



Catalytic addition of alkenylzirconocene chloride to 3,4-dihydroisoquinoline and its enantioselective reaction

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ABSTRACT

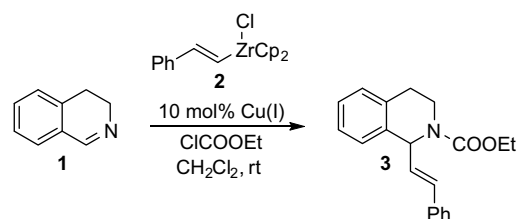
The addition of alkenylzirconocene chloride to 3,4-dihydroisoquinoline in the presence of a stoichiometric amount of acylating agent such as (Boc)₂O or ClCOOEt was carried out in the presence of a catalytic amount of Cu(I) (10 mol %) to give an alkenylation–carbamation product. The enantioselective addition (56–75% ee) of the alkenylzirconocene chloride was also achieved under Cu(I)/chiral amine (10 mol %) conditions.

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1. Introduction

Organozirconocene chloride complexes are readily accessible by the hydrozirconation of unsaturated compounds with Schwartz reagent [Cp₂Zr(H)Cl] or by the treatment of alkenyl halide with Negishi reagent [Cp₂Zr-*n*Bu₂].¹ The poor nucleophilic reactivity of organozirconocene chloride complexes to aldehydes, ketones, and imines, however, has kept them from being used in organic syntheses. Thus, the search for new reactions of organozirconocene complexes for the formation of carbon–carbon bond is significant in terms of chemoselective reactions. Recently, several procedures to attain the nucleophilic reactivity of alkenylzirconocene chloride toward electrophiles have been reported.² Among the procedures, transmetalation of the alkenylzirconocene species have been proven to be an useful procedure for the nucleophilic addition of the alkenyl group of the alkenylzirconocene species.³ The transmetalation of the alkenylzirconocene chloride, however, requires the stoichiometric use of metal salts or organometallics,^{3,4} and therefore we seek a catalytic process for the reaction of the alkenylzirconocene chloride. Previously, we reported that rhodium(I)-catalyzed additions of alkenylzirconocene chloride to *N*-*p*-toluenesulfonyl aldimines proceeded in good yields to give alkenylation products, and the transient generation of an alkenyl-rhodium species as a reactive intermediate through transmetalation was suggested.⁵ Herein, we report the copper(I)-catalyzed addition of alkenylzirconocene chloride to 3,4-dihydroisoquinoline (**1**) in the presence of a stoichiometric amount of acylating agent and the enantioselective formation of 1-alkenyltetrahydroisoquinoline,⁶ which has received considerable attention due to intriguing biological activities (see Scheme 1).⁷

Nucleophilic additions of organometallics to the imine C=N double bond of 3,4-dihydroisoquinoline (**1**) in an enantio- or dia-



Scheme 1.

stereoselective manner would be considered a simple procedure for the preparation of 1-substituted tetrahydroisoquinoline derivatives, and thus, a variety of metallic reagents has been employed for that purpose.^{7a} Typical organometallics such as Grignard or organolithium reagent are often problematic in the tolerability of the functional group due to their high reactivity and strong basicity. To the best of our knowledge, the catalytic enantioselective alkenylation of imine C=N double bond by using alkenylzirconocene chloride has not been reported.⁸ The aforementioned rhodium(I) catalyst did not catalyze the addition of alkenylzirconocene chloride to the aldimines derived from aliphatic amine.⁵

2. Results and discussion

At the outset, we examined the reaction of **1** with (*E*)-styrylzirconocene chloride (**2**) in CH₂Cl₂ at an ambient temperature, and we confirmed that the reaction did not take place. However, premixing a stoichiometric amount of ethyl chloroformate (ClCOOEt) with **1** in CH₂Cl₂ at an ambient temperature for 0.5 h followed by the addition of **2** to the reaction mixture afforded an alkenylation–carbamation product **3** in 36% yield after being stirred at an ambient temperature for 16 h (Table 1, entry 1).

