reaction was accelerated dramatically and went for completion within just 2 h at 15 °C. Besides, the enantioselectivity also increased to 84%. This result encouraged us to optimize other alcohols as solvents with use of both trisoxazoline **2a**/$Cu(OTf)_2$ and **2a**/$Cu(ClO_4)_2 \cdot 6H_2O$ as the catalysts.

As described in Table 3, all the alcohols tested promoted this reaction in satisfactory rates, and the employment of alcohols as solvents could also improve the enantioselectivity in most cases (entries 3−10, Table 3). It should be noted that bulkier alcohols afforded better enantioselectivity (MeOH < EtOH < *n*-PrOH < *i*-PrOH < BuOH), suggesting the plausible coordination of alcohol to copper center of the active intermediate. When isobutyl alcohol was used as the solvent at 15 °C, the reaction was complete in 3 h with 90% ee. Lowering the temperature to −25 °C further improved the enantiomeric excess to 94% with full conversion. Interestingly, both $Cu(OTf)_2$ and $Cu(ClO_4)_2 \cdot 6H_2O$ have similar reactivity but $Cu(OTf)_2$

(29) For representative examples of catalytic processes that utilize alcohols as additives see: (a) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (c) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640. (d) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403. (e) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650. (f) Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1571.

TABLE 4. Solvent-Promoted Reversal of Enantioselectivity[a]



entry	solvent	additive[b]	time (h)	yield[c] (%)	ee[d] (%)
1	CCl_4	HFIP	18	77	−9
2	CH_2ClCH_2Cl	no	28	32	−20
3	$CFBr_2CFBr_2$	HFIP	3	92	−20
4	$CHCl_2CH_2Cl$	HFIP	20	48	−25
5	$PhCF_3$	HFIP	17	44	−25
6	toluene	HFIP	21	99	−26
7	$CHCl{=}CCl_2$	HFIP	18	74	−28
8	$CH_2ClCHClCH_2Cl$	HFIP	15	80	−33
9	$CHCl_3$	HFIP	27	75	−34
10	CH_3CCl_3	HFIP	20	45	−50
11	CH_2Cl_2	no	24	60	−51
12	TTCE	no	15	76	−65
13	TTCE	HFIP	15	71	−64

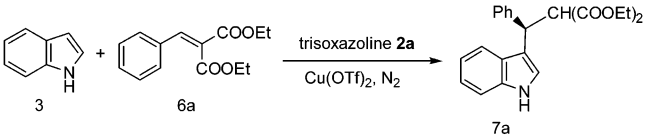
[a] Reactions carried out at 15 °C under N_2 atmosphere, using 12 mol % of ligand **2a** and 10 mol % of $Cu(OTf)_2$, [Cu] = 0.01 M. [b] Two equivalents of HFIP relative to malonate **6a**. [c] Isolated yield. [d] Determined by chiral HPLC.

gave better enantioselectivity in most cases (Table 3). Noticeably, trisoxazoline **2a**/Cu(II) is water- and air-stable and the reactions were carried out in commercial alcohols under air atmosphere. It is also noted that the use of alcohols as the solvents not only accelerates the reaction dramatically but also improves the enantioselectivity.[30]

In the screening process, it was found that the reaction in dichloromethane afforded product with opposite configuration with −51% ee. Considering that the strong coordinating solvents shown in Tables 1−3 afforded the product with *S*-configuration and the weak coordinating solvents gave the product with the opposite configuration (entries 4 and 5 in Table 1), it was postulated that the reversal of enantioselectivity resulted from the change of the coordination geometry of copper center in different solvents. To further understand the origin of this reversal and to find a convenient way to prepare both enantiomers of the alkylation adducts selectively, we studied the solvent effects in details using $Cu(OTf)_2$ as the Lewis acid because it proved to be superior to $Cu(ClO_4)_2{\cdot}6H_2O$ in reversing the enantioselectivity (entries 4, 5 in Table 1). Several halogenated solvents as well as toluene were examined, and the results were shown in Table 4. As expected, all of them gave *R*-enantiomer as the major product, despite the enantiomeric excess ranging from low to moderate. Encouragingly, 1,1,2,2-tetrachloroethane (TTCE) proved to be the best solvent for the synthesis of *R*-enantiomer in our screened conditions and up to 65% ee was observed. It was also found that the addition of 2 equiv of HFIP relative to malonate **6a** had almost no effect on both the reactivity and the enantioselectivity in this case.

(30) Selected for the use of alcohols as the solvents in the chiral Lewis acid-catalyzed reactions, please see: (a) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692. (b) Knudsen, K. R.; Bachmann, S.; Jørgensen, K. A. *Chem Commun*. **2003**, 2602.

TABLE 5. Effect of the Ratio of Ligand 2a and $Cu(OTf)_2$, Temperature, and Catalyst Loading[a]



entry	ligand/Cu	$Cu(OTf)_2$ (mol %)	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	1.2/1.0	10	15	15	76	−65
2	1.0/1.0	10	15	8.5	47	−65
3	1.0/1.25	10	15	8.5	51	−64
4	1.0/1.5	10	15	8.5	66	−74
5[d]	*1.0/1.5*	*10*	*15*	*1.5*	*99*	*+81*
6	1.0/2.0	10	15	8.5	25	−65
7	**1.0/1.5**	**10**	**0**	**22**	**86**	**−80**
8	1.0/1.5	20	0	19	77	−78
9	1.0/1.5	15	−10	40	63	−68

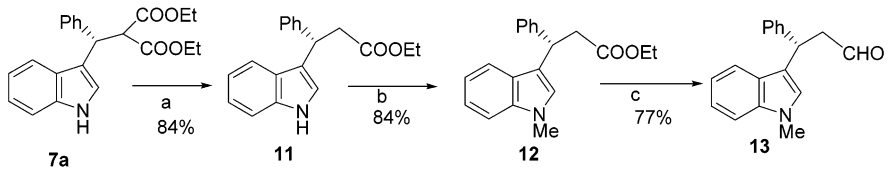
[a] Reactions were carried out in TTCE under N_2 atmosphere, [Cu] = 0.01 M. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Reaction was carried out in isobutyl alcohol under air atmosphere.

