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Catalytic Enantioselective Friedel−Crafts/Michael Addition Reactions of Indoles to Ethenetricarboxylates

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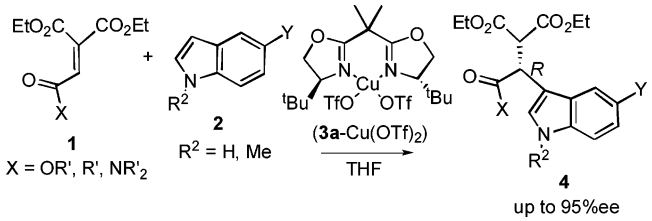

The Friedel−Crafts reaction is an important reaction for the formation of new C−C bonds. Recently, catalytic enantioselective Friedel−Crafts reaction of alkylidene malonates has been reported. However, the substituents in alkylidene malonates are limited. To explore new substituents such as carboxyl and carbonyl groups, catalytic enantioselective Friedel−Crafts reactions of reactive ethenetricarboxylates and acyl-substituted methylenemalonates **1** were investigated. The reaction of **1** with indoles in the presence of catalytic amounts of chiral bisoxazoline copper(II) complex (10%) in THF at room temperature gave alkylated products in high yields and up to 95% ee. The enantioselectivity can be explained by the secondary orbital interaction on approach of indole to the less hindered side of the **1**−Cu(II)−ligand complex.

Introduction

The Friedel−Crafts reaction is an important reaction for the formation of new C−C bonds,[1] and catalytic enantioselective versions have been developed.[2] Recently, catalytic enantioselective Friedel−Crafts reactions of various α,β-unsaturated carbonyl compounds have been studied[3] and have been shown to proceed with high enantioselectivity. Among α,β-unsaturated carbonyl compounds, catalytic enantioselective reaction of alkylidene malonates and indoles using bisoxazoline or trisoxazoline copper(II) complexes has also been reported.[4] Although enantioselectivity of C_2-symmetric bisoxazoline−Cu(II)-catalyzed Mukaiyama−Michael reaction of alkylidene malonates and enolsilanes was discussed in view of the Cu(II)−ligand complex X-ray structure,[5] the origin of the enantioselectivity in Friedel−Crafts/Michael addition reactions of indoles to alkylidene malonates is not yet clearly understood. In the earlier studies, the substituents in alkylidene malonates were also limited to aryl or Me groups.[4]

We have shown recently that ethenetricarboxylate derivatives work as highly electrophilic C═C components in Lewis acid-promoted reactions.[6] Examination of new reactivity and utility of ethenetricarboxylates is of interest. To explore new substituents such as carboxyl and carbonyl groups in catalytic

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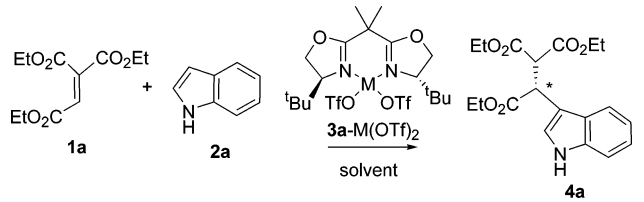
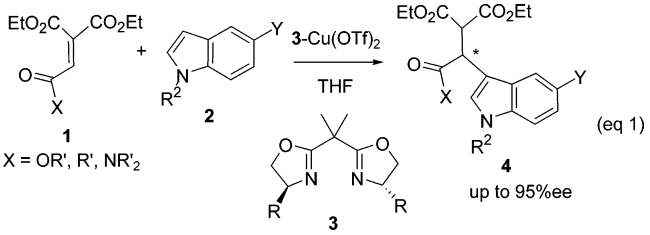
TABLE 1. Reaction of 1a and 2a



entry	metal	solvent	temp	yield (%)	ee (%)[a]	$[\alpha]_D$ (deg)[c]
1	Cu	THF	rt	96	68	−99
2	Cu	THF	−20 °C	74	83	−117
3	Cu	CH_2Cl_2	rt	89	45	−59
4	Cu	^{i}PrOH	rt	87	68	−96
5	Zn	THF	rt	83	15[b]	+23

[a] Determined by chiral HPLC. [b] Opposite enantiomer. [c] In $CHCl_3$ solution.

enantioselective Friedel−Crafts reaction of methylene malonates for further transformations and structural diversity and to obtain some insight to the mechanism, reaction of ethenetricarboxylates and acyl-substituted methylenemalonates **1** was investigated. Herein, we report the results of the reaction of **1** with indoles **2** in the presence of catalytic amounts of chiral bisoxazoline **3**−Cu(II) complex to give alkylated products **4** in high ee (eq 1).

