Synthesis of Cyclopropane-containing Building Blocks via Ir-Catalyzed Enantioselective Allylic Substitution Reaction†

Xia, Jibao(夏纪宝) Zhuo, Chunxiang(卓春祥) You, Shuli(游书力)

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Chiral cyclopropane-containing building blocks, which are very important synthetic intermediates for natural products or pharmaceuticals, were easily synthesized via Ir-catalyzed enantioselective allylic substitution reaction.

Keywords iridium, asymmetric catalysis, allylic alkylation, allylic amination, regioselectivity

Introduction

Cyclopropane subunit occurs in many pharmaceuticals and natural products that show bioactivities.[1] For example, chromene-typed compound **A**, which bears a cycolpropyl group, has been reported to have submicromolar activities against pathogenic microorganisms such as *Staphylococcus aureus* and *Pseudomonas carinii* (Figure 1).[2] Recently, a series of cyclopropane-containing corticotropin-releasing factor-1 (CRF1) receptor antagonists, which showed important biological activities, were synthesized by Bristol-Myers Squibb.[3] Consequently, the synthesis of enantiopure cyclopropane-containing compounds **I** is highly desirable (Scheme 1). The enantiopure **I** (X＝NH_2 or NHBn) could be obtained by resolution.[4] Alternatively, there were reports on the synthesis of enantiopure **I** (X＝NH_2) employing chiral auxiliary.[5] To our knowledge, the catalytic asymmetric methods for the synthesis of enantiopure cyclopropane-containing compounds **I** are rare.

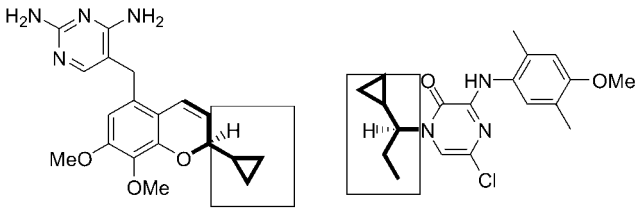
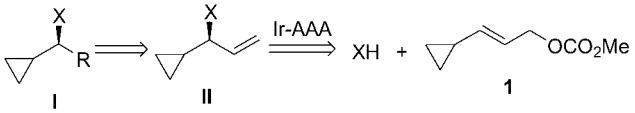


Figure 1 Cylcopropane-containing biologically important compounds.

Results and discussion

Ir-catalyzed asymmetric allylic substitution reactions have been studied extensively in the past decade.[6,7] Recently, studies by Hartwig *et al.* and Helmchen *et al.* demonstrated the cyclometallated iridium as the active catalytic species.[8] With this catalytic system, we envisaged that the use of (*E*)-3-cyclopropylallyl methyl carbonate **1** as substrate could afford the enantioenriched cyclopropane-containing compounds **II** with XH as versatile nucleophiles (Scheme 1). Herein, we report our studies on the Ir-catalyzed enantioselective synthesis of cyclopropane-containing compounds **II**, which are very useful building blocks for construction of complicated molecules.

Scheme 1 Synthesis of cyclopropane-containing **II** via Ir-catalyzed asymmetric allylic substitution reaction



The Ir-catalyzed enantioselective allylic alkylation of sodium dimethyl malonate to methyl carbonate **1** was first investigated. Excellent regioselectivity (91/9) and enantioselectivity (95% *ee*) were obtained using ligand **L1** (Table 1, Entry 1). Superior results were obtained when ligand **L2** was used. The branched alkylation product **2a** was obtained in 90% isolated yield with improved regioselectivity (96/4) and excellent enantioselectivity (99% *ee*) (Table 1, Entry 2). Under the modified conditions, sodium diethyl malonate and sodium diisopropyl malonate were also investigated and good results were obtained (Table 1, Entries 3 and 4). In the case of product **2c**, the *ee* value was underestimated due to the difficulty in chiral HPLC separation.

Next, the Ir-catalyzed enantioselective allylic amination of phthalimide was investigated.[9] Several bases were investigated based on previous optimal conditions (Table 2, Entries 1—3). The highest *ee* of 95% was ob-

* E-mail: slyou@mail.sioc.ac.cn
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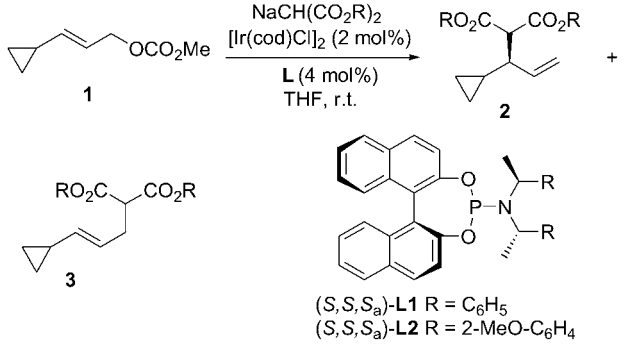
Table 1 Ir-catalyzed asymmetric allylic alkylation