The solvent-promoted reversal of enantiofacial selectivity probably resulted from the change of catalytic species in different solvents. Taking into account that pseudo-trisoxazoline **2a** is a tridentate ligand, the aggregation state of the chiral catalyst may vary with the ratio of the ligand and copper salt. Thus, we next examined the effect of the ratio of ligand and $Cu(OTf)_2$ on the enantioselectivity using TTCE as the solvent. Indeed, it was found that the ratio of ligand and $Cu(OTf)_2$ strongly influenced the enantiomeric excess. As was demonstrated in Table 5, the enantioselectivities were almost the same in the presence of equivalent or an excess of ligand (entries 1 and 2). Interestingly, when the ratio of ligand and $Cu(OTf)_2$ was changed from 1.0 to 1.5 (entry 4), the enantioselectivity was obviously improved to −74%. Further increasing the ratio of $Cu(OTf)_2$ and ligand to 2.0 decreased the ee to −65% (entry 6). In contrast to the increase of enantiomeric excess in TTCE, the enantioselectivity decreased in isobutyl alcohol in the presense of an excess of copper salt (entry 5). The increase of catalyst loading from 10% to 20% could not improve enantioselectivity at all (entry 8). Lowering the temperature to 0 °C increased the enantiomeric excess up to −80% (entry 7). Further lowering the temperature to −10 °C led to a loss of enantioselectivity (entry 9).

A comparative study was also carried out through evaluating the effect of substituents on trisoxazolines both in isobutyl alcohol and in TTCE. As is shown in Table 6, trisoxazoline **2a** was not the unique structure in reversing the enantioselectivity. Under the same reaction conditions, both trisoxazoline **2b** and **2c** could also tune the selectivity although the effect was not as promising as that of trisoxazoline **2a** when changing isobutyl alcohol to TTCE (entries 3 and 4). Surpringly, isopropyl-pybox **10**/$Cu(OTf)_2$ complex did not promote this reaction in either isopropyl alcohol or TTCE (entry 5).

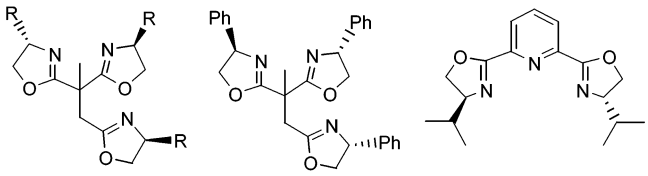
Therefore, *the* enantioselectivity could be reversed easily from the *S*-configuration (94% ee) to the *R*-configuration (−80% ee) with the same chiral ligand and Lewis acid just by changing reaction solvents. And thus, either one of the enantiomers could be obtained at will with high selectivity (>99% ee could be obtained after

SCHEME 4[a]



[a] Reagents and conditions: (a) wet DMSO, NaCl, 120 °C; (b) NaH, CH_3I/THF, 0 °C; (c) DIBAL-H, −100 to −90 °C.

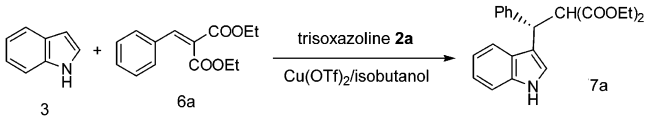
TABLE 6. Ligand Survey



		condition A[a]			condition B[b]		
entry	ligand	ligand/ Cu(II)	yield (%)[c]	ee (%)[d]	ligand/ Cu(II)	yield (%)[c]	ee (%)[d]
1	**2a**	1.1/1.0	99	+90	1.2/1.0	76	−65
2	**2a**	1.0/1.5	99	+81	1.0/1.5	86	−80
3	**2b**	1.1/1.0	99	+85	1.0/1.5	48	−30
4	**2c**	1.1/1.0	99	−73	1.0/1.5	44	+33
5	**10**	1.1/1.0			1.0/1.0		

[a] Condition A: reactions in isobutyl alcohol were carried out at 15 °C under air atmosphere, using 10 mol % of $Cu(OTf)_2$, [Cu] = 0.005 M. [b] Condition B: reactions in anhydrous TTCE were carried out at 0 °C under N_2 atmosphere, using 10 mol % of $Cu(OTf)_2$, [Cu] = 0.01 M. [c] Isolated yield. [d] Determined by chiral HPLC.

TABLE 7. Water Tolerance of Catalyst 2a/Cu(OTf)$_2$



entry	H_2O/cat. (mol/mol)	temp (°C)	time (h)	conv[a] (%)	ee[b] (%)
1[c]	no	−33	43	40	94
2[d]	no	−33	43	40	94
3	10	−33	43	27	94
4	20	−33	43	13	94
5	30	−33	43	13	94
6	50	−33	43	9	94
7	50	15	21	75	90
8	100	15	21	50	90
9	200	15	21	28	89
10	400	15	21	<15	nd
11[e]	no reaction				

[a] Conversion by ^{1}H NMR analysis. [b] Determined by chiral HPLC. [c] Anhydrous isobutyl alcohol used under N_2. [d] Commercial isobutyl alcohol used in air. [e] The mixed solvent of isobutyl alcohol/H_2O (9/1, v/v) was used.

recrystalization) in high yield. In literature,[31] there are only a few reports concerning the employment of the same ligand and the same metal salt to reverse enantioselectivity just by changing reaction conditions such as additives,[32] temperature,[33] and solvent.[4d,34] As for reversing enantioselectivity just by changing solvents to provide both enantiomers with high enantioselectivity, the most successful example to date is reported by Jørgensen et al., in which the ee value could be changed from −79% to +60% in the HDA reaction between ethyl glyoxylate and 1,3-cyclohexadiene in the presence of bisoxazoline **1b**/$Cu(OTf)_2$.[35] To the best of our knowledge, the result described above in the indole alkylation is one of the best results for the reversal of enantioselectivity just by changing solvents in Lewis acid-catalyzed reactions.

Determination of Absolute Configuration of 7a. To determine the absolute stereochemistry of **7a**, it was transformed to 3-(1-methyl-1*H*-indol-3-yl)-3-phenylpropanal **13** in 54% overall yield via the following three steps: (a) compound **7a** underwent facile decarboethoxylation by heating the malonate ester in wet DMSO at 120 °C in the presence of NaCl, to afford ester **11** in 84% yield;[36] (b) ester **11** was deprotonated with NaH in THF at 0 °C, followed by the treatment with MeI to afford compound **12** in 84% yield; and (c) reduction of ester **12** by DIBAL-H afforded the known aldehyde **13** in 77% yield. By comparison of the optical rotation of **13** with that of the known compound,[20a] product **7a** was obtained as the (*S*)-enantiomer when using isobutyl alcohol as the solvent, while as the (*R*)-enantiomer in TTCE.

