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Enantioselective Friedel–Crafts Alkylation of *N*-Methylindoles with Nitroalkenes Catalyzed by Chiral Bifunctional Abietic-Acid-Derived Thiourea-Zn^{II} Complexes

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The catalytic asymmetric Friedel–Crafts alkylation of *N*-methylindoles with nitroalkenes catalyzed by bifunctional abietic-acid-derived thiourea-Zn^{II} complexes was investigated. Various types of the nitroalkylated indoles were synthesized under mild conditions and obtained with excellent yields (up to 99%) and good enantioselectivities (up to 86% *ee*). These chiral thiourea catalysts are easily available from the commercial abietic acid.

Introduction

The Friedel–Crafts alkylation[1] of indoles with nitroalkenes is one of the most powerful and classical approaches to carbon–carbon bond formation in asymmetric synthesis and has become a matter of current interest.[2] As one of the most ubiquitous scaffolds, the indole skeleton is widely distributed in a number of natural products and pharmaceutical molecules, agrochemicals, and functional materials.[3] Furthermore, nitroalkenes are very attractive Michael acceptors,[4] and their adducts are amenable to transformation into a wide range of valuable synthetic building blocks.[5] Due to the usefulness of nitroalkylated indole compounds, the development of new strategies to synthesize indole derivatives remains a challenging topic.

Over the past two decades, many types of chiral thiourea catalysts,[6] especially bifunctional thiourea catalysts,[6a,7] have been designed, synthesized, and emerged for asymmetric catalytic reactions. Naturally available commercial abietic acid derivatives promise to be marvelous starting materials for preparing chiral ligands because of their absolute optical purities and very stable stereochemistry structures. In our previous works, we have reported that abietic acid derivatives have been used in the separations of D/L amino acids by capillary electrophoresis.[8] Furthermore, our current study has shown that crown ethers based on abietic acid are highly efficient in chiral recognition.[9] Encouraged by the successful use of abietic acid derivatives, we speculated that the strategy of modifying its functional groups might be additionally exploited to design a new class of chiral thiourea catalysts for Friedel–Crafts reactions.

Extensive studies on the Friedel–Crafts reaction of indoles with nitroalkenes have been well documented, however, the reaction between nitroalkenes and *N*-blocked indoles has only been explored with very limited success. Previous efforts by Connon[10] and Jørgensen[11] used a chiral bis-arylthiourea catalyst and a chiral bis-sulfonamide catalyst to improve the reaction between challenging substrates such as *N*-methylindole and nitroalkenes. However, only moderate yields and enantioselectivities (up to 91% and 50% *ee*, respectively) were obtained and long reaction times (up to 287 h and 60 h, respectively) and low temperatures (–30 °C and –24 °C, respectively) were required with the above catalysts. Recently, Wan and coworkers[2d] investigated a bis-sulfonamide diamine–Cu(OTf)$_2$ complex for the Friedel–Crafts alkylation of indole with nitroalkenes, affording excellent yields and enantioselectivities except in the case of substrates of *N*-methylindole (51% yield, 17% *ee*), which suggests that *N*-blocked indole was not an effective substrate in the catalytic system. Moreover, Du and coworkers[12] have developed a more practical and efficient catalytic asymmetric Friedel–Crafts alkylation of indole derivatives with nitroalkenes using a bifunctional tridentate bis(oxazoline)–Zn(OTf)$_2$ catalyst. However, the search for new catalysts for this reaction is still challenging and desirable, and to the best of our knowledge, there is no report on the Friedel–Crafts alkylation of indole with nitroalkene catalyzed by primary amine–thiourea catalysts. Herein, we first report the synthesis of chiral thiourea bifunctional