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Table 1
Cu(I)-catalyzed addition of **2** to **1**^a

Entry	Catalyst ^b	Time (h)	Yield ^c (%)
1	None	16	36
2	CuBr	2	68
3	CuCN ^d	2	51
4	CuOTf	2	81
5	[Cu(CH ₃ CN) ₄]PF ₆	2	87
6	[RhCl(cod)] ₂	4	48
7	(CH ₃) ₂ Zn ^e	2	80

^a Ratio of reagents: **1**:[CICOEt]:**2** = 1:1:2.

^b 10 mol %.

^c Isolated yield.

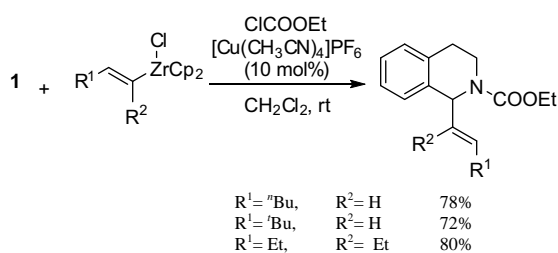
^d 50 mol %.

^e 150 mol %.

A catalytic amount of CuBr (10 mol %) accelerated the reaction, and **3** was obtained in 68% yield in less than 2 h (TLC monitoring) (entry 2).⁹ It turned out that (Boc)₂O, instead of CICOEt, was also an efficient additive for the reaction. It should be mentioned that the CuBr-catalyzed addition of **2** to **1** did not occur in the absence of CICOEt or (Boc)₂O. These observations suggest that the activation of the imine portion by the formation of *N*-acyl iminium ion is essential for the present Cu(I)-catalyzed reaction.¹⁰ Among the examined copper(I) catalysts (entries 2–5), [Cu(CH₃CN)₄]PF₆ indicated notable catalytic efficiency (entry 5). Although the sole use of Rh(I) catalyst did not give a product, the presence of CICOEt showed the formation of **3** (48%) as well (entry 6). The use of a stoichiometric amount of dimethylzinc, transmetalation from Zr to Zn,^{2,3} under otherwise identical conditions gave **3** in 80% yield (entry 7). The Cu(I)-catalyzed addition of alkenylzirconocene chloride to **1** was confirmed to be quite general (Scheme 2). However, the reaction of **1** with 3-phenylpropylzirconocene chloride, which is generated by the hydrozirconation of 3-phenylpropene, did not give an alkylation–acylation product.¹¹

It is worth commenting that the reaction of **2** with heteroaromatic compounds such as quinoline or isoquinoline proceeded efficiently without the use of a Cu(I) catalyst to give alkylation–acylation products at an ambient temperature (Scheme 3). In these reactions, the presence of an acylating agent was also crucial as in the case of the reaction of **1** with **2**, since the absence of ethyl chlorocarbonate did not afford any products.

Based on the described results, we examined the enantioselective alkylation of **1** using **2**, since highly enantioselective additions of organometallics to **1** or related heterocycles have been reported.^{7,12} Results of the examination of chiral amine ligands (10 mol %) under the present Cu(I)-catalyzed conditions are shown in Table 2.¹³ It is important to note that the Cu(I) catalyst affects



Scheme 2.

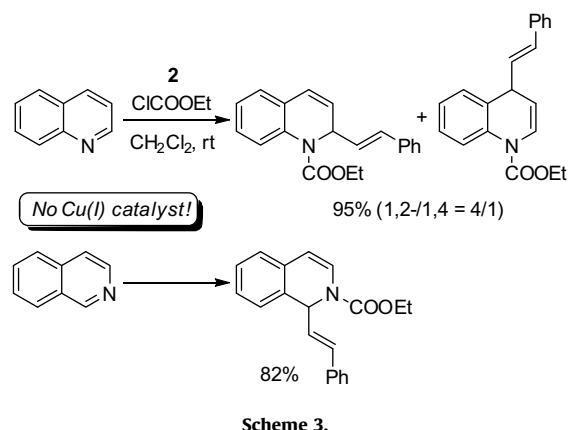
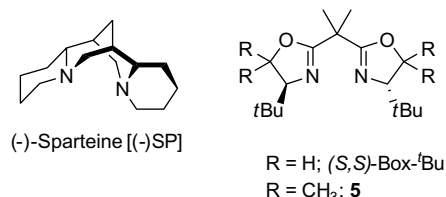


