[17] Clusters with the labile Al^{III}, Fe^{III}, and In^{III} ions were resolved by the same method and also show exceedingly high stability towards racemization.

[18] M. Ziegler, A. von Zelewsky, *Coord. Chem. Rev.* **1998**, *177*, 257.

[19] Crystal structure of $\Delta\Delta\Delta\Delta$-$[(Et_4N)\subset Ga_4\mathbf{2}_6]\cdot x$(solvent): Crystal data were collected using a Siemens SMART diffractometer equipped with a CCD area detector[25], crystal size 0.30 × 0.20 × 0.15 mm, $T = -125\,°C$, graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), cubic, space group $I23$ (No. 197), $a = 22.572(1)$ Å, $V = 11500.5(9)$ Å^3, $Z = 2$, $\mu = 0.528\ cm^{-1}$, $F(000) = 3706$, $\rho_{calcd} = 1.07\ Mg\,m^{3-}$, $2\Theta_{max} = 37.64°$. Of the 15524 reflections measured, 1510 were unique ($R_{int} = 0.087$). The structure was solved by direct methods and refined on F^2 using SHELXTL.[26] Data were corrected for Lorentz and polarization effects. A semi-empirical absorption correction was applied using XPREP (ellipsoidal model, $R_{int} = 0.0486$, $T_{max} = 0.812$, $T_{min} = 0.755$).[26] The carbonyl oxygen atom of the ligand is disordered over two positions with 1/2 occupancy, and the naphthalene backbone of the ligand is disordered across an imaginary line connecting the two carbon atoms affixed to the nitrogen atoms of the amide. This disorder was modeled as a twist of this backbone around its center with both orientations having 1/2 occupancy. A disordered NEt_4^+ ion is present in the cavity of the cluster. The nitrogen atom is located on the 23 special position, and the methylene groups are disordered over two sites with 1/2 occupancy. The methyl carbon atoms were disordered over the threefold axes and 12 sites with 1/3 occupancy. There was also a high degree of disorder among the other cations and solvent molecules present. As a result, only the encapsulated NEt_4^+ ion was found and constrained to be rigid in the disorder model described. The other 11 cations and solvent molecules are included as "x (solvent)" in the chemical formula and accounted for by a SWAT parameter. As a result of the lack of high angle data (1.2 Å resolution) only the gallium atoms, amide nitrogens, and catecholate oxygen atoms were refined anisotropically. All other atoms were refined isotropically. Hydrogen atoms were included on all appropriate atoms of the ligand that were not disordered but were not refined. Weighting scheme: $1/[\sigma^2(F_o^2) + (0.1763p)^2 + 2.7183p]$, where $p = (F_o^2 + 2F_c^2)/3$. Final $R_1 = 0.0837$ for 1022 reflections with $F_o > 4\sigma(F_o)$ (1162 Friedel unique data, 157 parameters, 6 restraints); for all 1510 data, $wR_2 = 0.269$, GOF = 1.118; Flack[27] parameter = 0.08(8); max/min residual density +0.28/−0.27 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145431. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[20] E. J. Enemark, T. D. P. Stack, *Angew. Chem.* **1998**, *110*, 977; *Angew. Chem. Int. Ed.* **1998**, *37*, 932.

[21] Other examples of partially resolved assemblies made from moderately labile octahedral metal ions (Ni^{II} and Co^{II}) and achiral ligands are dinuclear triple helicates.[22, 23]

[22] R. Kramer, J. M. Lehn, A. DeCian, J. Fischer, *Angew. Chem.* **1993**, *105*, 764; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 703.

[23] L. J. Charbonniere, G. Bernardinelli, C. Piguet, A. M. Sargeson, and A. F. Williams, *J. Chem. Soc. Chem. Commun.* **1994**, 1419.

[24] J. I. Seemann, J. F. Whidby, *J. Org. Chem.* **1976**, *41*, 3824.

[25] SMART, Area Detector Software Package, **1995**, Siemens Industrial Automation, Inc., Madison, WI, USA.