Water Tolerance of Catalyst. Further studies showed that a trace amount of water in isobutyl alcohol did not influence the reactivity, since the reaction showed almost the same reactivity in commercial isobutyl alcohol under air atmosphere or in anhydrous isobutyl alcohol under N_2 (entries 1 and 2, Table 7). However, increasing the amounts of water to 400 equiv greatly impaired the activity of the catalyst and less than 15% conversion was observed by ^{1}H NMR analysis of the reaction mixture (entry 10). When the mixed solvent of isobutyl alcohol/H_2O (9/1, v/v) was used, reaction was completely inhibited

(31) (a) Sibi, M. P.; Liu, M. *Curr. Org. Chem.* **2001**, *5*, 719. (b) Zanoni, G.; Castronovo, F.; Franzini, M.; Vidari, G.; Giannini, E. *Chem. Soc. Rev.* **2003**, *32*, 115.

(32) For the reversal of stereochemistry by additives in catalysis, please see: (a) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (b) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *50*, 11623. (c) Desimoni, G.; Faita, G.; Righetti, P. P. *Tetrahedron Lett.* **1996**, *37*, 3027. (d) Desimoni, G.; Faita, G.; Invernizzi, A. G.; Righetti, P. *Tetrahedron* **1997**, *53*, 7671. (e) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483. (f) Carbone, P.; Desimoni, G.; Faita, G.; Filippone, S.; Righetti, P. *Tetrahedron* **1998**, *54*, 6099. (g) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3213. (h) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. P. *Tetrahedron Lett.* **1999**, *40*, 2001. (i) Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. *J. Am. Chem. Soc.* **2002**, *124*, 2888.

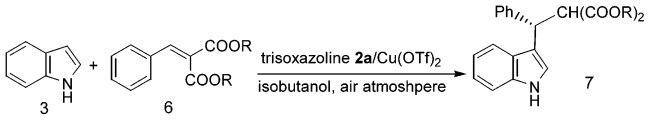
(33) For the reversal of stereochemistry by temperature in catalysis, please see: (a) Sibi, M. P.; Gorikunti, U.; Liu, M. *Tetrahedron* **2002**, *58*, 8357. (b) Otera, J.; Sakamoto, K.; Tsukamoto, T.; Orita, A. *Tetrahedron Lett.* **1998**, *39*, 3201.

(34) For the reversal of stereochemistry by solvents in catalysis, please see: (a) Johannsen, M.; Jørgensen, K. A. *Tetrahedron* **1996**, *52*, 7321. In a stoichiometric process: (b) Kanai, M.; Koga, K.; Tomioka, K. *J. Chem. Soc., Chem. Commun.* **1993**, 1248.

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

(36) Krapcho, A. P. *Synthesis* **1982**, 805.

TABLE 8. Effect of Ester Group[a]



entry	product (R)	15 °C conv[b]/ ee[c] (%)	0 °C conv[b]/ ee[c] (%)	−25 °C conv[b]/ ee[c] (%)
1	**7b**, R = Me	99/87	99/89	93/91
2	**7a**, R = Et	99/90	99/92	99/94
3	**7c**, R = ^{i}Bu	99/93	99/95	90/98
4	**7d**, R = ^{i}Pr	80/83	20/89	26/91

[a] Reactions were carried out under air atmosphere, using 11−12 mol % of trisoxazoline **2a** and 10 mol % of $Cu(OTf)_2$, [Cu] = 0.005 M. [b] Conversion based on malonate **6**. [c] Determined by chiral HPLC.

(entry 11). The reason was probably that water molecules occupy the coordination sites of the catalyst so that it prevented the activation of malonate since we noticed that the solution of complex trisoxazoline **2a**/$Cu(OTf)_2$ in anhydrous isobutyl alcohol was clearly green but turned blue as soon as water was added. Noticeably, with the addition of water, only a little deterioration of the enantioselectivity was observed although the erosion of catalytic activity was observed (entries 2−8, Table 7).

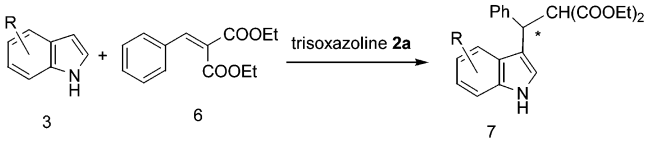
Effect of Ester Group. Based on the fact that the ee value is dependent on the size of the alcohol, we envisaged that the size of the ester group of the alkylidene malonate might also influence the enantioselectivity. Thus, a number of benzylidene malonates with different ester groups were tested. When these substrates were subjected to the catalyzed reaction at 15, 0, and −25 °C, indole adducts of methyl, ethyl, and isobutyl ester were formed in quantitative conversion (entries 1−3 in Table 8). The enantioselectivity improved with increasing ester size: methyl < ethyl < isobutyl. At any of the temperatures examined, the bulky isobutyl ester provided the best enantioselectivity, and the smallest methyl ester gave the lowest selectivity. These results suggested that the ester gearing hypothesis[7e] might be effective in our reaction system. It was also concluded that lowering the temperature benefited the enantioselectivity whatever the ester used.

Obscurely, compared with other esters examined, isopropyl ester was less reactive and enantioselective (entry 4, Table 8). When reaction was carried out at 15 °C, for example, all other esters went to full conversion within 4 h, but only 80% conversion was achieved for isopropyl ester even when the reaction time was prolonged to 8 h (entry 4).

Reaction Scope. To study the generality of this reaction, a variety of indoles with different structures were examined under optimized conditions. As shown in Table 9, it is noteworthy that substituents on the indole ring strongly influenced the enantiofacial selectivity with trisoxazoline **2a**/$Cu(OTf)_2$ as the catalyst. When the reaction was carried out in isobutyl alcohol, 4- or 5-substituted indoles gave excellent enantioselectivities (4-methoxy = 98% ee, 5-methoxy = 94% ee, 5-methyl = 95% ee, entries 2, 3, and 4). High enantioselectivity was also achieved for 7-methylindole (+89% ee, entry 5).