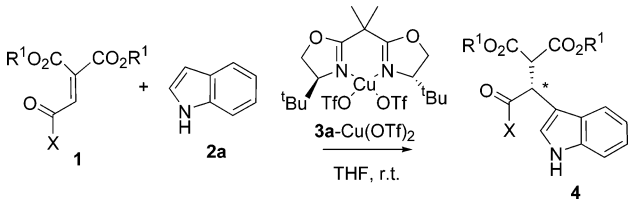


Results and Discussions

Reaction Conditions. Since bisoxazoline Cu(II) complexes have been shown to be effective catalysts for reactions between alkylidene malonates and indoles, reaction conditions involving bisoxazoline **3**−Cu(II) complexes were examined first.[4a] The reaction of triethyl ethenetricarboxylate **(1a)** with indole (**2a**) in the presence of a catalytic amount of chiral bisoxazoline ((*S*,*S*)-2,2′-isopropylidenebis-(4-*tert*-butyl-2-oxazoline) (**3a**)) copper(II) complex, **3a**−$Cu(OTf)_2$ (10%), in THF at room temperature overnight gave an alkylated product **4a** in 96% yield and 68% ee (Table 1, entry 1). When the reaction temperature was decreased to −20 °C, the ee% value of compound **4a** increased (83%), but the chemical yield decreased (74%). The solvent effect was also examined. The reaction of **1a** and **2a** in CH_2Cl_2 and ^{i}PrOH gave an alkylated product in 45 and 68% ee, respectively. Thus, THF and ^{i}PrOH are better solvents than CH_2Cl_2. The catalyst **3a**−$Zn(OTf)_2$ gave a low ee% value with opposite enantioselectivity. The conditions in entry 1 were used for examining the effect of β-ester or β-acyl groups, as described next.

Effect of β-Ester and β-Acyl Groups. A number of β-ester and β-acyl groups of α-diethyl esters were examined in this reaction (Table 2). ^{i}Pr, ^{t}Bu, benzyl, and substituted benzyl esters gave alkylated products **4** in 74−90% yield and 73−87% ee (entries 1−5). β-Phenyl ester **4g** was obtained in lower yield and ee% (43% yield 50% ee, entry 6). The results of β-acyl derivatives are shown in entries 8 and 9. The β-benzoyl derivative **1j** gave as high a ee% value as ethyl ester, but acetyl

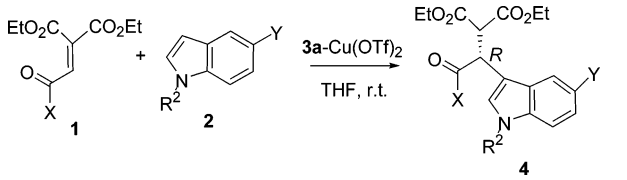
TABLE 2. Reaction of 1 and 2a



entry	sub-strate	R^1	X	prod-uct	yield (%)	ee (%)[a]	$[\alpha]_D$ (deg)[c]
1	**1b**	Et	O^{i}Pr	**4b**	71	74	−92
2	**1c**	Et	O^{t}Bu	**4c**	75	73	−82
3	**1d**	Et	OCH_2Ph	**4d**	81	84	−105
4	**1e**	Et	$OCH_2C_6H_4$-4-Br	**4e**	90	82	−61
5	**1f**	Et	$OCH_2C_6H_3$-3,5-di-OMe	**4f**	74	87	−94
6	**1g**	Et	OPh	**4g**	43	50	−72
7	**1h**	Et	N-$(CH_2)_5$-	**4h**	92	53	−193
8	**1i**	Et	Me	**4i**	86	38	−124
9	**1j**	Et	Ph	**4j**	92	69 (>99)[b]	−302
10	**1k**	Me	O^{t}Bu	**4k**	59	68	−99
11	**1l**	^{i}Pr	O^{t}Bu	**4l**	43	44	−58

[a] Determined by chiral HPLC. [b] Number in parentheses is ee after recrystallization. [c] In $CHCl_3$ solution.

