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Highly Enantioselective Friedel–Crafts Reaction of Indole with Alkylidenemalonates Catalyzed by Heteroarylidene Malonate-Derived Bis(oxazoline) Copper(II) Complexes

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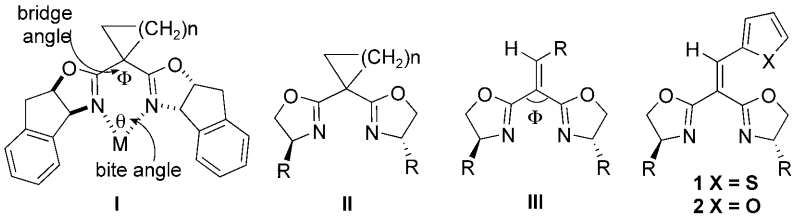
Abstract: A series of cheap and easily accessible heteroarylidenemalonate-derived bis(oxazoline) ligands **1** and **2** were synthesized and their copper(II) complexes were applied to the catalytic Friedel–Crafts reaction between indoles and diethyl alkylidenemalonates, Excellent asymmetric enantioselectivities were afforded for the *S*-enantiomer (up to >99% *ee*) in isobutyl alcohol, and the *R*-enantiomer (up to 96.5% *ee*) in dichloromethane.

Keywords: asymmetric catalysis; bis(oxazolines); Friedel–Crafts reaction; heteroarylidenemalonates; indoles

The Friedel–Crafts reaction is one of the most powerful carbon-carbon bond-forming reactions in synthetic organic chemistry.[1] During the past decade the catalytic asymmetric Friedel–Crafts alkylation reaction of indole derivatives with a variety of conjugated α,β-unsaturated carbonyl compounds has been extensively developed,[2] owing to the importance of indolea as building blocks in a variety of interesting natural products and potential medicinal agents.[3] Among the publications, the Friedel–Crafts alkylation between indole and alkylidenemalonate has intrigued some chemists' interest. In 2001, Jørgensen et al. reported the first example of this reaction. The addition proceeded smoothly under the catalysis of *t*-Bu-BOX-Cu(II) catalyst with excellent yields and moderate enantioselectivities (up to 69% *ee*).[4] Subsequently, Tang et al. explored the pseudo-C_3-symmetrical tris-(oxazoline)-Cu(II) complex to catalyze the the same reaction. The desired adducts were obtained in excellent yields with up to 93% *ee* in isobutyl alcohol, while in 1,1,2,2-tetrachloroethane the opposite enantiomer of the product was formed with up to 89% *ee*.[5] The enantioselectivity of the model reaction of indole with diethyl benzylidenemalonate was further improved to >99% *ee* by Reiser et al. by using aza-BOX-Cu(II) complexes. The fine control of the ratio of chiral ligand to copper proved to be a critical factor.[6] Recently, Feng et al. reported Friedel–Crafts alkylation of different indole derivatives with alkylidenemalonates using the chiral *N*′,*N*′-dioxide-scandium(III) complexes as catalyst.[7] Despite these impressive contributions, the highly efficient chiral catalyst for this type of reaction is still limited. The development of cheap, easily accessible and highly effecient chiral ligands is still one great challenge in asymmetric catalysis. Herein we would like to document a series of heteroarylidenemalonate-derived bis(oxazoline) ligands **1** and **2** and their Cu(II) complexes in the highly enantioselective Friedel–Crafts alkylation of indole with alkylidenemalonates.

For bis(oxazoline) (BOX) ligands derived from malonate and its analogues, the bridge angle Φ, correlating with the bite angle Θ of the BOX-metal complex, is regarded as an important structural factor influencing the enantioselectivity (Scheme 1). 1n 1996, Davis reported the copper(II) complex of BOX ligand **I** containing different spirorings catalyzed Diels–Alder reactions.[8] A conclusive trend has been obtained: the larger the value of Φ (hence the ligand bite angle Θ), the higher the observed enantioselectivity. As the spiroring size decreased, the bridge angle Φ correspondingly increased, then the highest *ee* value (96%) was afforded by the copper complex of BOX ligand **I** bearing a cyclopropyl group at the bridge carbon. On the contrary, in 2000 Denmark et al. reported the tuning of the chelation bridge angle Φ in bis(oxazoline) ligands **II** (Scheme 1)