When reaction was carried out in TTCE, the reversal of enantioselectivity was observed for all the substituted

TABLE 9. Effect of Substituent on Indole Structure



entry	product (R)	condition A[a] yield[d]/ ee[e] (%)	condition B[b] yield[d]/ ee[e] (%)	condition C[c] yield[d]/ ee[e] (%)
1	**7e** (2-methyl)	99/−**73**	99/−**53**	90/+**60**
2	**7f** (4-methoxy)	97(100[f])/+**91**	90(100)/+**98**	90(14)[f]/−**61**
3	**7g** (5-methoxy)	92/+**93**	79/+**94**	67/−**60**
4	**7h** (5-methyl)	73/+**91**	89/+**95**	75/−**73**
5	**7i** (7-methyl)	95/+**74**	82/+**89**	90/−**56**

[a] Condition A: reactions were run in acetone−ether (1:3 v/v) at −20 °C, using 11−12 mol % of ligand **2a** and 10 mol % of $Cu(ClO_4)_2 \cdot 6H_2O$. [b] Condition B: reactions were carried out in isobutyl alcohol at −25 °C under air atmosphere, using 11−12 mol % of ligand **2a** and 10 mol % of $Cu(OTf)_2$, [Cu] = 0.005 M. [c] Condition C: reactions were carried out in TTCE at 0 °C under N_2 atmosphere, using 6.7 mol % of ligand **2a** and 10 mol % of $Cu(OTf)_2$, [Cu] = 0.01 M. [d] Isolated yield. [e] Determined by chiral HPLC. [f] Number in parentheses referred to conversion.

indoles. It was found that substituents on the indole ring generally had a negative effect on the enantioselectivity in TTCE. For example, although the reversal of enantioselectivity was found in the case of 2- and 7-methylindole, the enantioselectivities were moderate (entries 1 and 5). 5-Methylindole provided good enantioselectivity for the *R*-enantiomer and 73% ee was observed (entry 4). When 5-methoxyindole was used, alkylation adduct was obtained with only 60% ee, inferior to that of 5-methylindole (entry 3 vs entry 4). The methoxy substituent on the 4-position of indole greatly impaired the reactivity in TTCE, and moderate enantioselectivity was given (condition C, entry 2). The detailed reason is unclear.

Arylidene malonates with different structures were also examined and the results are tabulated in Table 10. In sharp contrast to the results with trisoxazoline **2a**/$Cu(ClO_4)_2 \cdot 6H_2O$ in the mixed solvent of acetone and ether (1/3, v/v) (condition A), in which electron-withdrawing substituents on the benzene ring of benzenylide malonates obviously accelerated the reaction and had almost no effects on enantioselectivity,[22] the corresponding substituents had strong effects on both the yields and enantioselectivities when isobutyl alcohol was used as the solvent. Electron-withdrawing substituents slowed the reaction in isobutyl alcohol while accelerating the reaction in TTCE (entries 4−7). In isobutyl alcohol, when reaction time was prolonged to 75 h in the case of trisoxazoline **2a**/$Cu(OTf)_2$, both 4-bromo- and 2-chlorobenzylidene malonates afforded the desired products in 100% yield with 93% and 97% ee, respectively. The strong electron-withdrawing substituent nitro group strongly decreased the reaction rate. For instance, *m*-nitrobenzylidene malonate only gave low conversion (less than 20%) in isobutyl alcohol at −25 °C even when the reaction was carried out for as long as 60 h. Raising the reaction temperature to 0 °C, both *m*-nitro- and *p*-nitrobenzylidene malonates worked well in isobutyl alcohol (entries 5 and 6), and 83% and 91% ee were obtained, respectively. In TTCE, however, the reaction of arylidene malonates with an electron-withdrawing group on benzene ring was obviously accelerated and

SCHEME 5

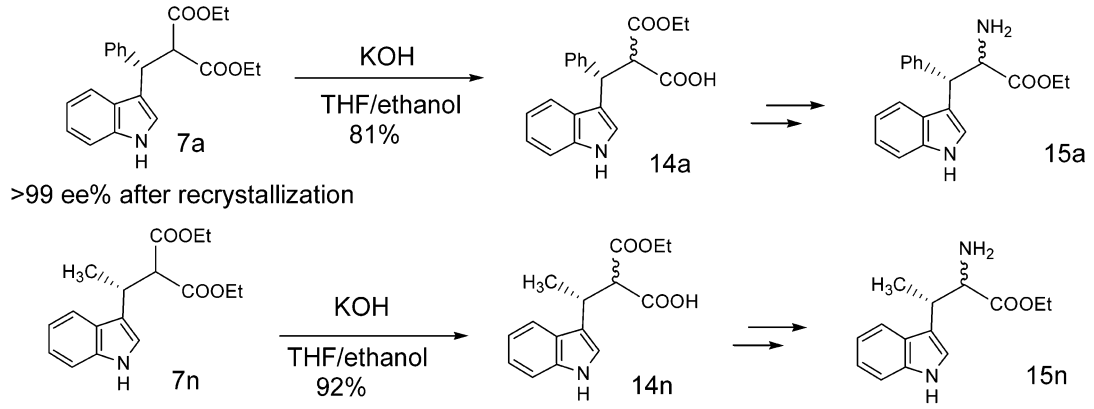
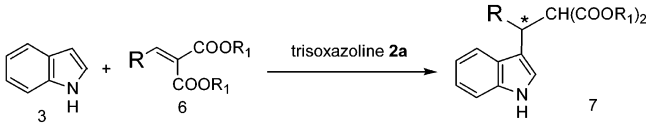


TABLE 10. Enantioselective Frediel−Crafts Reaction of Indole with Alkylidene Malonates



a R = Ph, R_1= Et
b R = Ph, R_1= Me
c R = Ph, R_1= ^{i}Bu
j R = *o*-Cl-C_6H_4, R_1 = Et
k R = *m*-NO_2-C_6H_4, R_1= Et
l R = *p*-NO_2-C_6H_4, R_1= Et
m R = *p*-Br-C_6H_4, R_1= Et
n R = CH_3, R_1= Et

entry	product	condition A[a] yield[d]/ee[e] (%)	condition B[b] time (h)/yield[d]/ee[e] (%)	condition C[c] yield[d]/ee[e] (%)
1	**7a**	84/+**89**	45/99/+**94**	86/−**80**
2	**7b**	98/+**88**	45/93/+**91**	83/−**65**
3	**7c**	35/+**86**	60/99/+**97**	73/−**75**
4	**7j**	99/+**92**	75/93/+**97**	99/−**85**
5	**7k**	99/+**91**	18/99/+**83**[f]	99/−**89**
6	**7l**	99/+**91**	19/99/+**91**[f]	99/−**81**
7	**7m**	95/+**90**	75/85/+**93**	93/−**71**
8	**7n**	78/+**85**[g]	20/90/+**12**[h]	60/−**25**[h]

[a] Condition A: reactions were run in acetone-ether (1:3 v/v) at −20 °C, using 11−12 mol % of ligand **2a** and 10 mol % of $Cu(ClO_4)_2 \cdot 6H_2O$. [b] Condition B: reactions were carried out in isobutyl alcohol at −25 °C under air atmosphere, using 11−12 mol % of ligand **2a** and 10 mol % of $Cu(OTf)_2$, [Cu] = 0.005 M. [c] Condition C: reactions were carried out in TTCE at 0 °C under N_2 atmosphere, using 6.7 mol % of ligand **2a** and 10 mol % of $Cu(OTf)_2$, [Cu] = 0.01 M. [d] Isolated yield. [e] Determined by chiral HPLC. [f] 0 °C. [g] −78 °C. [h] −35 °C.

better enantiomeric excess was achieved (entries 4−6). In isobutyl alcohol, compared with in the mixed solvent of acetone and ether (1:3, v/v), their reactions gave comparable or higher ee values, except for *m*-nitrobenzylidene malonate (entry 5).