TABLE 3. Reaction of 1 and 2



entry	sub-strate	X	indoles	R^2	Y	prod-uct	yield (%)	ee (%)[a]	$[\alpha]_D$ (deg)[c]
1	**1a**	OEt	**2b**	Me	H	**4m**	58	43	−146
2	**1c**	O^{t}Bu	**2b**	Me	H	**4n**	71	83	−108
3	**1d**	OCH_2Ph	**2b**	Me	H	**4o**	74	86	−103
4	**1e**	$OCH_2C_6H_4$-4-Br	**2b**	Me	H	**4p**	57	81	−76
5	**1i**	Me	**2b**	Me	H	**4q**	79	27	−75
6	**1j**	Ph	**2b**	Me	H	**4r**	87	95	−309
7	**1c**	O^{t}Bu	**2c**	H	OMe	**4s**	96	86	−99
8	**1c**	O^{t}Bu	**2d**	H	Cl	**4t**	88	74	−86
9	**1m**	N-$(CH_2)_4$-	**2d**	H	Cl	**4u**	78	65	−118
10	**1j**	Ph	**2d**	H	Cl	**4v**	75	93	−318
11	**1c**	O^{t}Bu	**2e**	H	Br	**4w**	84	80	−87
12	**1n**	$OCH_2C_6H_4$-3-NMe_2	**2e**	H	Br	**4x**	47	72	−71
13	**1j**	Ph	**2e**	H	Br	**4y**	72	83	−269
14	**1h**	N-$(CH_2)_5$-	**2e**	H	Br	**4z**	59	56 (>99)[b]	−140 (−198)[b]

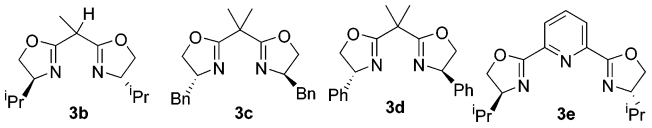
[a] Determined by chiral HPLC. [b] Number in parentheses is ee after recrystallization. [c] In $CHCl_3$ solution.

derivative **1i** showed a lower ee%. Larger β-substituents appear to give better ee% values. On the other hand, the reaction of α-diisopropyl ester **1l** gave a lower yield and ee% than those of the corresponding α-diethyl ester **1c** (entry 11).[7]

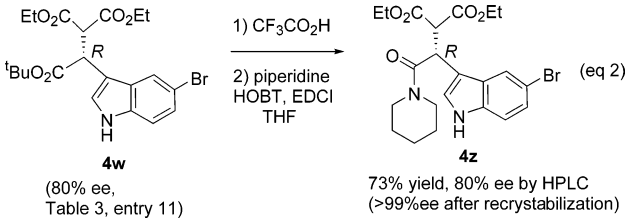
Reaction with Other Indole Derivatives and Absolute Stereochemistry Determination. As shown in Table 3, reaction of **1** with *N*-methylindole (**2b**) also gave Friedel−Crafts alkylated products **4** enantioselectively. Similar to the results in the reaction of **1** and indole (**2a**), smaller β-substituted derivatives **1a** and **1i** gave lower ee% values. The reaction of 5-substituted indoles and related compounds was also examined. The reaction also gave **4** in high ee%. Absolute stereochemistry of compound **4z** was performed by X-ray analysis and deter-

(7) Lower chemical yields and ee's of ^{i}Pr esters compared to those of Et esters have been also reported for the reaction of benzilidene malonates and enolsilanes.[5]

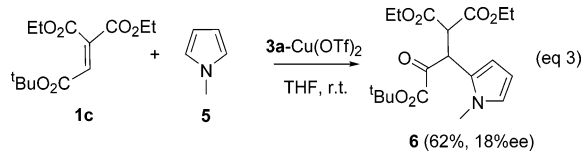
SCHEME 1



mined as shown as *R* (Figure S1 in Supporting Information).[8] Transformation of triester **4w** to **4z** also shows that **4w** has the same stereochemistry as **4z** (*R*) (eq 2). The obtained stereochemistry in this work, in terms of *β*-substituents, is also in accord with that of the reported alkylidene malonates and indole in the presence of the same catalyst **3a**−Cu(OTf)$_2$.[4]