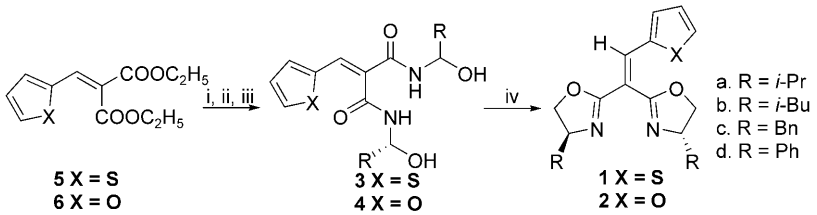


Scheme 1. Rational design of new bis(oxazolines) **1** and **2**.

through variation of the spiroring size,[9] the worst enantioselectivity was afforded for the BOX ligand bearing a cyclopropyl group in the asymmetric addition of methyllithium to imines. How is the better enantioselective correlated with the larger or smaller bridge angle in the catalytic asymmetric reaction? Much more experimental proof will be needed. Triggered by the above-described work, a straight strategy to tune the bridge angle was introduced as illustrated in the type of BOX ligand **III**, in which two oxazoline rings are attached to an sp^2 hybridized carbon and then generally provide a larger bridge angle than those with sp^3 hybridized bridge carbon. So far very few reports involving this type of BOX ligand have appeared in the literature.[10] For convenience, through further rationally modification we designed the heteroarylidenemalonate-derived bis(oxazoline) ligands **1** and **2** in which an approximately 120° bridge angle would be formed between the two oxazoline ring.

The requisite chiral bis(oxazoline) **1** and **2** were conveniently synthesized from commercially available material diethyl 2-thienyldicarboxylate **5** and 2-furyldicarboxylate **6** in 4 steps sequence as illustrated in Scheme 2.[11] Hydrolysis of diethyl dicarboxylates **5** and **6** by the solution of NaOH in a mixture of water and ethanol gave the corresponding dicarboxylic acid, which reacted with oxalyl chloride in the presence of DMF to afford the diacyl chloride. The diacyl chloride condensed with chiral β-amino alcohols in the presence of Et_3N to give the corresponding chiral intermediate dihydroxy diamides **3** and **4** in 74–88% yields, which were treated with methanesulfonyl chloride and excess Et_3N in dichloromethane to afford heteroarylidenemalonate-derived bis(oxazoline) ligands **1** and **2** in good yields (70–78%).

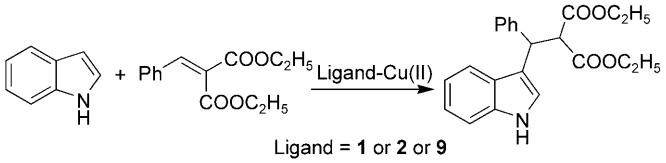
With the new ligands **1a–d** and **2a–d** in hand, we first optimized the ligand structure for the model asymmetric Friedel–Crafts alkylation of indole with diethyl benzylidenemalonate as summarized in Table 1. The reaction proceeded well in isobutyl alcohol. Full conversion and excellent yields (95–99%) can be achieved within 12 h under the catalysis of 10 mol% ligand-$Cu(OTf)_2$ complexes for all ligands tested. However, the enantiomeric excesses of the indole adducts were significantly affected by the ligand structure. Ligand **1a** and **2a** with an isopropyl group on the oxazoline ring gave 98.3% and 97.5% *ee*, respectively (entries 1 and 5). Such a phenomenon was basically in agreement with reports on Tang's tris(oxazoline) and Reiser's aza-BOX that the Cu(II) complexes of oxazoline with an isopropyl substituent usually result in the highest *ee* values.[5,6] Surprisingly, under the same conditions **1c** and **2c** with a benzyl group on the oxazoline ring also afforded excellent *ee* values (98.7 and 99.3%, entries 3 and 7). To the best of our knowledge, this is the first report to find that the Cu(II) complex of an oxazoline ligand bearing a benzyl substituent gives such excellent results in this type of reaction. On the contrary, **1b** and **2b** with an isobutyl group on the oxazoline ring gave almost racemic products (3.0 and 5.5% *ee* respectively, entries 2 and 6). For ligands **1d** and **2d**, 73.0% and 11.0% *ee* were obtained (entries 4 and 8). The enantioselectivity can be enhanced to >99.0% when the temperature was lowered to 0 °C (entries 9 and 10). As comparison the known ligand benzylidene-BOX **9** was synthesized and tested in the same reaction.[10] Although a high