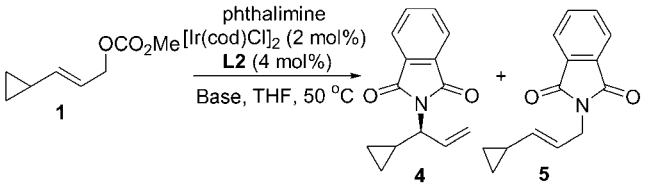


Entry	R	L	*t*/h	Conv.[c]/%	2	Yield[b]/%	2/3[c]	*ee*[d]/%
1	Me	**L1**	48	88	**2a**	86	91/9	95
2	Me	**L2**	48	>99	**2a**	90	96/4	98
3	Et	**L2**	12	>99	**2b**	92	97/3	98
4	*i*-Pr	**L2**	24	96	**2c**	86	95/5	>86

[a] **1** (0.2 mol•L^{-1}) in THF with the following molar ratio: *n*(**1**) : *n*(NaCH(CO$_2$R)$_2$) : *n*([Ir(cod)Cl]$_2$) : *n*(**L**) = 1 : 1.5 : 0.02 : 0.04. [b] Isolated yield of **2**. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Determined by chiral HPLC analysis.

tained using DBU as base, although the reaction was sluggish at room temperature (Table 2, Entry 3). This issue was successfully addressed when the reaction was carried out at 50 ℃ (Table 2, Entry 5). The allylic amination product **4** was obtained in 77% yield with good regioselectivity (85/15) and excellent enantioselectivity (97% *ee*).

Table 2 Ir-catalyzed asymmetric allylic amination with phthalimide[a]

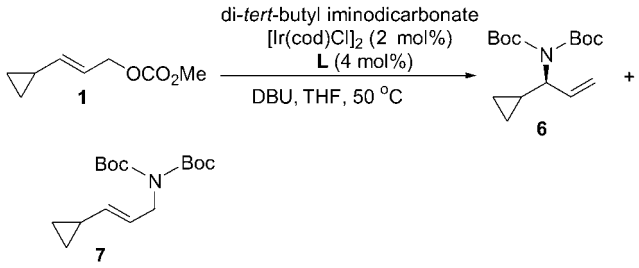


Entry	Base	*T*/℃	*t*/h	Conv.[b]/%	Yield[c]/%	4/5[b]	*ee*[d]/%
1	Et_3N	r.t.	74	79	43	84/16	93
2	DABCO	r.t.	48	<10	5	—	90
3	DBU	r.t.	48	14	5	—	95
4	DABCO	50	2	>99	79	84/16	84
5	DBU	50	12	>99	77 (11)	85/15	97

[a] **1** (0.2 mol•L^{-1}) in THF with the following molar ratio: *n*(**1**) : *n*(NuH) : *n*([Ir(cod)Cl]$_2$) : *n*(**L2**) : *n*(base) = 1 : 1.2 : 0.02 : 0.04 : 1. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Isolated yield of **4**, the number in the parenthesis indicates the yield of linear product **5**. [d] Determined by chiral HPLC analysis.

Ir-catalyzed enantioselective allylic amination of di-*tert*-butyl iminodicarbonate was also investigated. Employing Han's reaction conditions,[10] allylic amination product **6** was obtained in 67% yield with good regioselectivity (83/17) and enantioselectivity (97% *ee*) (Table 3, Entry 5).

Table 3 Ir-catalyzed asymmetric allylic amination with di-*tert*-butyl iminodicarbonate[a]

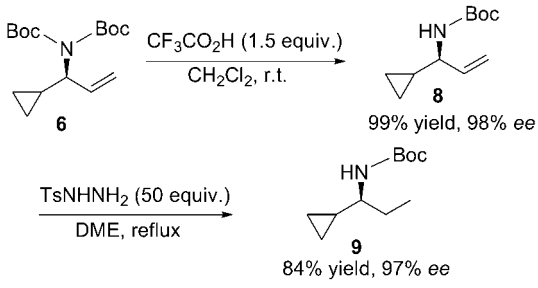


Entry	L	DBU/equiv.	*T*/℃	*t*/h	Conv.[c]/%	Yield[d]/%	6/7[c]	*ee*[e]/%
1[b]	**L1**	1	r.t.	72	<5	—	—	—
2[b]	**L2**	1	r.t.	48	52	37	92/8	—
3[b]	**L2**	1	50	48	73	—	88/12	—
4	**L2**	1	r.t.	48	67	40	87/13	—
5	**L2**	0.2	50	5	>99	67 (10)	83/17	98

[a] **1** (0.2 mol•L^{-1}) in THF with the following molar ratio: *n*(**1**) : *n*(NuH) : *n*([Ir(cod)Cl]$_2$) : *n*(**L**) = 1 : 1.2 : 0.02 : 0.04. [b] The precatalyst was activated with *n*-PrNH$_2$. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Isolated yield of **6**, the number in the parenthesis indicates the yield of linear product **7**. [e] Determined by chiral HPLC analysis after transformed into **8**.