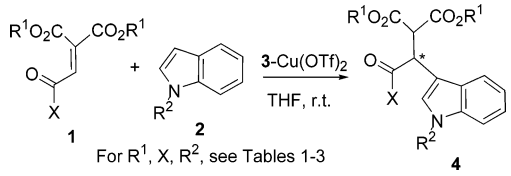
The reaction of **1b** with *N*-methylpyrrole (**5**) gave 2-alkylated pyrrole **6** in 62% yield and 18% ee (eq 3). The lower ee% value of *N*-methylpyrrole than that of indoles is similar to the reaction of alkylidene malonates. The Friedel−Crafts reaction of **1a** with electron-rich benzene derivatives such as *N*,*N*-dimethylaniline and 1,3-dimethoxybenzene did not proceed under the reaction conditions.



Ligand Effect. To improve enantioselectivity and to obtain some insight to the mechanism, chiral ligands of catalysts were screened (Scheme 1, Table 4). **3a**−**c** gave similar ee% values, and Ph derivative **3d** was inferior compared to **3a**−**c** (entries 5, 11, 16, 26, and 28). By use of (*S*,*S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine (**3e**), the reaction did not proceed (entry 6). For the formation of diisopropyl ester product **4l**, use of isopropyl derivative **3b**[4b] and benzyl derivative **3c** gave better results than use of **3a** (entries 20−22).

Reaction Mechanism. To understand the stereochemical model for this reaction and the structure of the chiral ligand complex, UB3LYP/LANL2MB calculations[9,10] of a model for **1**, trimethyl ethenetricarboxylate (**1o**), Cu(II), and ligand **3a** complex were performed. Out of the possible complexes, a six-membered bidentate complex **1o**−Cu(II)−**3a** was considered to be the most stable (Figure 1). The obtained structure shows that the Cu(II) center is disposed in a distorted square-planar (but also distorted tetrahedral) geometry and similar to the X-ray structures of Cu−bisoxazoline complexes.[11] Calculated O5−Cu−N7−C9 and O6−Cu−N8−C10 dihedral angles are 29.8° and 24.9°, respectively, and close to those of **3a**−Cu−2(H$_2$O)$^{2+}$·2(SbF$_6$)$^-$ (30.0° and 36.0°) and **3a**−Cu−2(H$_2$O)$^{2+}$·2(OTf)$^-$ (27.9° and 23.2°). The structure shows that both *π*-faces of **1o**−Cu(II)−**3a** are not obviously sterically differentiated. C2 is a prochiral center with the Cu(II) coordination.

TABLE 4. Reaction of 1 and 2 with 3−Cu(OTf)$_2$



entry	substrate	indole	**3**	configuration of **3**	product	yield (%)	ee (%)[a]	$[\alpha]_D$ (deg)[b]
1	**1a**	**2a**	**3a**[c]	*S*	**4a**	96	68	−99
2	**1a**	**2a**	**3b**	*S*	**4a**	79	69	−100
3	**1a**	**2a**	**3b**[d]	*S*	**4a**	91	70	−96
4	**1a**	**2a**	**3c**	*R*	**4a**	91	72	+103
5	**1a**	**2a**	**3d**	*R*	**4a**	75	44	+66
6	**1a**	**2a**	**3e**	*S*	**4a**	0		
7	**1b**	**2a**	**3a**[e]	*S*	**4b**	71	74	−92
8	**1b**	**2a**	**3b**	*S*	**4b**	71	65	−109
9	**1c**	**2a**	**3a**[e]	*S*	**4c**	75	73	−82
10	**1c**	**2a**	**3c**	*R*	**4c**	90	80	+110
11	**1c**	**2a**	**3d**	*R*	**4c**	84	51	+64
12	**1d**	**2a**	**3a**[e]	*S*	**4d**	81	84	−105
13	**1d**	**2a**	**3b**	*S*	**4d**	92	88	−88
14	**1j**	**2a**	**3a**[e]	*S*	**4j**	92	69	−302
15	**1j**	**2a**	**3b**	*S*	**4j**	91	87	−300
16	**1j**	**2a**	**3d**	*R*	**4j**	83	49	+168
17	**1k**	**2a**	**3a**[e]	*S*	**4k**	59	68	−99
18	**1k**	**2a**	**3b**	*S*	**4k**	79	62	−79
19	**1k**	**2a**	**3c**	*R*	**4k**	76	68	+92
20	**1l**	**2a**	**3a**[e]	*S*	**4l**	43	44	−58
21	**1l**	**2a**	**3b**	*S*	**4l**	83	76	−102
22	**1l**	**2a**	**3c**	*R*	**4l**	52	79	+107
23	**1a**	**2b**	**3a**[f]	*S*	**4m**	58	43	−146
24	**1a**	**2b**	**3c**	*R*	**4m**	79	25	+46
25	**1c**	**2b**	**3a**[f]	*S*	**4n**	71	83	−108
26	**1c**	**2b**	**3d**	*R*	**4n**	67	14	−19
27	**1j**	**2b**	**3a**[f]	*S*	**4r**	87	95	−309
28	**1j**	**2b**	**3d**	*R*	**4r**	58	0	+6