The alkylation of indoles with arylidene malonates proceeded smoothly with high and tunable enantioselectivity. Reactions between indole and ethylidene malonate also worked well (entry 8). Up to 85% ee was obtained when using trisoxazoline **2a**/$Cu(ClO_4)_2 \cdot 6H_2O$ as the chiral catalyst in the mixed solvent of acetone and ether (1:3, v/v) at −78 °C. Unfortunately, although the reversal of enantioselectivity was observed in TTCE, the enantioselectivity was low (25% ee).

Product Elaboration. A synthetically useful aspect of the present reaction is that the Friedel−Crafts alkylation adducts can be easily transformed to the corresponding β-substituted tryptophans, one of the useful tools in medical chemistry.[37] For example, treating alkylation adducts **7a** and **7n** with KOH in the mixed solvent of THF and ethanol (1:1, v/v) afforded hemiacid esters **14a** and **14n** in high yields. Compounds**14a** and **14n** can be readily transformed to the corresponding β-substituted tryptophans **15a** and **15n** by using the documented procedures (Scheme 5).[38,39] One of the advantages of this process is that both enantiomers of the alkylation adduct **7a** can be obtained in mild conditions with high enantioselectivity (both above 99% ee after recrystalization) from the same catalyst trisoxazoline **2a**/$Cu(OTf)_2$ complex just by changing the solvent from isobutyl alcohol to TTCE.

Reaction Mechanism. The proposed catalytic cycle in alcohol for the trisoxazoline **2a**/$Cu(OTf)_2$-catalyzed reaction between indole and benzylidene malonate is outlined in Scheme 6. Chelation of benzylidene malonate to the Cu(II) center produces the activated substrate−catalyst complex, which undergoes nucleophilic addition to provide the Cu(II)-alkylation adduct. Subsequent H-transfer, followed by decomplexation affords the product and concomitantly regenerates the catalyst **2a**/$Cu(OTf)_2$.

First, to determine if the rate acceleration in alcohol resulted from the fact that alcohol promoted the dissociation of product and regeneration of catalyst, a certain amount of product was added to the reaction system during malonate activation (before indole was added to the reaction system) in both conditions when using isobutyl alcohol (entries 2 and 3, Table 11) and acetone as the solvents (entries 5 and 6), respectively.[40] As shown in Table 11, similar conversions in isobutyl alcohol after 2 h at 15 °C were examined: 76% conversion for the reaction without the addition of product additive and 78% conversion for reactions with 1 or 2 equiv of product additive. In acetone after 20 h at 15 °C, 43% conversion was detected in the absence of product additive, 45%

(37) For reviews, see: Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585.

(38) (a) Jeannin, L.; Nagy, T.; Vassileva, E.; Sapi, J.; Laronze, J.-Y. *Tetrahedron Lett*. **1995**, *36*, 2057. (b) Nemes, C.; Jeannin, L.; Sapi, J.; Laronze, M.; Seghir, H.; Augé, F.; Laronze, J.-Y. *Tetrahedron* **2000**, *56*, 5479 and references therein.

(39) For literature methods to prepare β-substituted tryptophans, please see: (a) Xiong, C.; Wang, W.; Cai, C.; Hruby, V. J. *J. Org. Chem*, **2002**, *67*, 1399. (b) Bruncko, M.; Crich, D. *Tetrahedron Lett*. **1992**, *33*, 6251. (c) Boteju, L. W.; Wegner, K.; Qian, X.; Hruby, V. J. *Tetrahedron* **1994**, *50*, 2391. (d) Bruncko, M.; Crich, D. *J. Org. Chem*. **1994**, *59*, 4239. (e) Han, G.; Lewis, A.; Hruby, V. J. *Tetrahedron Lett*. **2001**, *42*, 4601. (f) Nagy, T.; Jeannin, L.; Sapi, J.; Laronze, J.-Y.; Renard, P.; Pfeiffer, B.; Bizot-Espiard, J.-G. *Eur. J. Med. Chem*. **1995**, *30*, 575.

SCHEME 6

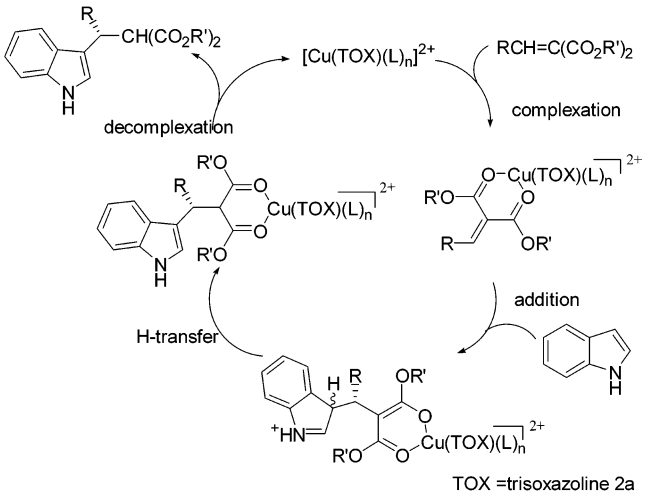
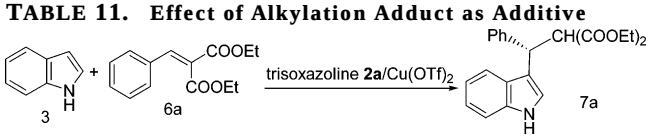


TABLE 11. Effect of Alkylation Adduct as Additive



entry	solvent	additive[a]	conversion[b] (%)
1	isobutyl alcohol	0	76
2	isobutyl alcohol	1	78
3	isobutyl alcohol	2	78
4	acetone	0	43
5	acetone	1	45
6	acetone	2	46

[a] Equivalent relative to malonate. [b] By ^{1}H NMR analysis.