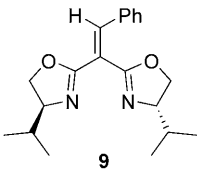


Reaction conditions: i) NaOH, C_2H_5OH; ii) $(COCl)_2$, DMF; iii) amino alcohol, Et_3N, 74 – 88% yield in 3 steps; iv) CH_3SO_2Cl, Et_3N, 70 – 78% yield.

Scheme 2. Synthesis of new chiral bis(oxazoline) ligands.

Table 1. Effect of ligands in $Cu(OTf)_2$-catalyzed Friedel–Crafts alkylation reaction.[a]





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Entry	Ligands	Temp. [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	15	99	98.3
2	**1b**	15	99	3.0
3	**1c**	15	96	98.7
4	**1d**	15	96	73.0
5	**2a**	15	98	97.5
6	**2b**	15	96	5.5
7	**2c**	15	97	99.3
8	**2d**	15	96	11.0
9	**1a**	0	99	99.3
10	**2a**	0	98	99.0
11	**9**	15	95	65.0

[a] Reactions in isobutyl alcohol were carried out under N_2 for 12 h using 11 mol% of ligand **1** and 10 mol% of $Cu(OTf)_2$.
[b] Isolated yield.
[c] Determined by chiral HPLC.

yield was obtained, the *ee* was only moderate (65.0%, entry 11).

Encouraged by preliminary results, other reaction conditions such as Cu(II) salts and solvents were further optimized for the four selected ligands (**1a**, **2a**, **1c**, **2c**), as summarized in Table 2. Initially, the Friedel–Crafts alkylation was conducted at 15 °C in isobutyl alcohol using $Cu(ClO_4)_4{\cdot}6H_2O$ as Lewis acid. High yields and enantioselectivities were obtained for ligands **1a** and **2a** (98.5% and 97.7% *ee*, entries 1 and 2), while inferior *ee* values were obtained for **1c** and **2c** under the same conditions (entries 3 and 4). Subsequently, the effect of solvents was tested using the **1a**-$Cu(OTf)_2$ complex as catalyst. In acetone-ether (1:1, v/v) or 1,2-dichloroethane (DCE), only moderate yields and very low *ee* values were obtained after 12 h (entries 5 and 6). In 1,1,2,2-tetrachloroethane (TTCE), the reaction worked well with up to 98% yield, while the *ee* value was only −16% (entry 7). Dichloromethane (DCM) was the best solvent for achieving the opposite enantiomer, whereby high yields and *ee* values were achieved (−96.5% *ee*, entry 8). This phenomenon was also found in the same and other reactions.[12,5b,c] To the best of our knowledge,

Table 2. Further optimization of ligands, Cu(II) salts, and solvents.[a]

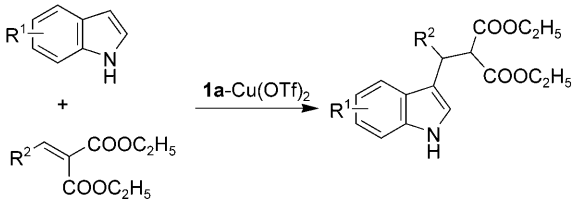
Entry	Ligand	Cu(II) salt	Solvent	Yield [%][b]	*ee* [%][c]
1	**1a**	$Cu(ClO_4)_2{\cdot}6H_2O$	*i*-BuOH	99	98.5
2	**2a**	$Cu(ClO_4)_2{\cdot}6H_2O$	*i*-BuOH	99	97.7
3	**1c**	$Cu(ClO_4)_2{\cdot}6H_2O$	*i*-BuOH	97	25.0
4	**2c**	$Cu(ClO_4)_2{\cdot}6H_2O$	*i*-BuOH	98	53.0
5	**1a**	$Cu(OTf)_2$	acetone/ether	40	23.0
6	**1a**	$Cu(OTf)_2$	DCE	54	−14.7
7	**1a**	$Cu(OTf)_2$	TTCE	99	−16.0
8	**1a**	$Cu(OTf)_2$	DCM	99	−96.5
9	**1a**	$Cu(OTf)_2$	MeOH	95	83.0
10	**1a**	$Cu(OTf)_2$	EtOH	98	98.0
11	**1c**	$Cu(OTf)_2$	DCM	97	−5.0
12	**1a**	$Cu(ClO_4)_2{\cdot}6H_2O$	DCM	98	−29.5
13	**2a**	$Cu(ClO_4)_2{\cdot}6H_2O$	DCM	96	−33.0
14	**2a**	$Cu(OTf)_2$	DCM	99	−48.2
15	**2c**	$Cu(OTf)_2$	DCM	99	−66.1