[a] Determined by chiral HPLC. [b] In $CHCl_3$ solution. [c] Results in Table 1. [d] ^{i}PrOH was used as a solvent. [e] Results in Table 2. [f] Results in Table 3.

Next, we considered the stereochemistry of the addition step with indoles. In the addition step, secondary orbital interactions between N in HOMO of indole (**2a**) and C4 in LUMO of **1**−Cu(II)−**3a** are likely, in addition to the major orbital interaction between C3′ in HOMO of **2a** and C2 in LUMO of **1**−Cu(II)−**3a** (Scheme 2). Two diasteromeric approaches A and B with the secondary orbital interactions can be possible, and approach

(8) The Flack parameter is 0.031 (13).

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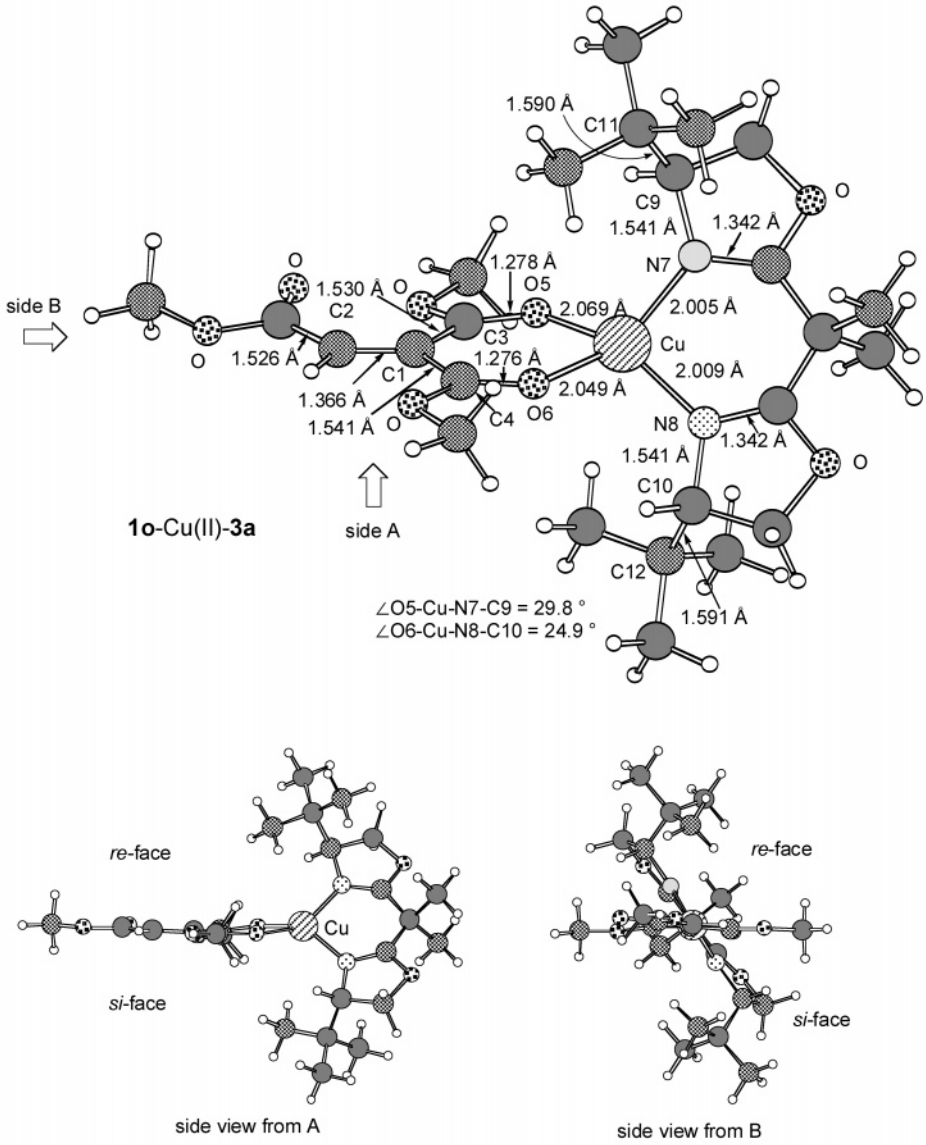
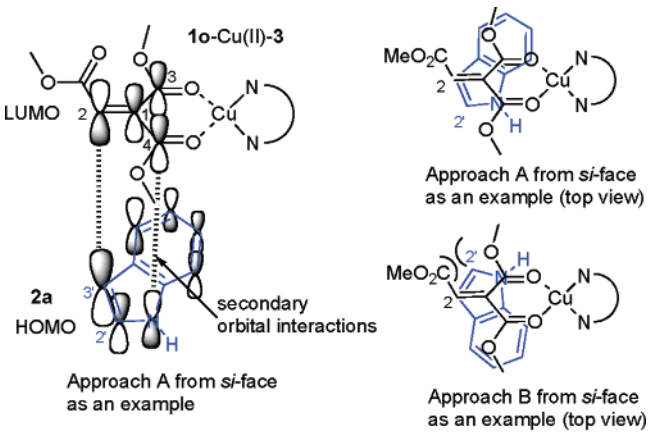