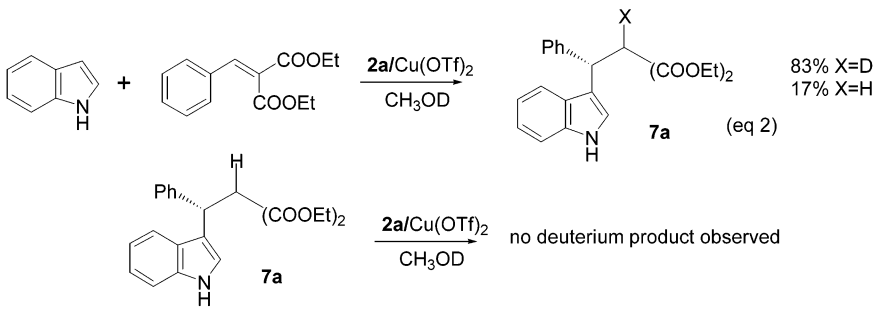
conversion was detected for the reaction with 1 equiv of product additive, and 46% conversion was detected for that with 2 equiv of product additive. Obviously, in either isobutyl alcohol or acetone, the addition of product did not slow the reaction, suggesting that the role of alcohol to accelerate reaction did not take place in the product decomplexation step when using trisoxazoline **2a**/Cu(OTf)$_2$ as the chiral catalyst.

Reactions were also performed with stoichiometric catalyst **2a**/Cu(OTf)$_2$ both in isobutyl alcohol and in acetone, respectively,[4d] and the conversion was determined by ^{1}H NMR analysis. A 73% conversion was obtained after 1.5 h of reaction in isobutyl alcohol at 15 °C. But in acetone, only 24% conversion was determined even when the reaction time was prolonged to 6 h. Chiral HPLC analysis of the products gave 90% ee in isobutyl alcohol and 76% ee in acetone, respectively, which were similar values to those observed under substoichiometric (10 mol %) condition, demonstrating that the fidelity of this catalyst system appeared to be high. The finding that the reaction employing stoichiometric amounts of trisoxazoline **2a**/Cu(OTf)$_2$ was much faster in isobutyl alcohol than in acetone further demonstrated that the role of isobutyl alcohol as the solvent to accelerate reaction had little to do with product decomplextion, and suggested that the first two steps of the catalytic cycle (i.e., complexation and additon) might proceed more rapidly in isobutyl alcohol.

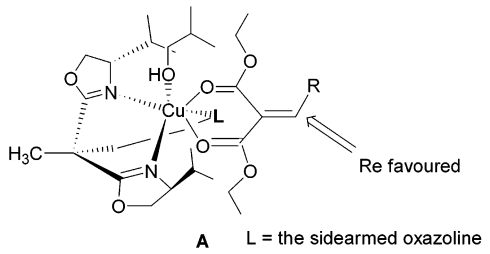
To understand if alcohol is related to the H-transfer step, we examined the reaction in CH_3OD. It was found that about 83% of the α-D product was isolated (Scheme 7). To determine if the α-D product originated from the exchange of the corresponding α-H compound **7a** with CH_3OD, a control experiment was carried out as follows: the α-H product was treated with trisoxazoline **2a**/Cu(OTf)$_2$ in CH_3OD at the same conditions but no α-D product was detected. This result demonstrated that alcohol, as the solvent, was involved in the H-transfer reaction in this catalytic reaction, which is probably one of the reasons that alcohol can accelerate this reaction.

Stereochemical Models. To understand the stereochemical model of this reaction and the structure of the catalyst, we first tried to develop the single crystal of the trisoxazoline **2a**/Cu(II) complex in several solvents but failed, since only buttery substance was obtained on concentration. NMR studies are also prevented by the paramagnetic nature of Cu(II). Evans reported that the crystal structure of {Cu[(*S*,*S*)-*t*-Bu-box](malonate)}-(SbF$_6$)$_2$ was a complex with a distorted square-planar geometry with the full dissociation of the SbF$_6$ counterion from the copper center, while the crystal structure of less steric demanding complex [Cu(*S*,*S*)-Ph-box(malonate)]-(SbF$_6$)$_2$ displayed a distorted octahedral geometry at the copper center with each SbF$_6$ counterion in a weak bonding interaction.[7e] Considering that the isopropyl group is probably less structurally flexible than the phenyl group, it was reasonable for the complex of trisoxazoline **2a**/Cu-malonate to assume a distorted octahedral geometry at the copper center, with two other coordinating groups in the structure of the trisoxazoline **2a**/Cu-malonate complex. As was mentioned above, the enantioselectivity improved greatly with the increase of alcohol size in the case of **2a**/Cu(OTf)$_2$ (Table 3), suggesting that alcohol might coordinate to the copper center and the alcohols influenced by the conformation of the ester substituents thereby relayed the influence of the chiral ligand closer to the reaction center. Thus, a

SCHEME 7

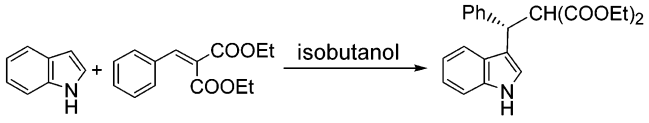


SCHEME 8



A L = the sidearmed oxazoline

SCHEME 9

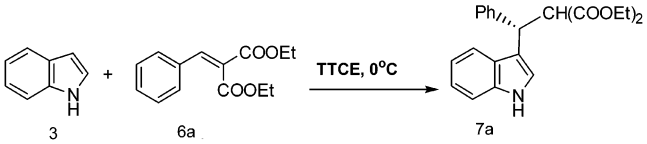


Catalyst	ee (%)	yield (%)
2a/Cu(OTf)$_2$ (1.1/1.0, mol/mol)	90	99
2a/Cu(OTf)$_2$ (1.0/1.5, mol/mol)	81	99
1c/Cu(OTf)$_2$ (1.1/1.0, mol/mol)	83	99

possible working model for the steorochemical course of trisoxazoline **2a**/Cu(II) in isobutyl alcohol was proposed in Scheme 8. In this model, the *si*-face of the chelating malonates was obstructed by the isopropyl substituent on the ligand, permitting nucleophilic attack favored only from the *re*-face to afford *S*-enantiomers. This working model was also supported by the following experimental observations (Scheme 9): (a) the alkylation of indole **3** with malonate **6a** afforded the desired product in 99% yield with 90% ee in isobutyl alcohol at 15 °C when the ratio of ligand and Cu(OTf)$_2$ was 1/1.0 and (b) changing the ratio of ligand and Cu(OTf)$_2$ from 1.1/1.0 to 1.0/1.5, the enantiomeric excess of the same reaction under the same conditions decreased from 90% to 81%, which was almost the same as the enantioselectivity (83%) obtained by the use of isopropyl bisoxazoline **1c**/Cu(OTf)$_2$ with a ratio of 1.1/1.0 (mol/mol) under the same reaction conditions (Scheme 9).[11f]