[26] G. Sheldrick, SHELXTL, Crystal Structure Determination Software Package, **1993**, Siemens Industrial Automation, Inc., Madison, WI, USA.

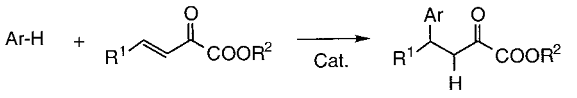
[27] H. Flack, *Acta Crystallogr. Sect. A* **1983**, *39*, 876.

Catalytic Asymmetric Friedel–Crafts Alkylation of β,γ-Unsaturated α-Ketoesters: Enantioselective Addition of Aromatic C–H Bonds to Alkenes**

Kim B. Jensen, Jacob Thorhauge, Rita G. Hazell, and Karl Anker Jørgensen*

Aromatic compounds are very important molecules in chemistry and the addition of these compounds to alkenes in the Friedel–Crafts alkylation constitutes one of the fundamental reactions in synthetic chemistry.[1]

The catalytic enantioselective addition of aromatic C–H bonds to alkenes leading to formation of a new C–C bond is of considerable interest and remains a long-term challenge for chemists. Such a reaction would provide a simple and attractive method for the formation of optically active aryl-substituted compounds from easily available starting materials. Recently, the first examples of catalytic enantioselective addition reactions of aromatic and heteroaromatic compounds to activated carbonyl compounds,[2] α-dicarbonyl compounds,[3] and imines were reported.[4] However, the development of a catalytic enantioselective version of the corresponding Friedel–Crafts alkylation reaction has, to the best of our knowledge, not been reported, although numerous examples can be given for the non-enantioselective version of this reaction.[1, 5] This paper presents the first catalytic highly enantioselective Friedel–Crafts alkylation, that is, the addition of aromatic C–H bonds to β,γ-unsaturated α-ketoesters catalyzed by chiral Lewis acids [Eq. (1)].



(1)

The reaction of indole (**1a**) with methyl 4-phenyl-2-oxo-3-butenoate (**2a**) can be catalyzed by various metal complexes, and the application of the chiral bisoxazoline (BOX) complexes[6, 7] [{(*S*)-*t*Bu-BOX}M] ((*S*)-**4a**–**c**; M = $Cu(OTf)_2$, $Cu(SbF_6)_2$, and $Zn(OTf)_2$, respectively) and [{(*S*)-Ph-BOX}M] ((*S*)-**4d**; M = $Cu(OTf)_2$) gives the optically active Friedel–Crafts alkylation product **3a**. Some representative screening results are presented in Table 1. The Friedel–Crafts alkylation reactions with (*S*)-**4a**–**c** and (*S*)-**4d** proceed with high conversion. For the reaction catalyzed by (*S*)-**4a**, product **3a** is formed with up to 88 % *ee* in CH_2Cl_2 (entry 3), while 74 % *ee* is found in THF (entry 6). In Et_2O, with 2 mol % of the catalyst,

---

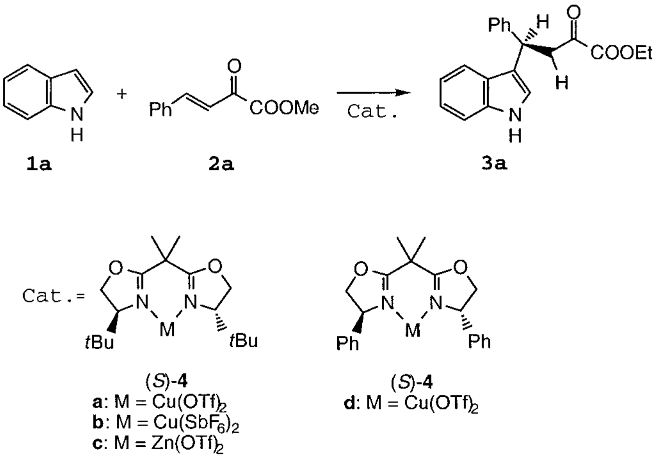
[*] Prof. Dr. K. A. Jørgensen, Dr. K. B. Jensen, J. Thorhauge,
Dr. R. G. Hazell
Center for Metal-Catalyzed Reactions
Department of Chemistry
Aarhus University
8000 Aarhus C (Denmark)
Fax: (+45) 86-19-61-99
E-mail: kaj@kemi.aau.dk