[a] Reactions were run with 10 mol% chiral catalyst at 15 °C for 12 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.

this is the best case for inversion of enantioselectivity in this type of reaction just through changing the solvent. Methanol and ethanol as solvent also gave good results (83% and 98% *ee*, respectively, entries 9 and 10). Finally, the copper(II) complexes of **1a, 2a, 1c** and **2c** as catalysts were further investigated using dichloromethane as solvent. Although high reactivity was observed, the *ee* values decreased drastically. Only the **2a-** and **2c**-$Cu(OTf)_2$ complexes furnished moderate *ee* (−48.2 and −66.1%, respectively, entries 14 and 15).

From the above experimental results, **1a** is the most effective ligand which exhibited more broad generality. Excellent results can be achieved with different Cu(II) salts [$Cu(OTf)_2$ and $Cu(ClO_4)_2{\cdot}6H_2O$] in different solvents (isobutyl alcohol and DCM). However, $Cu(OTf)_2$ seems to be the superior copper source. The scope of the **1a**-$Cu(OTf)_2$ complex in the Friedel–Crafts alkylation was tested using a variety of structurally different indole derivatives and arylidenemalonates (Table 3). In most cases the reaction worked well to afford the desired products in good to excellent yields. When a Cl atom is located at the *ortho*-position of the phenyl group, the reaction became very sluggishly so that a prolonged reaction time was essential for obtaining good yield (entry 4). Enantiomeric excesses ranging from 97.5–99.5% were obtained for various arylidenemalonates (entries 1–5), except for diethyl ethylidenemalonate (33.7% *ee*, entry 6). The diethyl benzylidene-substituted malonate reacted with 5-methoxyindole, 5-methyindole, 5-

Table 3. **1a**-$Cu(OTf)_2$-catalyzed Friedel–Crafts reaction of indole derivatives with alkylidenemalonates.[a]



Entry	R^1	R^2	Time	Yield [%][b]	*ee* [%][c]
1	H	4-MeO-C_6H_4	12	99	97.5
2	H	4-Me-C_6H_4	12	99	98.3
3	H	3-Br-C_6H_4	12	96	98.6
4	H	2-Cl-C_6H_4	72	70	99.5
5	H	2-thienyl	12	98	99.3
6	H	Me	12	95	33.7
7	5-MeO	Ph	12	99	99.3
8	5-Me	Ph	12	98	97.3
9	5-Cl	Ph	12	99	95.2
10	6-Cl	ph	12	98	97.9

[a] Reactions were run in isobutyl alcohol under N_2 with 10 mol% chiral catalyst at 0 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC

chloroindole and 6-chloroindole to afford the adducts in excellent yields and *ee* values (95.2–99.3% *ee*, entries 7–10), indicating that the substituents on indole ring had little effect on the enantioselectivity.