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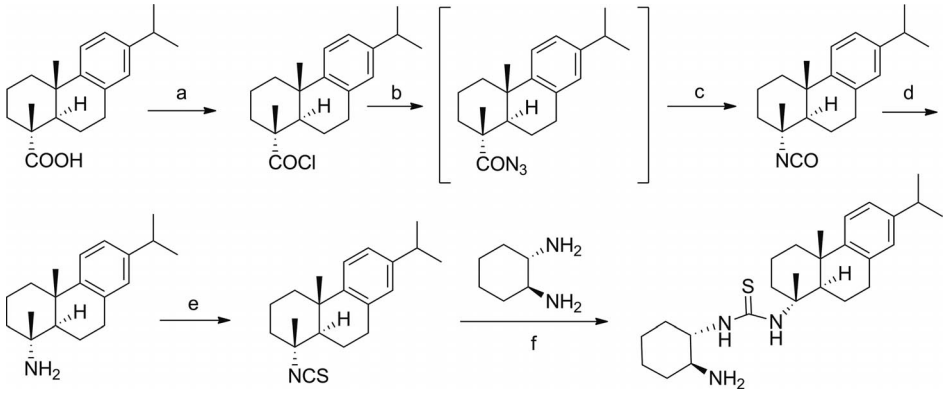
based on abietic acid and their metal complexes as catalysts, and aim to expand the applications of abietic acid derivatives and promote the asymmetric Friedel–Crafts alkylation of *N*-methylindole with nitroalkenes under mild conditions.

Results and Discussion

Initially, our attention was especially focused on abietic-acid-derived thioureas containing a primary amine[13] or amino alcohol[14] moiety as bifunctional catalysts. As shown in Scheme 1, starting from commercially available natural abietic acid derivatives, nordehydroabietic isothiocyanate (NDHAIC) was designed, and we first synthesized a novel primary amine-thiourea bifunctional catalyst **L3** by condensation of the chiral (*S*,*S*)-1,2-diaminocyclohexane with NDHAIC. Using the same procedure, thiourea catalysts **L1**, **L2**, and **L4**–**L7** were also synthesized[15] (Figure 1) and evaluated as chiral catalysts for the asymmetric Friedel–Crafts alkylation of *N*-methylindole with nitroalkenes; the results are summarized in Table 1.

We firstly examined the reaction between *N*-methylindole and nitrostyrene with 10 mol-% of thiourea catalysts **L1**–**L7** in toluene at room temperature, however, the reaction proceeded slowly in low yields (16–53%) after 48 h and the enantiomeric excess of the product was zero or negligible. Inspired by the ability of a metal complex and an organic molecule to cooperatively catalyze an asymmetric reaction,[2a–2c,12a–12c] we employed $Zn(OTf)_2$ as a Lewis acid. To our delight, in the presence of 10 mol-% of $Zn(OTf)_2$, indole reacted smoothly with nitrostyrene (Table 1, Entries 1–7), giving the product **3a** in high yields (up to 99%) and with good enantioselectivities (up to 78%). In particular, **L3** was found to be the best choice of catalyst and gave a fast reaction (within 5 h) and excellent yield (99%) (Table 1, Entry 3). These results indicated that $Zn(OTf)_2$ might efficiently coordinate with bifunctional thiourea catalysts. Notably, catalysts **L1**–**L4**, which contain a primary amine moiety, could obtain higher yields and required shorter reaction times than those of **L5**–**L7** (Table 1, Entries 1–4 vs. Entries 5–7).



Scheme 1. Preparation of abietic-acid-derived thiourea catalysts. Reagents and conditions: (a) $SOCl_2$, dry dichloromethane (DCM), 8 h, 95%; (b) NaN_3, H_2O; (c) 100 °C; (d) HCl, NaOH, toluene, 24 h, 72%; (e) CS_2, *N*,*N*′-dicyclohexylcarbodiimide (DCC), dry Et_2O, 15 h, 92%; (f) CH_2Cl_2, 16 h, 75%.