[**] This work was made possible by a grant from the Danish National Research Foundation.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

1433-7851/01/4001-0160 $ 17.50+.50/0

Table 1. Catalytic enantioselective Friedel–Crafts alkylation reaction of indole (**1a**) with methyl 4-phenyl-2-oxo-3-butenoate (**2a**) under various reaction conditions.[a]



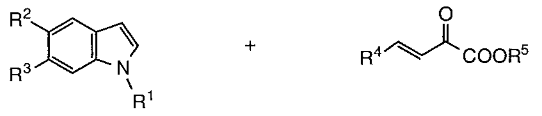
Entry	Catalyst	Solvent	T [°C]	t [h]	Conv. [%][b]	*ee* [%][c]
1	–	CH_2Cl_2	20	24	27	0
2	(*S*)-**4a**	CH_2Cl_2	0	0.5	100	36
3	(*S*)-**4a**	CH_2Cl_2	–78	3	100	88
4	(*S*)-**4a**	Et_2O	0	0.5	100	88
5	(*S*)-**4a**	Et_2O	–78	16	100	97
6	(*S*)-**4a**	THF	–78	1	100	74
7	(*S*)-**4a**	CH_2Cl_2/pentane 1:2	–78	16	99	89
8[d]	(*S*)-**4a**	Et_2O	–78 → –30	64	100	99.5
9	(*S*)-**4c**	Et_2O	0 → 20	18	100	87
10	(*S*)-**4d**	Et_2O	–78	16	100	42[e]

[a] The reactions were performed on a 0.4 mmol scale with 10 mol% catalyst. Indole (**1a**) and the enone **2a** were used in a 1:1 ratio. For further details, see the Supporting Information. [b] Determined by ^1H NMR spectroscopy of the crude product. [c] Determined by HPLC. [d] The reaction was performed on a 2 mmol scale with 2 mol% catalyst. [e] The opposite enantiomer of **3a** to that shown in the scheme was obtained.

only one enantiomer of **3a** can be detected by chiral HPLC (entry 8). The reaction can also proceed with only 0.5 mol% of (*S*)-**4b** as the catalyst, to give **3a** in >95% isolated yield and with 84% *ee*. The reaction time required is dependent on the reaction temperature; after only 30 min the reaction of **1a** with **2a** catalyzed by (*S*)-**4a** in Et_2O at 0 °C is completed and **3a** is formed with 88% *ee* (entry 4). Catalyst [{(*S*)-*t*Bu-BOX}Zn(OTf)$_2$] ((*S*)-**4c**), which is a more air-stable catalyst than the corresponding copper complex (*S*)-**4a**, is also an effective catalyst for the reaction of **1a** with **2a** giving **3a** with up to 87% *ee* (entry 9), while catalyst (*S*)-**4d** produces the opposite enantiomer of **3a** with an *ee* value of only 42% (entry 10).[8]

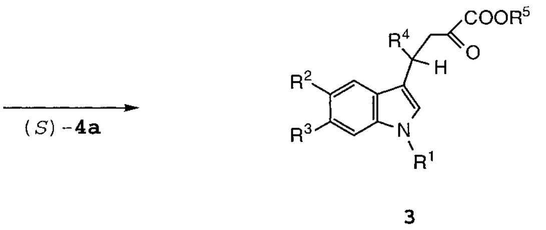
The scope of the catalytic enantioselective Friedel–Crafts alkylation reaction is shown by the reaction of various aromatic compounds **1a**–**g** with different β,γ-unsaturated α-ketoesters **2a**–**d** in the presence of (*S*)-**4a**,**b** as the catalysts [Eq. (2); Bn = benzyl]. The results are presented in Table 2; the compounds **2a**–**d** are chosen to show the span of alkene substituents in the reaction as both alkyl, aromatic, and protected alcohols can be present.