Regarding the reaction mechanism, according to several catalytic processes of BOX-Cu(II) complex already disclosed,[13] and considering the change trend in the catalytic results and dramatic solvent effect are all consistent with Tang's report, the two catalytic systems may have similar mechanism. In Tang's system, the three oxazoline rings coordinate simultaneously to the Cu(II) center in dichloromethane, while one oxazoline ring is replaced by one molecule of alcohol when isobutyl alcohol is used as solvent. In our system, the thiophene or furan moiety directs away from the two oxazoline rings and the copper(II) center, however, the heterocycle moiety may participate in intermolecular coordination in solution as a weak ligand, the direct evidence was observed for the crucial role of the heterocycles on the high enantioselectivity in comparison to inferior result obtained by Burke's benzylidene-bis(oxazoline) ligand **9** in the same reaction.[10] However, the role of the different electronic and steric natures of heterocycles and phenyl group cannot be excluded at this stage. The inversion of the absolute configutation is mainly dependent on the change of solvent, In the catalytic process, the counterion OTf^- or ClO_4^- can coordinate with Cu(II) as a weak bonding interaction, however, the better enantioselectivity obtained by $Cu(OTf)_2$-BOX than $Cu(ClO_4)\cdot 6H_2O$-BOX is probably due to the fact that the triflate anion can tune the chiral space better than ClO_4^-. Further investigations of the mechanism are underway in our laboratory.

In conclusion, we demonstrated that the simple hetetoarylidenemalonate-derived bis(oxazoline) Cu(II) complexes with a larger bridge angle than the 2,2-dialkylmalonate-derived ligands have exciting asymmetric catalytic properties in the Friedel–Crafts alkylation of indoles with arylidenemalonates. In isobutyl alcohol, the $Cu(OTf)_2$ complexes of ligands **1a**, **2a**, **1c** and **2c** gave the same high enantioselectivity (97.5–99.3% *ee*), while the complexes of $Cu(ClO_4)_2\cdot 6H_2O$ with ligands **1a**, **2a** were also very efficient (>97% *ee*). Very interestingly, when complex **1a**-$Cu(OTf)_2$ was used, changing the solvent from isobutyl alcohol to dichloromethane resulted in the inversion of the product's absolute configuration with up to 96.5% *ee*. In the same reaction for structurally different indoles and diethyl arylidenemalonates, our new chiral catalysts **1a**-$Cu(OTf)_2$ gave higher enantioselectivity than the previously reported methods in most cases,[4,5,6,7] which indicated the good potential for wide application. All the catalytic reactions proceeded well under mild condition (0–15 °C). Our results on the tuning of the bridge angle for the malonate-derived bis(oxazoline) ligand may shed light on the design of novel and efficient chiral catalystic systems. Further investigations on the catalytic asymmetric Friedel–Crafts reactions of other substances and other asymmetric reactions using our heteroarylidenemalonate-derived bis(oxazoline) system are in progress in our group.

Experimental Section

Representative Example for Asymmetric F-C Alkylation Reaction of Indoles with Alkylidenemalonates

To a Schlenk tube $Cu(OTf)_2$ (0.025 mmol) was added, followed by ligand **1a** (0.0275 mmol) in the solvent isobutyl alcohol (1.0 mL) under N_2, the solution was stirred for 1.5 h at room temperature, a mixture of diethyl benzylidenemalonate (0.25 mmol) in the above solvent (1.0 mL) was added. The resulting mixture was kept stirring for 15 min, cooled to 0 °C and stirred for another 15 min before the indole (0.25 mmol) was added. After stirring for 12 h at 0 °C, the solution was concentrated under reduced pressure, The crude product was purified by flash column chromatography on silica gel [eluted with ethyl acetate/petroleum ether (1/5, v/v)] to afford the (*S*)-ethyl 2-ethoxycarbonyl3-(3-indolyl)-3-phenylpropanoate as a white solid in near quantitative yield (99%); mp 179–180 °C; $[\alpha]_D^{25}$: +45.6 (10 mg/2 mL CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$–1.03 (m, 6H), 3.93–4.04 (m, 4H), 4.28 (d, $J = 11.7$ Hz, 1H), 5.07 (d, $J = 11.7$ Hz, 1H), 7.00–7.07 (m, 1H), 7.09–7.37 (m, 8H), 7.55 (d, $J = 8.0$ Hz, 1H), 8.04 (brs, 1H); HPLC analysis (Chiralcel OD-H, *n*-hexane/2-PrOH, 88:12, 0.8 mL min^{-1}, 254 nm): t_r (minor) = 10.03 min, t_r (major) = 12.03 min; 99.3% *ee*.

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