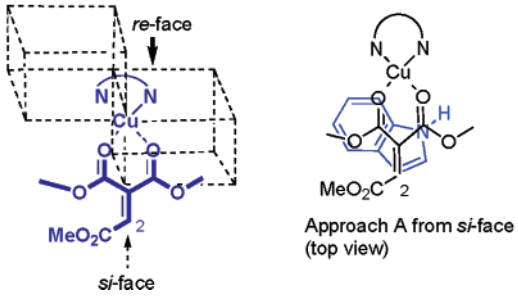
FIGURE 1. UB3LYP/LANL2MB optimized structure of (**1o**-Cu-**3a**)$^{2+}$.

SCHEME 2



A seems to be more stable than approach B because of the steric interaction of C2′ and the ester group with the C2−CO_2Me-(CO_2R′) bond free rotation. In the real system, larger ester (CO_2R′), amide, or ketone groups have more effective steric

SCHEME 3



interaction. When the approaches from the *re*-face and *si*-face of **1**−Cu(II)−**3a** are compared, the *si*-face approach is favored because of steric interaction between the benzene ring of indole and substituents of ligand **3a** (Figure 1 and Scheme 3). Thus, the obtained enantioselectivity could be explained by the diastereomeric approach of indole to prochiral C2 in the complex **1**−Cu(II)−**3a**.

Indoles have been extensively used for catalytic Friedel−Crafts reactions owing to not only their potential application

for bioactive compounds but also their high reactivity and stereoselectivity. In this work, a monocyclic system such as *N*-methylpyrrole (**5**) did not afford a good ee%. The lower ee% observed for **5** probably arises from less effective steric interaction of **5** with chiral ligand−Cu(II) and the ethenetricarboxylate **1** complex. For the reaction of indoles, the parallel overlap of two π-faces may cause high stereoselection although the reaction center C2 of **1**−Cu(II)−**3a** does not reside near the ligand chirality.

The reaction of benzilidene malonate and enolsilanes was explained as a nucleophilic attack to the *si*-face of benzylidene malonates supported by X-ray structure.[5] However, Friedel−Crafts reaction of benzylidene malonates can be also possibly explained by the diastereomeric approach of indole (**2a**) to prochiral C2 of benzylidene malonates. The structure of dimethyl benzilidene malonate (**7**)−Cu(II)−**3a** was optimized by UB3LYP/LANL2MB (Figure S2 in the Supporting Information), and it shows the distorted square-planar (but also distorted tetrahedral) geometry similar to that of **1o**−Cu(II)−**3a**. Calculated O5−Cu−N7−C9 and O6−Cu−N8−C10 dihedral angles are 27.3° and 26.3°, respectively. They are larger than those of the X-ray structure of **7**−Cu(II)−**3a**·$(SbF_6)_2$ (13.6° and 17.4°). The calculated structure also shows that both π-faces of **7**−Cu(II)−**3a** are not obviously sterically differentiated, unlike the X-ray structure. However, the *re*-facial selectivity can be explained by the diastereomeric approach of **2a** with secondary orbital interactions, similar to Schemes 2 and 3 (Schemes S1 and S2) (note that the *re*- and *si*-face nomenclature of **1o** and benzilidene malonate is opposite). The facial selectivity is in agreement with the reaction of benzilidene malonates and indole catalyzed by **3a**−Cu(II) reported by Jørgensen and co-workers.[4a]