The catalytic enantioselective Friedel–Crafts alkylation reaction proceeds well for both heteroaromatic and aromatic compounds. For many of the reactions reported chromatographic purification is not necessary as the optically active products can be isolated directly by filteration of the chiral catalyst followed by evaporation of the solvent. Entries 1–9 show the results for the reaction of the different indoles **1a**–**e** with **2a**–**c** giving the Friedel–Crafts alkylation products **3a**–**i** [Eq. (2)][9] in high yields and with excellent enantiose-



1
a: R^1-R^3 = H
b: R^1 = Me, R^2 = R^3 = H
c: R^1 = R^3 = H, R^2 = OMe
d: R^1 = R^2 = H, R^3 = Cl
e: R^1 = R^2 = H, R^3 = COOMe

2
a: R^4 = Ph, R^5 = Me
b: R^4 = Me, R^5 = Et
c: R^4 = CH_2OBn, R^5 = Et



(2)

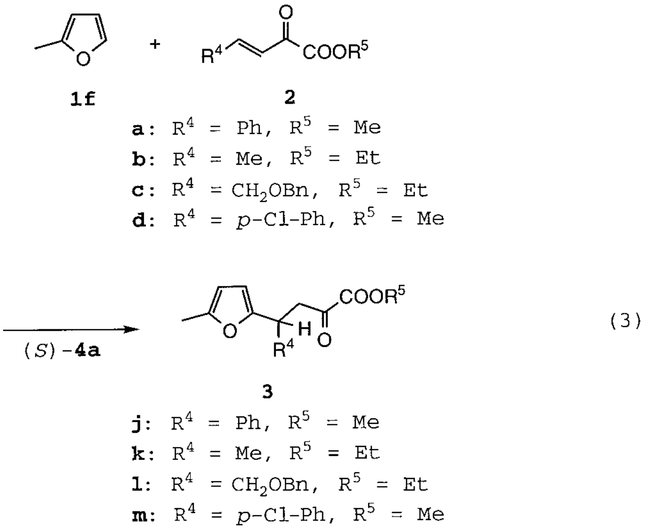
3
a: R^1-R^3 = H, R^4 = Ph, R^5 = Me
b: R^1 = Me, R^2 = R^3 = H, R^4 = Ph, R^5 = Me
c: R^1 = R^3 = H, R^2 = OMe, R^4 = Ph, R^5 = Me
d: R^1 = R^2 = H, R^3 = Cl, R^4 = Ph, R^5 = Me
e: R^1 = R^2 = H, R^3 = COOMe, R^4 = Ph, R^5 = Me
f: R^1-R^3 = H, R^4 = Me, R^5 = Et
g: R^1 = R^3 = H, R^2 = OMe, R^4 = Me, R^5 = Et
h: R^1 = R^2 = H, R^3 = Cl, R^4 = CH_2OBn, R^5 = Et
i: R^1 = R^3 = H, R^2 = OMe, R^4 = CH_2OBn, R^5 = Et

Table 2. Catalytic enantioselectivities in Friedel–Crafts alkylation reactions between different aromatic compounds and β,γ-unsaturated α-ketoesters [Eqs. (2)–(4)].[a]

Entry	Product	Cat. [mol%]	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
1	**3a**	2	–78 → –30	64	77	99.5
2	**3b**	5	–78 → –30	48	98	96
3	**3c**	5	–78	1	95	>99.5
4	**3d**	10	–20 → 0	16	69	97[d]
5	**3e**	10	–20 → 0	16	82	94
6	**3f**	5	–78	16	96	95
7	**3g**	5	–78	1	95	>99.5
8	**3h**	10	–20 → 0	16	70	80
9	**3i**	5	–78	1	98	95
10	**3j**	10	0	48	99	88
11	**3k**	10	0	24	93	88
12	**3l**	10	0	24	90	80
13	**3m**	10	0	18	90	79
14	**3n**[e]	10	0	2	65	89
15	**3o**	10	–60	28	68	60

