Catalytic enantioselective alkylation of heteroaromatic compounds using alkylidene malonates

Wei Zhuang, Tore Hansen and Karl Anker Jørgensen*

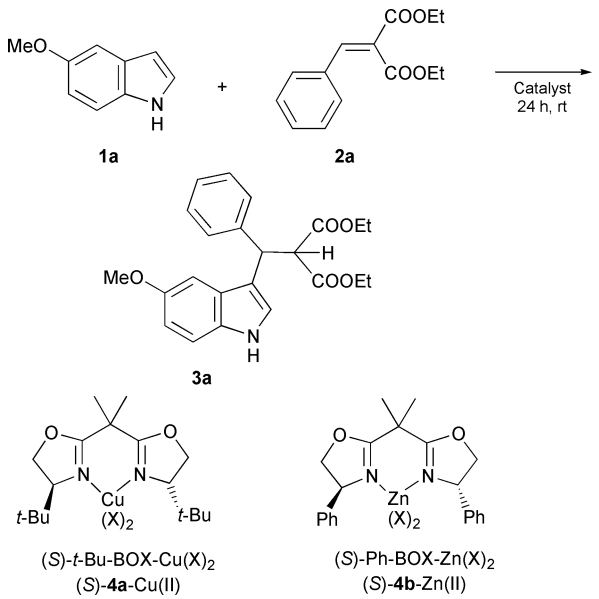
Center for Metal Catalysed Reactions, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark. E-mail: kaj@kemi.aau.dk

Received (in Cambridge, UK) 8th November 2000, Accepted 15th January 2001
First published as an Advance Article on the web 7th February 2001

A catalytic enantioselective alkylation of heteroaromatic compounds using alkylidene malonates has been developed; the reaction proceeds for different heteroaromatic compounds with alkylidene malonates in high yield and enantiomeric excess.

The addition of aromatic C–H bonds to alkenes, the Friedel–Crafts alkylation, is a highly important reaction in synthetic chemistry for the formation of new C–C bonds.[1] A challenge for the Friedel–Crafts alkylation is to perform the reaction in a catalytic enantioselective fashion as this would be a simple and attractive method for the synthesis of optically active aromatic compounds using easily available starting materials. The first examples of catalytic enantioselective addition reactions of aromatic compounds to conjugated compounds such as carbonyls and imines have recently appeared.[2] In the following we will present the first catalytic enantioselective alkylation of heteroaromatic compounds using alkylidene malonates catalyzed by chiral Lewis acids.

The reaction of indole **1a** with alkylidene malonate **2a**[3] in the presence of the chiral bisoxazoline–metal(II) complexes, (*S*)-**4a**-Cu(II), (*S*)-**4b**-Zn(II), as the catalysts[4] proceeds well giving the Friedel–Crafts alkylation adduct **3a** in good yield and high ee [eqn. (1)]. Table 1 gives some representative results for the screening of catalysts and reaction conditions.



(1)

The reactions were performed with 2 eq. of hexafluoro-*i*-PrOH (HFIP) and 10% catalyst loading.[5] No reaction took place with (*S*)-**4a**-Cu(OTf)$_2$ in MeCN or $MeNO_2$ as solvents, while in Et_2O high conversion to **3a** and good ee was achieved (entries 1–3). The catalyst (*S*)-**4b**-Zn(OTf)$_2$ also gave high conversion, however, the enantioselectivity was low (entry 4). The catalytic activity of (*S*)-**4a**-Cu(OTf)$_2$ in THF was very good and **3a** was obtained in 91% yield and 60% ee (entry 5). The activity increased further by changing counterion from OTf to SbF_6 in CH_2Cl_2 giving high conversion at 0 °C, however, the ee of **3a** dropped from 57 to 35% ee (entry 6 and 7). The effect of addition of HFIP to the reaction was found to be negligible; the reaction rate decreased only slightly and the ee was essentially unchanged in the absence of HFIP (entry 3 *vs.* 8).[5] The effect of other parameters such as lower catalyst loading, concentration and temperature all gave lower conversion to **3a** with very little increase in ee.