The reversal of enantioselectivity just by changing reaction solvents, we believed, originated from the change of both the aggregation state of the chiral catalyst and preorganization of the chiral catalyst−substrate in different solvents, which alter the coordination fashion of the copper center. In the Mukaiyama Michael addition of alkylidene malonates and enolsilanes, Evans reported the crystal structure of {Cu[(*S*,*S*)-*t*-Bu-box](malonate)}-(SbF$_6$)$_2$ in which malonate binds to catalyst in a distorted square-planar geometry. Following up this model, we could explain the enantiofacial selectivity obtained by chiral catalyst **1c**/Cu(OTf)$_2$ complex in this reaction, but we were unable to explain the effect of triflate on the enantioselectivity when using TTCE as the solvent (Table 12) and the enantiofacial selectivity obtained by chiral catalyst **1a**/Cu(II) complex in this reaction.[11c] The departure from this binding motif necessitated us to develop a new model to explain the observed product stereochemistry. In the bisoxazoline **1a**/Cu(II)-catalyzed asymmetric Dields−Alder reaction, Evans et al. proposed that triflate anion might coordinate to the copper center throughout

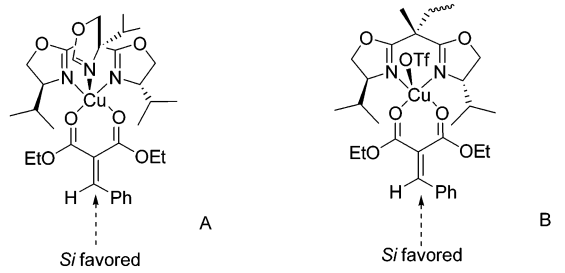
TABLE 12. Effect of KOTf as Additive[a]



entry	ligand	copper salt	ligand/Cu	KOTf/Cu(OTf)$_2$	time (h)	yield[b] (%)	ee[c] (%)
1	**2a**	Cu(ClO$_4$)$_2$·6H$_2$O	1.0/1.5	0	22	64	−35
2	**2a**	Cu(ClO$_4$)$_2$·6H$_2$O	1.0/1.5	1	22	80	−40
3	**2a**	Cu(ClO$_4$)$_2$·6H$_2$O	1.0/1.5	5	22	76	−74
4	**2a**	Cu(OTf)$_2$	1.0/1.5	0	22	86	−80
5	**1c**	Cu(ClO$_4$)$_2$·6H$_2$O	1.0/1.0	0	22	85	−55
6	**1c**	Cu(ClO$_4$)$_2$·6H$_2$O	1.0/1.0	1	22	82	−70
7	**1c**	Cu(OTf)$_2$	1.0/1.0	0	22	89	−71
8	**1c**	Cu(BF$_4$)$_2$[d]	1.0/1.0	0	22	88	−43
9	**1c**	Cu(BF$_4$)$_2$[d]	1.0/1.0	1	22	82	−70

[a] Reactions were carried out under N$_2$ atmosphere, using 10 mol % of chiral catalyst (based on the copper ion) at 0 °C in TTCE, [Cu] = 0.01 M. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Anhydrous complex prepared from CuBr$_2$ and AgBF$_4$.

SCHEME 10



the catalytic cycle, and they also obtained the crystal of [Cu((*S*,*S*)-*t*-Bu-box)(H$_2$O)$_2$](OTf)$_2$, which revealed a distorted square-pyramidal geometry, with one triflate counterion weakly bound to the metal center.[5c] Very recently, Jørgensen et al. developed a square-pyramidal geometry working model in several bisoxazoline **1**/Cu-(II)-catalyzed asymmetric reactions.[10b,12b,41] We noticed that the anions of the copper salts strongly influenced the enantioselectivity of this reaction in TTCE (Table 12), and the experimental fact that higher ee was achieved when the ratio of ligand with Cu(OTf)$_2$ was changed from 1.2/1.0 to 1.0/1.5. Combining all the evidence described above, a five-coordinated model, with a distorted square-pyramidal geometry at the copper center, was proposed in Scheme 10 to account for the stereochemical induction in TTCE and the effect of triflate on the enantioselectivity when reaction was carried out in TTCE.

When the ratio of trisoxazoline **2a** and Cu(OTf)$_2$ was 1.2/1.0, both trisoxazoline and malonate bound to the copper center in a distorted square-pyramidal geometry, and the attack to the *si*-face of malonate was favored (**A**, Scheme 10). When the ratio of trisoxazoline **2a** and Cu-(OTf)$_2$ was 1.0/1.5, the pendant oxazoline might coordinate to the excess Cu(II). Thus, trisoxazoline in a bidentate fashion, together with the triflate and malonate coordinated to the copper center, also in a square-pyramidal geometry (**B**, Scheme 10). The difference of enantioselectivity between **A** and **B** is probably due to

(40) It should be noted that product with 90% ee was added to isobutyl alcohol solution while product with 77% ee was added to acetone solution, since reaction afforded product with 90% ee in isobutyl alcohol but 77% ee in acetone at 15 °C.

(41) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992.