[a] For the reactions in entries 1–13, catalyst (*S*)-**4a** was used and the aromatic compound was added in 1–1.33 equivalents. For entries 14, 15, (*S*)-**4b** was added and the aromatic compound was used in three equivalents. For further details see the Supporting Information. [b] Yield of isolated product. [c] Determined by HPLC or GC. [d] After recrystallization an *ee* value of 99% was measured. [e] Some double-addition product is also formed.

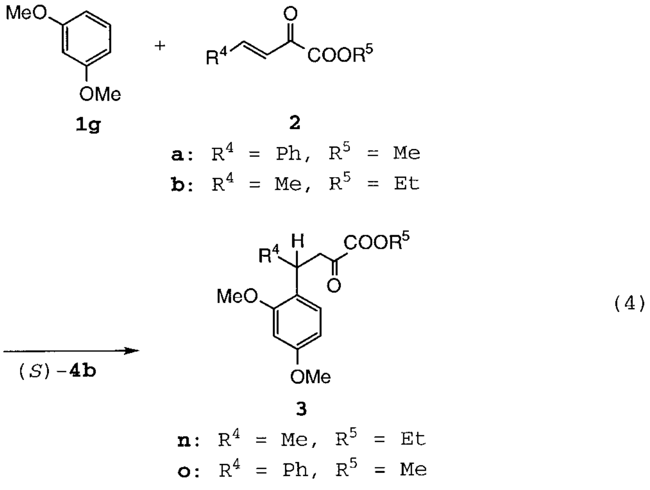
lectivities; for example, 5-methoxy-1*H*-indole (**1c**) reacts with **2a**–**c** to give **3c** and **3g** as enantiopure compounds (> 99.5% *ee*), while **3i** is formed with 95% *ee*. Indoles **1d** and **1e**, substituted with electron-withdrawing substituents, also react with **2a** in a highly enantioselective manner and *ee* values of 97% and 94% *ee* are obtained for **3d** and **3e**, respectively. Indoles substituted with methyl and phenyl in the 2-position give the corresponding Friedel–Crafts alkylation products in good yield (60–70%) and moderate enantioselectivity (≈50% *ee*; results not shown). Other heteroaromatic compounds, such as 2-methylfuran (**1f**), react with **2a**–**d** catalyzed by (*S*)-**4a** as shown in Equation (3) (entries 10–13 in Table 2). The Friedel–Crafts products **3j**–**m**[10] are all formed in >90% yield and with high enantiopurity (up to 88% *ee* is obtained). The enantioselective Friedel–Crafts alkylation reaction also proceeds for aromatic compounds, such as 1,3-dimethoxybenzene (**1g**) [Eq. (4)], and entries 14, 15 in Table 2 show the results for the reaction of **1g** with **2a** and **2b**. These reactions give the corresponding *o*,*p*-dimethoxy-substituted aromatic products and **3n** is formed in 89% *ee* at 0 °C after 2 h reaction time, while **3o** is formed in 60% *ee*.



a: R^4 = Ph, R^5 = Me
b: R^4 = Me, R^5 = Et
c: R^4 = CH_2OBn, R^5 = Et
d: R^4 = *p*-Cl-Ph, R^5 = Me

(3)

j: R^4 = Ph, R^5 = Me
k: R^4 = Me, R^5 = Et
l: R^4 = CH_2OBn, R^5 = Et
m: R^4 = *p*-Cl-Ph, R^5 = Me



a: R^4 = Ph, R^5 = Me
b: R^4 = Me, R^5 = Et

(4)

n: R^4 = Me, R^5 = Et
o: R^4 = Ph, R^5 = Me

For catalytic enantioselective Friedel–Crafts alkylation reactions that take place at below −50 °C with indoles, the enol product is formed. The enol form of the product can be isolated and characterized for several of the compounds. However, treatment of the enol product with MeOH at room temperature leads to a smooth formation of the keto form of the Friedel–Crafts products.