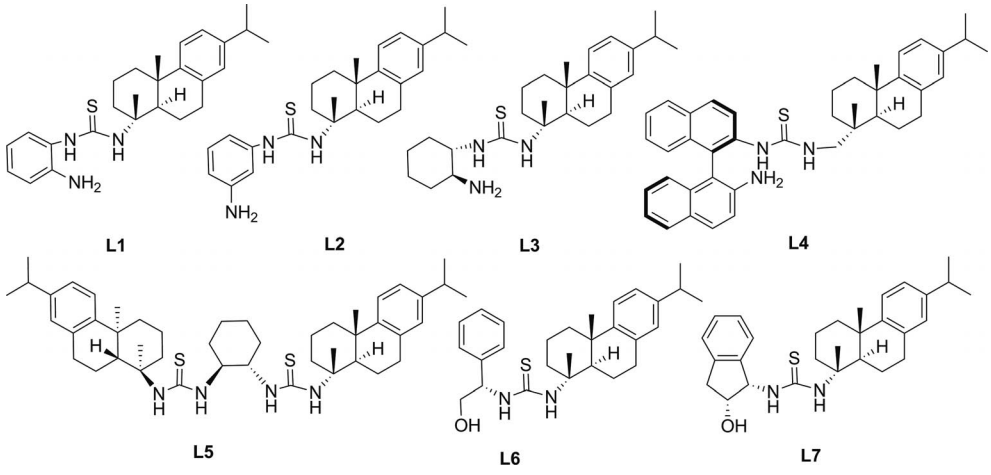
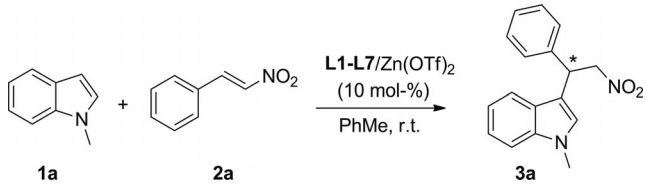


Figure 1. Chiral thiourea bifunctional catalysts used in this study.

Table 1. The application of ligands **L1**–**L7**/$Zn(OTf)_2$ in the asymmetric Friedel–Crafts alkylation of indole **1a** with nitrostyrene **2a**.[a]



1a **2a** **3a**

Entry	Ligand	Time [h]	Yield [%][b]	*ee* [%][c]
1	**L1**	7	98	4 (*S*)
2	**L2**	6.5	98	5 (*S*)
3	**L3**	5	99	78 (*R*)
4	**L4**	6	98	2 (*R*)
5	**L5**	24	76	5 (*S*)
6	**L6**	24	71	2 (*S*)
7	**L7**	24	86	12 (*S*)

[a] Reaction conditions: indole **1a** (0.75 mmol) with nitrostyrene **2a** (0.50 mmol) in 2 mL of toluene using 10 mol-% **L1**–**L7** and 10 mol-% $Zn(OTf)_2$ as the catalyst at room temp. [b] Isolated yield. [c] The *ee* values were determined by HPLC with a Daicel Chiracel AS-H column (hexane/2-propanol = 90:10, 1.0 mL/min), and the configuration was assigned by comparison of the HPLC data and specific rotation with literature data.[12a]

Having identified the best catalyst (**L3**) for the conjugate addition, we further screened different metal salts, solvents, temperature, and catalyst loading. As shown in Table 2, among the Lewis acids used, $Zn(OTf)_2$ gave the best result (Table 2, Entry 6). On the contrary, when other metallic triflate salts (Entries 1–5) or other zinc metal Lewis acids (Entries 7 and 8) were employed as a Lewis acid in situ with **L3**, the results were not satisfactory.

Table 2. Asymmetric Friedel–Crafts alkylation of indole **1a** with nitrostyrene **2a** catalyzed by chiral **L3**-Lewis acid complexes.[a]

Entry	Lewis acid	Time [h]	Yield [%][b]	*ee* [%][c]
1	$Fe(OTf)_3$	24	86	0
2	$Cu(OTf)_2$	24	75	6
3	AgOTf	24	83	1
4	$Bi(OTf)_3$	12	98	2
5	$Sc(OTf)_3$	9	99	8
6	$Zn(OTf)_2$	5	99	78
7	$Zn(OAc)_2$	24	trace	n.d.[d]
8	$ZnCl_2$	24	48	5

[a] Reaction conditions: indole **1a** (0.75 mmol) with nitrostyrene **2a** (0.50 mmol) in 2 mL of toluene using 10 mol-% **L3** and 10 mol-% Lewis acid as the catalyst at room temp. [b] Isolated yield. [c] Determined by HPLC with a Daicel Chiracel AS-H column (hexane/2-propanol = 90:10, 1.0 mL/min). [d] n.d.: not determined.