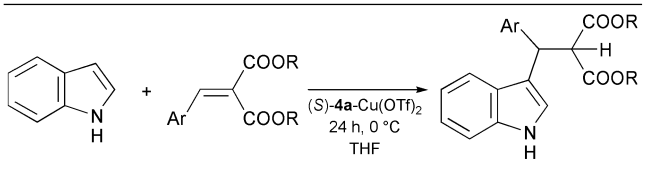
Table 1 Screening of chiral Lewis acids and reaction conditions for the reaction of indole **1a** with alkylidene malonate **2a**

Entry	Catalyst	Solvent	X	Conv.[a] (%)	Ee[bc] (%)
1	(*S*)-**4a**-CuX$_2$	MeCN	OTf	—	—
2	(*S*)-**4a**-CuX$_2$	$MeNO_2$	OTf	—	—
3	(*S*)-**4a**-CuX$_2$	Et_2O	OTf	95	60
4	(*S*)-**4b**-ZnX$_2$	Et_2O	OTf	89	8[d]
5	(*S*)-**4a**-CuX$_2$	THF	OTf	91	60 (93)
6	(*S*)-**4a**-CuX$_2$	CH_2Cl_2	OTF	71	57
7[e]	(*S*)-**4a**-CuX$_2$	CH_2Cl_2	SbF_6	92	35
8[f]	(*S*)-**4a**-CuX$_2$	Et_2O	OTf	93	57

[a] Determined by ^{1}H-NMR spectroscopy. [b] Determined by chiral HPLC. [c] Number in parentheses is ee after recrystallization. [d] Opposite enantiomer. [e] Reaction performed at 0 °C. [f] No HFIP used.

A selection of β-substituted alkylidene malonates **2a**–**e** were examined in this reaction with indole **1b** catalyzed by (*S*)-**4a**-Cu(OTf)$_2$ (Table 2). Indole **1b** reacted with **2a** to give the Friedel–Crafts alkylation product **3b** in 73% yield and 60% ee (entry 1).† The dimethyl benzylidene malonate **2b** was significantly more reactive compared to the diethyl derivative (**2a**) giving the addition product in 95% isolated yield, however, the ee was lower for **3b** (entry 1 *vs.* 2). The reactivity of dimethyl *p*-nitrobenzylidene malonate **2c** was comparable to **2b**, and product **3d** was formed in high yield and with 56% ee

Table 2 Reaction of indole **1b** with various β-substituted alkylidene malonates **2a**–**e** catalyzed by (*S*)-**4a**-Cu(OTf)$_2$



1b **2a-e** **3b-f**

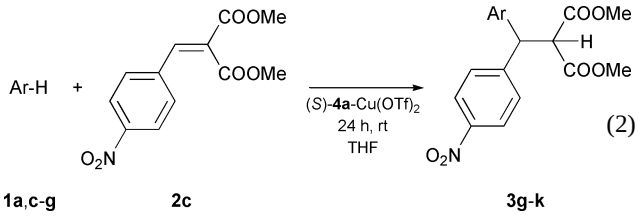
Entry	R, Ar	Yield[a] (%)	Ee[bc] (%)
1	Et, Ph–**2a**	**3b**–73	60 (92)
2	Me, Ph–**2b**	**3c**–95	50
3	Me, 4-NO_2-Ph–**2c**	**3d**–92	56
4	Et, 4-Br-Ph–**2d**	**3e**–45	50
5[d]	Et, 2-Cl-Ph–**2e**	**3f**–87	69

[a] Isolated yield after column chromatography. [b] Determined by chiral HPLC. [c] Number in parentheses is ee after recrystallization. [d] Reaction performed at 30 °C.

DOI: 10.1039/b009008p

(entry 3). The diethyl 2-chlorobenzylidene malonate derivative **2e** was considerably less reactive compared to the other malonates and required a 30 °C reaction temperature for the reaction to go to completion. The enantioselectivity of **3f** was 69% ee, the highest enantioselectivity obtained in this selection.

Dimethyl *p*-nitrobenzylidene malonate **2c** was then used as a standard substrate to probe the reactivity of different aromatic compounds **1a**, **c**–**f** in this Friedel–Crafts alkylation reaction [eqn. (2)] (Table 3).