In order to obtain insight into the mechanism for this new catalytic enantioselective Friedel–Crafts alkylation reaction, the absolute configuration of the indole-derived product **3d**, obtained by reaction of **1d** with **2a** catalyzed by (*S*)-**4a**, has been determined by X-ray analysis. The X-ray crystal structure of **3d** shown in Figure 1 leads to an assignment of the chiral center formed in the reaction as *R*.

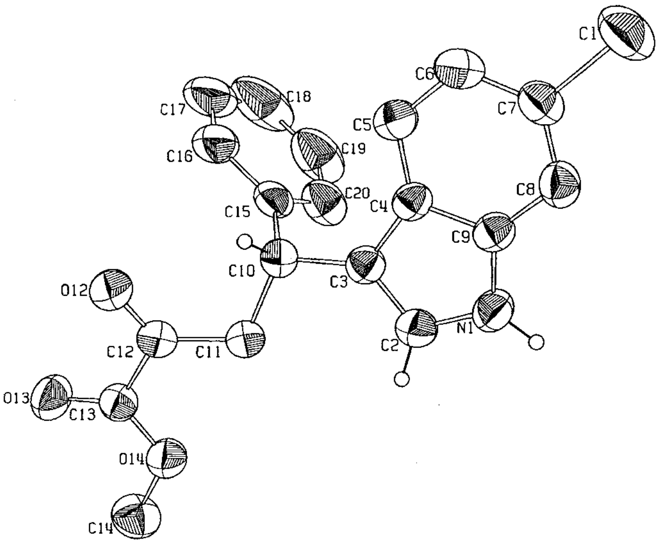


Figure 1. X-ray crystal structure of **3d** for determination of the absolute configuration of the chiral center formed during the reaction of **1d** with **2a** in the presence of (*S*)-**4a**. Only the hydrogen atoms on the chiral carbon atom and a part of the indole ring are shown, the rest are omitted for clarity.

Based on the absolute configuration of the chiral Friedel–Crafts product formed, it is postulated that the β,γ-unsaturated α-ketoester coordinates in a bidentate fashion to the (*S*)-**4a** catalyst; this leads to a square-planar intermediate.[6b–d] Such an intermediate has the *Re* face of the reacting alkene carbon atom available for approach of the aromatic compound. In Figure 2 the approach of the indole to the β,γ-

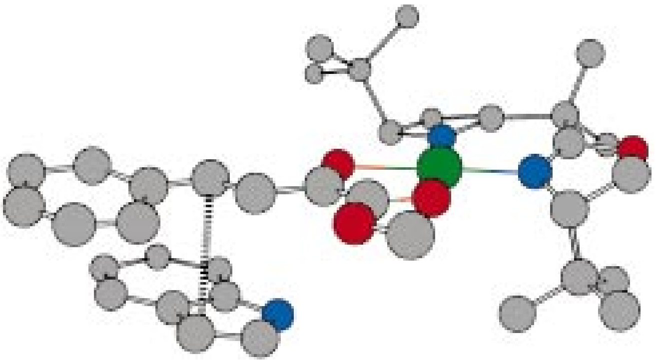


Figure 2. A model for the approach of indole to the β,γ-unsaturated α-ketoester **2a** coordinated to (*S*)-**4a** in a square-planar fashion. This model can account for the absolute configuration of the formed Friedel–Crafts product **3d**. Color scheme: gray = carbon, red = oxygen, green = copper, blue = nitrogen.

unsaturated α-ketoester coordinated to the chiral [{(*S*)-*t*Bu-BOX}Cu(OTf)$_2$] ((*S*)-**4a**) catalyst is shown. This approach can account for the absolute configuration of the product obtained, but at the present stage of investigations we do not fully understand which orientation the incoming aromatic compound has relative to the intermediate.