Besides toluene, other solvents such as ethyl acetate, chloroform, dichloromethane, tetrahydrofuran and chlorobenzene were screened, and the results showed that toluene was the best choice (Table 3, Entry 1).

As shown in Table 3, increasing the temperature evidently increased the reaction rate (Entries 7–11). Notably, nitrostyrene was almost completely converted to adduct at 45 °C after just 1.5 h. When the reaction was performed at 35 °C, the best result was obtained (Entry 10). Furthermore, with a catalyst loading of 5 or 20 mol-%, the result did not show any beneficial effect to this reaction (Entries 12 and 13). Therefore, we finally determined that using 10 mol-% **L3**/$Zn(OTf)_2$ in toluene at 35 °C to catalyze the reaction was the most efficient.

Table 3. Effect of ligands in the $Zn(OTf)_2$-catalyzed Friedel–Crafts alkylation of indole **1a** with nitrostyrene **2a**.[a]

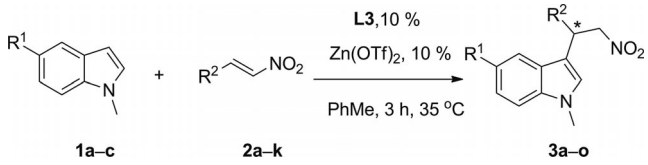
Entry	Solvent	*T* [°C]	Cat. [mol-%]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	toluene	r.t.	10	5	99	78
2	EtOAc	r.t.	10	7	98	0
3	$CHCl_3$	r.t.	10	6.5	98	8
4	DCM	r.t.	10	5	97	53
5	THF	r.t.	10	5	96	7
6	PhCl	r.t.	10	9	98	48
7	toluene	–20	10	24	0	n.d.
8	toluene	0	10	24	trace	n.d.
9	toluene	20	10	8	98	73
10	toluene	35	10	2	99	80
11	toluene	45	10	1.5	99	76
12	toluene	35	5	10	98	72
13	toluene	35	20	2	99	81

[a] Reaction conditions: indole **1a** (0.75 mmol) with nitrostyrene **2a** (0.50 mmol) in toluene (2 mL) using 10 mol-% **L3**/$Zn(OTf)_2$ complex as the catalyst. [b] Isolated yield. [c] Determined by HPLC with a Daicel Chiracel AS-H column (hexane/2-propanol = 90:10, 1.0 mL/min).

In order to extend the scope of the reaction, a wide range of nitroalkenes and *N*-methylindoles were catalyzed by the **L3**/$Zn(OTf)_2$ complexes under the optimized reaction conditions (Table 4). In most cases, excellent yields and good *ee* values were obtained for the corresponding products (up to 99% yield and 86% *ee*). As summarized in Table 4, the electronic effects were almost negligible, i.e., the electron-withdrawing systems (Table 4, Entries 2–5) reacted smoothly, as well as the electron-donating (Table 4, Entries 6–8) and neutral systems (Table 4, Entry 1). A heteroaromatic nitroalkene was also found to react successfully with *N*-methylindole to generate adduct **3j** in 99% yield and 79% *ee* (Table 4, Entry 10). Furthermore, a nitroalkene bearing a polycyclic aromatic substituent, 2-naphthylnitroalkene, was treated with *N*-methylindole to give the corresponding product in excellent yields and good enantioselectivities (Table 4, Entries 11 and 15). The nitroalkene derived from 1,3-benzodioxole also gave the adduct in 76% *ee* (Table 4, Entry 9). However, due to steric hindrance on *ortho* substitution of the phenyl group of aromatic nitroalkenes, this catalytic system also suffered from lower enantioselectivities. For example, 2-methoxy-substituted aromatic nitroalkene and 2-fluoro-substituted aromatic nitroalkene were treated with *N*-methylindole to afford the desired products in high yields but only 30% and 16% *ee*, respectively (Table 4, Entries 16 and 17). Furthermore, the substituent effects of *N*-methylindole were also examined (Table 4, Entries 12–15). The electronic properties of the 5-substituent of *N*-methylindole had little effect on this reaction, and the yields and *ee* values were relatively decreased (96–98% yields and 70–72% *ee*). Meanwhile, we also tried other *N*-blocked indole derivatives such as *N*-benzylindole, and found that it could successfully react with nitroalkene

in 98% yield and 41% *ee* (Table 4, Entry 18). However, the reaction was attempted with some nitroalkenes bearing alkyl groups R that reacted with low yield and *ee*.