Table 2
CuI-catalyzed addition of **2** to **1**

Entry	Catalyst	Ligand ^a	Yield ^b (%)	ee ^c (%)
1	CuBr	(–)-SP	63	18 ^d
2	[Cu(CH ₃ CN) ₄]PF ₆	(–)-SP	86	63 ^d
3	CuOTf	(–)-SP	78	56 ^d
4	CuOTf	(<i>S,S</i>)-Box- ^t Bu	74	44
5	[Cu(CH ₃ CN) ₄]PF ₆	(<i>S,S</i>)-Box- ^t Bu	90	50
6	[Cu(CH ₃ CN) ₄]PF ₆	5 ^e	65	75

^a



^b Isolated yield.

^c Determined by chiral HPLC (DAISEL chiralpak AD, 2-propanol/hexane = 1:19)

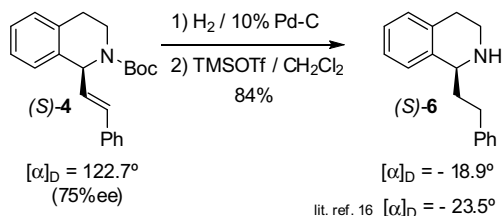
^d (*R*)-**4** was obtained as a major enantiomer.

^e 0 °C, 24 h.

the yields and optical purity of **4**. Thus, [Cu(CH₃CN)₄]PF₆ catalyst was preferable to CuX (X = halogen) or CuOTf catalyst in terms of both chemical and optical yields (Table 2, entry 2). Most of the Cu(I)-catalyzed reactions of **2** using various chiral amine ligands proceeded to give **4** in good yields (63–90%), albeit disappointingly low enantioselectivity (18–56%ee) (entries 1–5). Among the examined Box ligand derivatives, the use of ^tbutyl-substituted (*S,S*)-Box ligand **5**¹⁴ showed somewhat improved results (65% yield, 75%ee) (entry 6). The use of (–)-sparteine (10 mol %)¹⁵ as a chiral ligand (entries 1–3) showed moderate enantiomeric inductions in a reversed enantioselectivity (86% yield, 63%ee).

The absolute configuration of (*S*)-**4**, 75%ee [α]_D 122.6 (c 1.0, CHCl₃), obtained by using ^tbutyl-(*S,S*)-Box ligand **5**, was determined by converting it to compound (*S*)-**6** whose absolute configuration has been established (Scheme 4).¹⁶

In summary, we indicated that the Cu(I)-catalyzed addition of an alkenylzirconocene chloride to 3,4-dihydroisoquinoline pro-



Scheme 4.

ceeds efficiently in the presence of a stoichiometric amount of an acylating agent to give an alkenylation–acylation product. It is also observed that a moderate induction of enantiomeric excess was achieved by the Cu(I)/chiral amine-catalyzed addition of the alkenylzirconocene chloride to 3,4-dihydroisoquinoline. Although the mechanism of the addition of alkenyl group to 3,4-dihydroisoquinoline under the present conditions is uncertain at present,¹⁷ the described reaction of the alkenylzirconocene chloride indicates a new possibility of organozirconocene complexes in organic synthesis.

3. Typical experimental procedure

Under an Ar atmosphere, to a solution of alkenylzirconocene chloride (1.0 mmol) in CH_2Cl_2 (2 mL) was added successively a pre-mixed (0.5 h at room temperature) solution of **1** (0.5 equiv) and $\text{ClCOOC}_2\text{H}_5$ (0.5 equiv) in CH_2Cl_2 (2 mL), and Cu(I) catalyst (10 mol % to **1**), and the mixture were stirred at room temperature for 28 h. The reaction was terminated by adding saturated aqueous solution of NaHCO_3 , and the resulting mixture was extracted with CHCl_3 . The combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated to dryness to give a crude product, which was purified by silica gel column chromatography (hexane–ethyl acetate = 30:1) to give a pure product. The analytical sample was obtained by a further MPLC purification (hexane–ethyl acetate = 30:1).

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