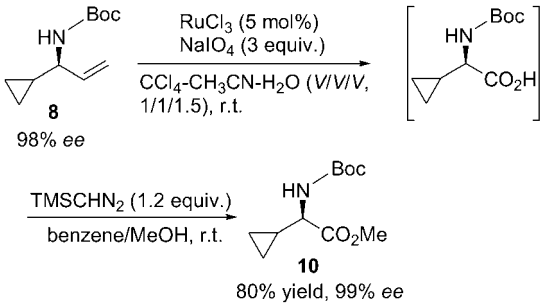
Selective deprotection of one Boc group of **6** was accomplished upon the treatment with TFA in CH_2Cl_2 (Scheme 2). The *N*-Boc protected product **8** was obtained in 99% yield with 98% *ee*. Compound **8** was then readily hydrogenated with $TsNHNH_2$ in refluxed DME to afford compound **9** in good yield without notable loss of optical purity.

Scheme 2



To explore the synthetic utility, the enantiopure *N*-Boc protected **8** was converted to its corresponding α-amino acid through oxidative cleavage by $RuCl_3$ and $NaIO_4$. The crude α-amino acid was then directly transformed into the corresponding ester **10** using $TMSCHN_2$ in mixed solvent of benzene and methanol (Scheme 3).

Scheme 3



Conclusions

In conclusion, cyclopropane-containing enantiopure compounds were easily synthesized via Ir-catalyzed asymmetric allylic substitution reaction. These allylic substitution products have been demonstrated important synthetic intermediates.

Experimental section

General methods

All manipulations were carried out under the argon atmosphere using standard Schlenk techniques. All glassware was oven or flame dried immediately prior to use. All solvents were purified and dried according to standard methods prior to use, unless stated otherwise. All reagents were obtained from commercial sources and used without further purification. ^{1}H NMR spectra were obtained at 300 MHz or 400 MHz and recorded relative to tetramethylsilane signal or residual protio-solvent. ^{13}C NMR spectra were obtained at 75 or 100 MHz, and chemical shifts were recorded relative to the solvent resonance ($CDCl_3$, δ 77.0). ^{19}F NMR spectra were obtained at 282 MHz or 376 MHz, and CF_3CO_2H was used as internal standard. Data for ^{1}H NMR are recorded as follows: chemical shift (δ), multiplicity (s＝singlet, d＝doublet, t＝triplet, m＝multiplet or unresolved, br＝broad singlet, coupling constant (J) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ).

General procedure for Ir-catalyzed asymmetric allylic alkylation reaction

Sodium dimethyl malonate was prepared as follows: NaH (96%, 19.0 mg, 0.75 mmol) was rinsed with *n*-pentane (5 mL×2), followed by dry THF (4 mL), and then suspended in dry THF (2 mL). Dimethyl malonate was then added dropwise under nitrogen and stirred at room temperature to afford a colorless solution, which was immediately used. $[Ir(cod)Cl]_2$ (6.7 mg, 0.01 mmol, 2 mol%), phosphoramidite ligand **L2** (12.0 mg, 0.02 mmol, 4 mol%) were dissolved in THF (0.5 mL) and propylamine (0.3 mL) in a dry Schlenk tube filled with argon. The reaction mixture was heated at 50 ℃ for 30 min and then the volatile solvents were removed under vacuum to give a yellow solid. After that, THF (0.5 mL) and (*E*)-3-cyclopropylallyl methyl carbonate **1** (78.1 mg, 0.50 mmol) were added. Then, the freshly prepared sodium dimethyl malonate (0.75 mmol in 2 mL THF) was added. The reaction was stirred at room temperature until the carbonate was fully consumed, monitored by TLC or ^{1}H NMR. Then the crude reaction mixture was filtrated through a pad of celite and washed with CH_2Cl_2, the solvent was removed under reduced pressure. The ratio of regioisomers (branched to linear) was determined by ^{1}H NMR of the crude reaction mixture. The crude residue was purified by flash column chromatography (ethyl acetate/petroleum ether) to afford the desired branched allylic product **2**.

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