Table 4. Friedel–Crafts alkylation of indoles **1** with nitroalkene **2** catalyzed by **L3**/$Zn(OTf)_2$ complexes.[a]



Entry	R^1	R^2	Yield [%][b]	*ee* [%][c]
1	H	Ph	99 (**3a**)	80
2	H	4-FPh	99 (**3b**)	79
3	H	4-ClPh	99 (**3c**)	80
4	H	3-ClPh	98 (**3d**)	79
5	H	4-BrPh	99 (**3e**)	81
6	H	4-MeOPh	99 (**3f**)	76
7	H	3-MeOPh	99 (**3g**)	86
8	H	4-MePh	99 (**3h**)	82
9	H	benzodioxolyl	96 (**3i**)	76
10	H	2-thienyl	99 (**3j**)	79
11	H	2-naphthyl	99 (**3k**)	81
12	MeO	Ph	96 (**3l**)	70
13	MeO	4-ClPh	97 (**3m**)	71
14	MeO	4-BrPh	98 (**3n**)	72
15	Br	2-naphthyl	98 (**3o**)	72
16[d]	H	2-FPh	93 (**3p**)	16
17[d]	H	2-MeOPh	91 (**3q**)	30
18[e]	H	Ph	98 (**3r**)	41

[a] Reaction conditions: indole **1** (0.75 mmol) with nitroalkene **2** (0.50 mmol) in toluene (2 mL) using 10 mol-% **L3**/$Zn(OTf)_2$ complexes as the catalyst at 35 °C for 3 h. [b] Isolated yield. [c] Determined by HPLC with a Daicel Chiracel AS-H column (hexane/2-propanol = 90:10, 1.0 mL/min). [d] Reaction time: 10 h. [e] Reaction conditions: *N*-benzyl indole (0.75 mmol) with nitrostyrene (0.50 mmol) in toluene (2 mL) using 10 mol-% **L3**/$Zn(OTf)_2$ complexes as the catalyst at 45 °C for 8 h.

Conclusions

We have developed a novel and efficient catalytic asymmetric Friedel–Crafts alkylation of *N*-methylindole with a variety of nitroalkenes using bifunctional abietic-acid-derived thiourea **L3**/$Zn(OTf)_2$ complexes as catalyst, which gives high yields (up to 99%) and good enantioselectivities (up to 86%) for a wide range of aromatic nitroalkenes under mild conditions. Further exploration of the mechanism and application of the chiral thiourea catalysts to other asymmetric reactions are in progress in our laboratory.

Experimental Sections

General Procedure for the Synthesis of Chiral Thiourea: Using the reported procedures,[14a,16] pure nordehydroabietic amine (NDHAA) was obtained as a white solid in 72% yield. Carbon disulfide (15 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (10 mmol) were added to a solution of NDHAA (10 mmol) in dry ether (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then warmed slowly to room temperature and stirred at room temperature overnight. After evaporation of the solvent, the residue was dissolved in hexane, and the precipitate was collected by filtration. Subsequently, the residue was purified through column chromatography on silica gel (eluent, hexane) to give nordehydroabietic isothiocyanate (NDHAIC) as a yellow oil (92% yield). Then NDHAIC (5 mmol, 1.57 g) was added over a period of 1.5 h to a stirred solution of (*S*,*S*)-1,2-diaminocyclohexane (5 mmol, 0.57 g) in dry dichloromethane (40 mL). The reaction mixture was stirred for a further 15 h at room temperature. The solvent was removed under reduced pressure. After column chromatography on silica gel (eluent, ethyl acetate/MeOH = 6:1), the product **L3** was obtained as a white solid in 75% yield.