Complete reversal of π-facial selectivity by solvents or substituents in ligands **3** has not been observed in the reaction of ethenetricarboxylates **1**. Thus, although in some reactions of alkylidene malonates various factors such as solvent, ligand structures, and counterions are important and they cause reversal of π-facial selectivity, the observed enantioselectivity in this reaction can be explained by the diastereomeric approach of indole toward β-substituents.

In summary, we have shown that the reaction of **1** with indoles **2** in the presence of catalytic amounts of chiral bisoxazoline **3**−Cu(II) complex gives alkylated products **4** in high ee. The present reaction provides an efficient enantioselective Friedel−Crafts alkylation of indoles for diversely substituted compounds. The highly functionalized products are suitable for further elaboration. A new utility of ethenetricarboxylates in organic synthesis has been demonstrated in this study. Further elaboration of the products and development to use ethenetricarboxylates in other catalytic asymmetric reaction are under investigation.

Experimental Section

Typical Procedure (Table 1, Entry 1). A powdered mixture of $Cu(OTf)_2$ (18 mg, 0.05 mmol) and **3a** (16 mg, 0.054 mmol) was dried under vacuum for 1 h. THF (1 mL) was added under N_2, and the solution was stirred for 1 h. Compound **1a** (0.122 g, 0.5 mmol) in THF (0.4 mL) was added and stirred for 15 min, followed by addition of **2a** (65 mg, 0.55 mmol). After 20 h, the reaction mixture was filtered through a plug of silica gel, washed with Et_2O, and dried ($MgSO_4$), and the solvent was removed. The residue was purified by column chromatography over silica gel, eluting with CH_2Cl_2 to give **4a** (173 mg, 96%). **4a** (R_f 0.1 (CH_2Cl_2)): Pale brown oil; HPLC (CHIRALPAK AS-H, hexane/^{i}PrOH = 9:1) minor peak t_{R1} 11.3 mim, major peak t_{R2} 12.4 min, 68% ee; $[\alpha]^{27}_D$ −99° (*c* 1.73, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.851 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.79−3.92 (m, 2H), 4.01−4.09 (m, 1H), 4.16−4.31 (m, 3H), 4.37 (d, J = 11.8 Hz, 1H), 4.64 (dd, J = 11.8, 0.5 Hz, 1H), 7.11−7.20 (m, 3H), 7.33 (d-like, J = 7.9 Hz, 1H), 7.74 (d-like, J = 7.9 Hz, 1H), 8.21 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.6 (q), 14.1 (q), 42.4 (d), 55.0 (d), 61.38 (t), 61.43 (t), 61.9 (t), 109.8 (s), 111.2 (d), 119.5 (d), 120.0 (d), 122.4 (d), 123.3 (d), 126.4 (s), 136.1 (s), 167.6 (s), 168.3 (s), 172.5 (s); IR (neat) 3404, 2983, 1732, 1458, 1370, 1301, 1174, 1029 cm^{-1}; MS (EI) *m*/*z* 361 (M^+, 39%), 287 (32%), 202 (43%), 170 (100%); exact mass M^+ 361.1530 (calcd for $C_{19}H_{23}NO_6$ 361.1525).

Theoretical Calculations. Density functional theory calculations of **1o**−Cu(II)−**3a** and **7**−Cu(II)−**3a** were carried out by UB3LYP/LANL2MB.[9,10] Geometries were fully optimized. Vibrational analyses were also performed to check whether the obtained geometries are either at the energy minima or at the saddle points. All calculations were conducted by the use of Gaussian03 installed at the Information Processing Center (Nara University of Education).

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Supporting Information Available: Additional experimental procedures and spectral data, Figures S1 and S2, X-ray crystallographic data, Schemes S1 and S2, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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