(2)

1a,c-g **2c** **3g-k**

Table 3 Friedel–Crafts alkylation reaction of different heteroaromatic compounds **1a**, **c**–**g** with dimethyl *p*-nitrobenzylidene malonate **2c** catalyzed by (*S*)-**4a**-Cu(OTf)$_2$

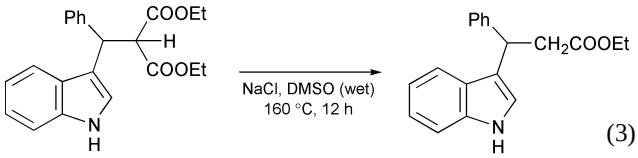
Entry	Ar	Yield[a] (%)	Ee[bc] (%)
1[d]	5-MeO-indole–**1a**	**3g**–99	58
2[e]	4-Cl-indole–**1c**	**3h**–62	46
3	*N*-Me-indole–**1d**	**3i**–99	48
4	*N*-Me-pyrrole–**1e**	**3j**–99	36
5	Pyrrole–**1f**	**3k**–99	28
6	2-Me-furan–**1g**	**3l**–99	12

[a] Isolated yield after column chromatography. [b] Determined by chiral HPLC. [c] Determined by chiral HPLC. [d] Reaction performed at 0 °C. [e] Reaction performed at 30 °C.

The reaction with 5-methoxyindole **1a** gave the Friedel–Crafts alkylation product **3g** in excellent yield and with 58% ee (entry 1). 4-Chloroindole **1c** reacted to give the desired product **3h**, although in a lower yield and ee compared to the more electron-rich indole (entry 2). *N*-Methylindole **1d** and *N*-methylpyrrole **1e** both yielded the alkylation products **3i** and **3j**, respectively, with great efficiency and with a small drop in ee (entries 3, 4). Both pyrrole **1f** and 2-methylfuran **1g** reacted in a Friedel–Crafts fashion in excellent yields, but the enantioselectivity of the products was low compared to the other substrates (entries 5, 6).

A further advantage of this Friedel–Crafts alkylation reaction is that the products all are solid and the optical purity can be greatly enhanced to > 90% ee by crystallization as shown for several of the entries in Table 1, 2.

The Friedel–Crafts adducts such as **3b** can undergo decarboxylation[6] to give the mono ester **5** in high yield [eqn. (3)], showing that the present reaction formally can be considered as a Friedel–Crafts alkylation of cinnamates.



(3)

3b **5**
74% isolated yield

In summary, a new catalytic enantioselective alkylation of heteroaromatic compounds using alkylidene malonates catalyzed by chiral bisoxazoline–copper(II) complexes has been presented. The reactions proceed in high yields and with moderate ee for different aromatic compounds and alkylidene malonates. The optical purity of the products can be enhanced by recrystallization and it is demonstrated that the reaction can be considered as a formal Friedel–Crafts alkylation of cinnamates.

We are indebted to The Danish National Research Foundation for financial support.

Notes and references

† *Representative experimental procedure*: A powdered mixture of Cu(OTf)$_2$ (18 mg, 0.05 mmol) and (*S*)-**4a**-Cu(OTf)$_2$ (16 mg, 0.054 mmol) was dried under vacuum for 1 h. THF (1 mL) was added under N_2 and the solution stirred for 1 h. Compound **2a** (113 μL, 0.5 mmol) was added and stirred for 15 min, followed by addition of **1b** (65 mg, 0.55 mmol). After 24 h the reaction mixture was filtered through a plug of silica gel, washed with Et_2O, and the solvent removed. The product **3b** was obtained as a white solid in 73% yield after purification by chromatography (CH_2Cl_2 as eluent). The ee was determined by HPLC analysis to be 60% (Chiralpack AS, 1.0 mL min^{-1}, 95:5 hexane–*i*-PrOH, R_t = 23 (major) and 26 (minor) min). $\delta_H(C_3D_6O$, 400 Hz) 10.1 (s, 1H), 7.56 (m, 1H), 7.47 (m, 3H), 7.33 (m, 1H), 7.21 (m, 2H), 7.13 (m, 1H), 7.05 (m, 1H), 6.95 (m, 1H), 5.03 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 3.96 (q, J = 7.2 Hz, 2H), 3.92 (q, J = 7.2 Hz, 2H), 0.98 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.2 Hz, 3H); $\delta_C(C_3D_6O$, 100 Hz) 167.7, 167.6, 142.5, 136.9, 128.6, 128.3, 127.1, 126.6, 121.7, 121.6, 119.0, 118.9, 116.7, 111.4, 60.9, 58.9, 43.0, 13.5; HRMS (ES) calcd for $C_{22}H_{23}NO_4$ 365.1627, found (M + Na)$^+$ 388.1525; mp 164–167 °C; $[\alpha]^{20}_D$ = +37.1° (69 mg mL^{-1} $CHCl_3$).

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