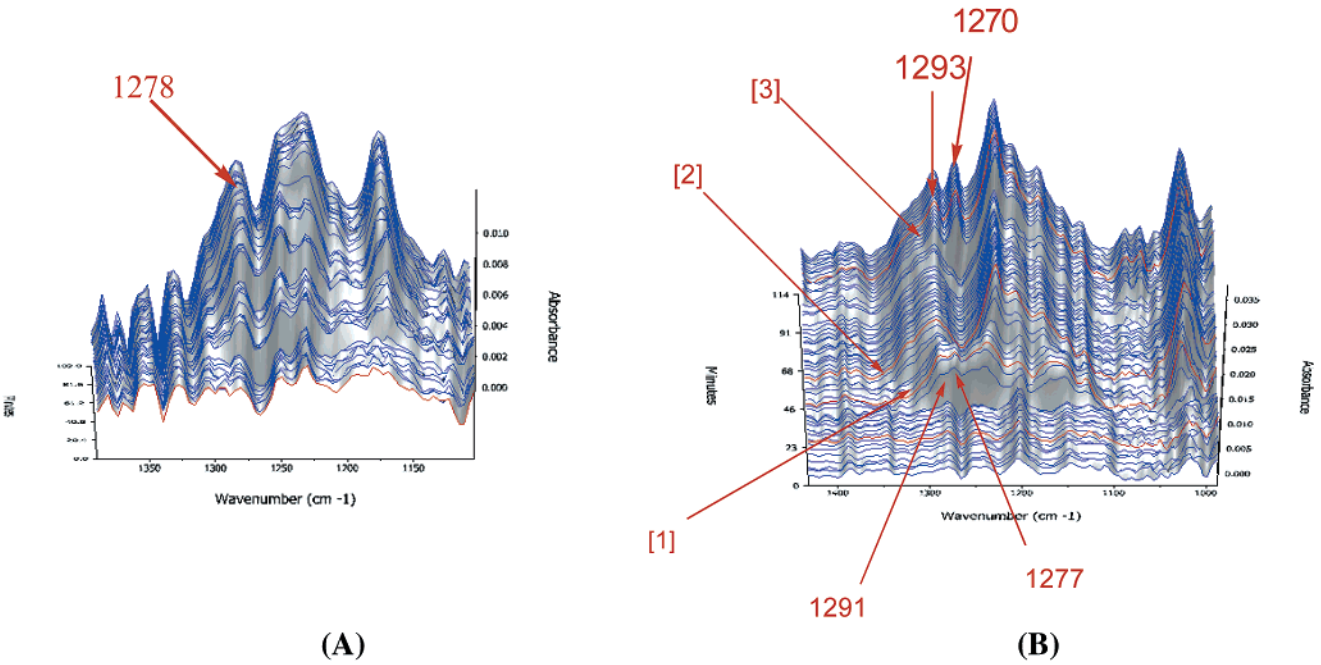


FIGURE 1. Results of in situ IR spectroscopy monitoring: (A) trisoxazoline **2a**/$Cu(OTf)_2$ in isobutyl alcohol; (B) bisoxazoline **1c**/$Cu(OTf)_2$ and malonate **6b** in TTCE. Conditions: [1] 0.5 equiv of $Cu(OTf)_2$ was added; [2] 1.0 equiv of $Cu(OTf)_2$ was added; [3] 1.0 equiv of malonate **6b** was added.

the fact that triflate tuned the chiral space better than the sidearmed oxazoline of trisoxazoline **2a**.

Results shown in Table 12 further supported the possible coordination of triflate anion to the copper center. In the case of trisoxazoline **2a**/$Cu(ClO_4)_2 \cdot 6H_2O$, only 35% ee was observed when the ratio of ligand **2a** and $Cu(ClO_4)_2 \cdot 6H_2O$ is 1.0/1.5 (entry 1, Table 12). It was found that the addition of 1 equiv of potassium triflate[42] relative to copper(II) slightly improved the enantioselectivity (entry 2). Noticably, the addtition of 5 equiv of potassium triflate greatly improved the enantioselectivity, which was almost similar to that obtained by trisoxazoline **2a**/$Cu(OTf)_2$ under the same conditions. Similar results were observed when bisoxazoline **1c** was used. In the case of bisoxazoline **1c**/$Cu(ClO_4)_2 \cdot 6H_2O$, 55% ee was achieved (entry 5), but the addition of 1 equiv of potassium triflate improved the enantioselectivity to 70% (entry 6), comparable to that obtained when bisoxazoline **1c**/$Cu(OTf)_2$ was used (entry 7). Bisoxazoline **1c**/$Cu(BF_4)_2$ promoted this reaction in 43% ee (entry 8), but the addition of 1 equiv of potassium triflate could also improve the enantioselectivity to 70% (entry 9). Since triflate anion is generally regarded as a stronger coordinating anion than BF_4^- and ClO_4^-,[43] these data strongly supported our working model shown in Scheme 10.

To obtain more information about the stereochemical model, in situ infrared spectroscopy was employed to analyze the possible triflate association with the catalyst−substrate complex through observation of the vibrational frequencies of bound and unbound triflate ions. Generally, the band near 1280 cm^{-1} for ionic $CF_3SO_3^-$ is shifted to higher wavenumber, appearing near 1380 cm^{-1} for monodentate-bound trifluoromethanesulfonate.[43a,5c] In isobutyl alcohol, $Cu(OTf)_2$ (1 equiv) was added to a solution of trisoxazoline **2a** (1 equiv) in five equal aliquots, and only the frequency at 1278 cm^{-1} was observed[44] even without the addition of benzylidene malonate, which suggested that triflate counterions are fully dissociated in isobutyl alcohol (A, Figure 1).

In TTCE, we tried to study if the three nitrogen atoms in trisoxazoline **2a** were all coordinated to the copper center with the IR spectrum but no conclusion was obtained. To simplify the inspection, bisoxazoline **1c** was chosen instead of trisoxazoline **2a** for our study. Frequencies at both 1277 and 1291 cm^{-1} were observed when 0.5 equiv of $Cu(OTf)_2$ was added to the solution of **1c** (1.0 equiv) in TTCE.

Obviously, the peak at 1277 cm^{-1} disappeared and only the frequency at 1293 cm^{-1} was observed when 1.0 equiv of $Cu(OTf)_2$ was added (B, Figure 1). Although a sharp peak at 1293 cm^{-1} was still observed after the addition of 1 equiv of malonate **6b**, we could not draw any conclusion of the triflate anion coordinating to copper center in this case, due to the disturbance of the vibrational frequency of the C−O bond (1270 cm^{-1}).[45]

Conclusions

Novel trisoxazolines **2a**−**c** were synthesized. By using the trisoxazoline **2a**/Cu(II) complex, highly enantioselective Friedel−Crafts alkylation of indoles with alkylidene malonates is developed. The absolute stereochemistry of

(42) Both bisoxazoline **1c**/KOTf and trisoxazoline **2a**/KOTf were unable to catalyze this reaction. In a recent report, KOTf was found to catalyze aza Diels−Alder reactions of Danishefsky's diene with imines in water smoothly, please see: Loncaric, C.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 574.

(43) (a) Lawrance, G. A. *Chem. Rev.* **1986**, *86*, 17. (b) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed.* **1995**, *34*, 798.

(44) For simplicity, the absorption changes which could be attributed to CF_3 and SO_3 vibrational modes are not discussed.

(45) For more information, please see the Supporting Information.

this reaction is shown to be dependent on the solvents. Thus, either one of both enantiomers of the alkylation adducts could be prepared at will with good to high selectivity, using the same trisoxazoline **2a**/$Cu(OTf)_2$ catalytic system, just by the subtle choice of solvents. In addition, using alcohols as solvents for the Lewis acid-catalyzed reaction is also noted.[30] The mild reaction conditions including water- and air-tolerance, cheap and easy synthesis of trisoxazoline−Cu (II) complexes, the synthetically useful product, and in particular the high and tunable enantioselectivity make our method potentially useful. Further study to extend this catalytic system to other asymmetric reaction is now in progress in our laboratory.

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Supporting Information Available: Characterization data for all compounds and experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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