1-[(1*S*,2*S*)-2-Aminocyclohexyl]-3-[(1*R*,4a*S*,10a*R*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl]thiourea (L3): White solid, m.p. 108–110 °C; 75% yield. $[a]_D^{20}$ = –80.1 (*c* = 1.02, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 6.88 (s, 1 H), 5.66 (br., 1 H), 2.97–2.86 (m, 2 H), 2.85–2.76 (m, 1 H), 2.69 (br., 1 H), 2.52 (sep, *J* = 7.0 Hz, 1 H), 2.26 (d, *J* = 12.5 Hz, 2 H), 2.03 (d, *J* = 5.5 Hz, 1 H), 2.00–1.89 (m, 2 H), 1.88–1.78 (m, 2 H), 1.78–1.65 (m, 4 H), 1.64–1.35 (m, 7 H), 1.35–1.04 (m, 14 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 181.4, 146.5, 145.7, 134.3, 126.9, 124.4, 124.1, 63.0, 59.7, 56.5, 48.9, 38.4, 37.6, 37.3, 34.7, 33.4, 32.2, 30.4, 25.3, 24.9, 24.6, 23.9, 23.9, 19.5, 19.3 ppm. IR: $\tilde{\nu}$ = 3269, 2929, 2862, 1531, 1495, 1382, 1336, 1235, 1103, 908, 820.751, 626 cm^{-1}. HRMS (ESI): $C_{26}H_{41}N_3S$ $[M - H]^+$ calcd. 426.29429; found 426.29430.

Typical Procedure for the Catalytic Asymmetric Friedel–Crafts Reaction: To a dried Schlenk tube were added $Zn(OTf)_2$ (18.6 mg, 0.05 mmol) and **L3** (21.4 mg, 0.05 mmol) under a N_2 atmosphere, followed by toluene (2 mL). The solution was stirred at 35 °C for 1 h under a N_2 atmosphere, and the nitroalkene **1a** (75 mg, 0.50 mmol) was added followed by *N*-methylindole (**2a**) (100 mg, 0.75 mmol). After 3 h, the solvent was removed under vacuum, and the residue was chromatographed on a silica gel column with ethyl acetate/hexane (1:8, *v*/*v*) to afford pure **3a**. Colorless oil; yield 99%. $[a]_D^{20}$ = –20.4 (*c* = 1.20, CH_2Cl_2); *ee* was determined by HPLC analysis (Chiralcel AS-H, *i*PrOH/hexane = 10:90, 1.0 mL/min, 254 nm): retention times t_{minor} = 22.49 min, t_{major} = 16.98 min, *ee* = 80%.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization data for chiral catalysts and HPLC chromatograms for all final products.

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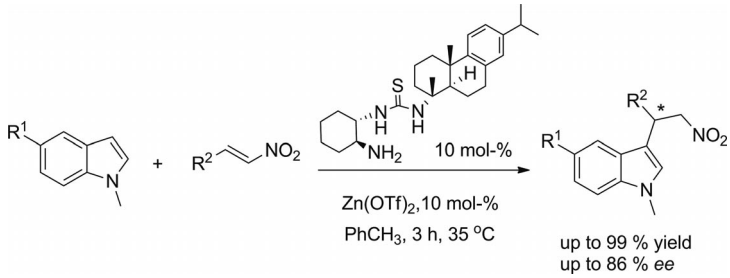

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Enantioselective Friedel–Crafts Alkylation of *N*-Methylindoles with Nitroalkenes Catalyzed by Chiral Bifunctional Abietic-Acid-Derived Thiourea-Zn^{II} Complexes

The catalytic asymmetric Friedel–Crafts alkylation of *N*-methylindoles with nitroalkenes catalyzed by abietic-acid-derived thiourea-Zn^{II} complexes was investigated. Nitroalkylated indoles were synthesized in excellent yields (up to 99%) and good enantioselectivities (up to 86% *ee*) under mild conditions. These chiral thiourea catalysts are easily available from the commercial abietic acid.

Keywords: Asymmetric synthesis / C–C coupling / Friedel–Crafts alkylation / Zinc / Aromatic substitution / Nitroalkenes