We have developed a highly catalytic enantioselective reaction for the addition of aromatic C–H bonds to β,γ-unsaturated α-ketoesters catalyzed by chiral bisoxazoline–copper(II) complexes. This new reaction, which is shown to be useful for the reaction of heteroaromatic and aromatic compounds with β,γ-unsaturated α-ketoesters having alkyl, aromatic, and protected alcohols as alkene substituents, is a simple and attractive method for the formation of optically active Friedel–Crafts alkylation compounds from easily available starting materials.

Received: September 22, 2000 [Z15848]

---

[1] For reviews of Friedel–Crafts alkylation reactions, see, for example: a) "Friedel–Crafts Alkylation": G. A. Olah, R. Krishnamurit, G. K. S. Prakash in *Comprehensive Organic Synthesic*, *Vol. 3* (Ed.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 293–339; b) R. M. Roberts, A. A. Khalaf, *Friedel–Crafts Alkylation Chemistry: A Century of Discovery*, Marcel Dekker, New York, **1984**; c) G. A. Olah, *Friedel–Crafts and Related Reactions*, *Vol. 2*, Wiley-Interscience, New York, **1964**, Part 1.

[2] a) F. Bigi, G. Casiraghi, G. Casnati, G. Sartori, G. Gasparri Fava, M. F. Belicchi, *J. Org. Chem.* **1985**, *50*, 5018; b) A. Ishii, V. A. Soloshonok, K. Mikami, *J. Org. Chem.* **2000**, *65*, 1597; c) A. Ishii, K. Mikami, *J. Fluorine Chem.* **1999**, *97*, 51.

[3] a) G. Erker, A. A. H. van der Zeijden, *Angew. Chem.* **1990**, *102*, 545; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 512; b) N. Gathergood, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2000**, *122*, 12517; c) N. Gathergood, W. Zhuang, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.*, in press.

[4] a) M. Johannsen, *Chem. Commun.* **1999**, 2233; b) S. Saaby, X. Fang, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 4280; *Angew. Chem. Int. Ed.* **2000**, *39*, 4114.

[5] See also, for example: a) T. Tsuchimoto, K. Tobita, T. Hiyama, S.-I. Fukuzawa, *J. Org. Chem.* **1997**, *62*, 6997; b) C. E. Song, W. H. Shim, E. J. Roh, J. H. Choi, *Chem. Commun.* **2000**, 1695; c) V. J. Bulbule, V. H. Deshpande, A. V. Bedekar, *J. Chem. Res. (S)* **2000**, 220.

[6] For reviews of C$_2$-bisoxazoline/Lewis acid complexes as catalysts, see, for example: a) A. K. Ghosh, P. Mathivanan, J Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1; b) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain, J. Thorhauge, *Acc. Chem. Res.* **1999**, *32*, 605; c) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325; d) K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 3558; *Angew. Chem. Int. Ed.* **2000**, *39*, 3702.

[7] For the use of these β,γ-unsaturated α-ketoesters in hetero-Diels–Alder reactions catalyzed by C$_2$-bisoxazoline–copper(II) complexes, see: a) J. Thorhauge, M. Johannsen, K. A. Jørgensen, *Angew. Chem.* **1998**, *110*, 2543; *Angew. Chem. Int. Ed.* **1998**, *37*, 2404; b) D. A. Evans, E. J. Olhava, J. S. Johnson, J. M. Janey, *Angew. Chem.* **1998**, *110*, 3554; *Angew. Chem. Int. Ed.* **1998**, *37*, 3373; c) D. A. Evans, J. S. Johnson, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635; d) W. Zhuang, J. Thorhauge, K. A. Jørgensen, *Chem. Commun.* **2000**, 459; e) H. Audrian, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2000**, *65*, 4497.

[8] For a discussion of this reversal enantioselectivity observed in other reactions catalyzed by C$_2$-bisoxazoline/Lewis acid complexes, see refs. [6b–d].

[9] The reaction takes place exclusively at the 3-position of the indole.

[10] The reactions give exclusively the 2-substituted 5-methylfurans.