Tetrahedron Letters 50 (2009) 587–589

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Akio Saito, Koichi Iimura, Miki Hayashi, Yuji Hanzawa *

Laboratory of Organic Reaction Chemistry, Showa Pharmaceutical University, 3-3165 Higashi-tamagawagakuen Machida, Tokyo 194-8543, Japan

ARTICLE INFO

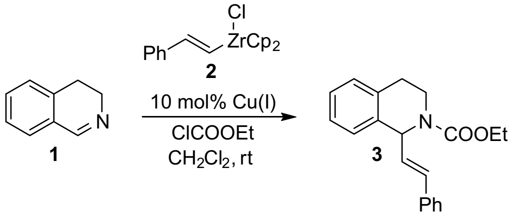
Article history:
Received 14 October 2008
Revised 18 November 2008
Accepted 20 November 2008
Available online 24 November 2008

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 $ClCOOC_2H_5$ 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.

1. Introduction

Organozirconocene chloride complexes are readily accessible by the hydrozirconation of unsaturated compounds with Schwartz reagent [$Cp_2Zr(H)Cl$] or by the treatment of alkenyl halide with Negishi reagent [Cp_2Zr-$n$$Bu_2$].[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, transmetallation 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 transmetallation 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 alkenylrhodium species as a reactive intermediate through transmetallation 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]



Scheme 1.

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

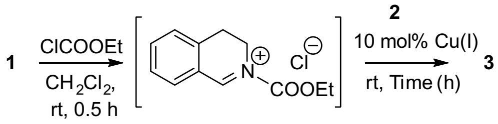
At the outset, we examined the reaction of **1** with (*E*)-styrylzirconocene chloride (**2**) in CH_2Cl_2 at an ambient temperature, and we confirmed that the reaction did not take place. However, premixing a stoichiometric amount of ethyl chlorocarbonate (ClCOOEt) with **1** in CH_2Cl_2 at an ambient 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).

---

* Corresponding author. Tel./fax: +81 (0) 42 721 1569.
E-mail address: hanzaway@ac.shoyaku.ac.jp (Y. Hanzawa).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.11.078

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

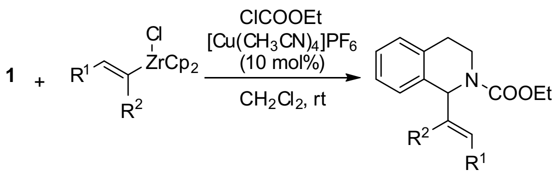


Entry	Catalyst[b]	Time (h)	Yield[c] (%)
1	None	16	36
2	CuBr	2	68
3	CuCN[d]	2	51
4	CuOTf	2	81
5	$[Cu(CH_3CN)_4]PF_6$	2	87
6	$[RhCl(cod)]_2$	4	48
7	$(CH_3)_2Zn$[e]	2	80

[a] Ratio of reagents: **1**:[ClCOOEt]:**2** = 1:1:2.
[b] 10 mol %.
[c] Isolated yield.
[d] 50 mol %.
[e] 150 mol %.

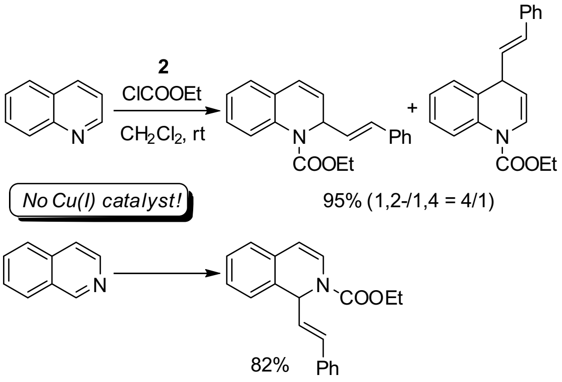
A catalytic amount of CuBr (10 mol %) accelerated the reaction, and **3** was obtained in 68% yield in less than 2 h (TLC monitoring) (entry 2).[9] It turned out that $(Boc)_2O$, instead of ClCOOEt, was also an efficient additive for the reaction. It should be mentioned that the CuBr-catalyzed addition of **2** to **1** did not occur in the absence of ClCOOEt 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), $[Cu(CH_3CN)_4]PF_6$ indicated notable catalytic efficiency (entry 5). Although the sole use of Rh(I) catalyst did not give a product, the presence of ClCOOEt showed the formation of **3** (48%) as well (entry 6). The use of a stoichiometric amount of dimethylzinc, transmetallation 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 alkenylation–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.



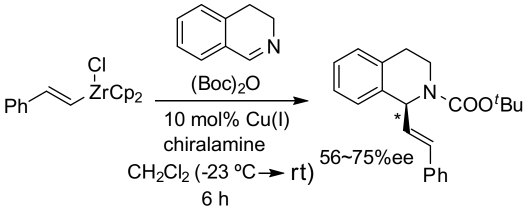
R^1= ⁿBu,	R^2= H	78%
R^1= ᵗBu,	R^2= H	72%
R^1= Et,	R^2= Et	80%

Scheme 2.



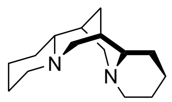
Scheme 3.

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

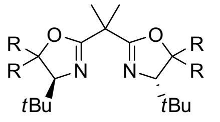


Entry	Catalyst	Ligand[a]	Yield[b] (%)	ee[c] (%)
1	CuBr	(−)-SP	63	18[d]
2	$[Cu(CH_3CN)_4]PF_6$	(−)-SP	86	63[d]
3	CuOTf	(−)-SP	78	56[d]
4	CuOTf	(*S*,*S*)-Box-ᵗBu	74	44
5	$[Cu(CH_3CN)_4]PF_6$	(*S*,*S*)-Box-ᵗBu	90	50
6	$[Cu(CH_3CN)_4]PF_6$	**5**[e]	65	75

[a]



(-)-Sparteine [(-)SP]



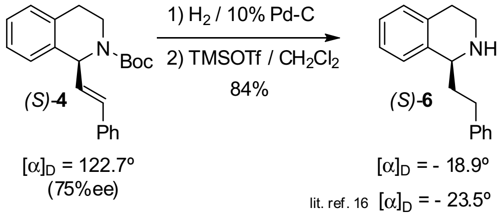
R = H; (*S*,*S*)-Box-ᵗBu
R = CH_3; **5**

[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.

Based on the described results, we examined the enantioselective alkenylation 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 the yields and optical purity of **4**. Thus, $[Cu(CH_3CN)_4]PF_6$ 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 $[\alpha]_D$ 122.6 (*c* 1.0, $CHCl_3$), 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 premixed (0.5 h at room temperature) solution of **1** (0.5 equiv) and $ClCOOC_2H_5$ (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).

Acknowledgment

This work was supported by Grant-in-Aid for Scientific Research (C), Japan Society for the Promotion of Science (No. 19590012).

References and notes

1. (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333; (b) Takahashi, T.; Kotora, M.; Fischer, R.; Nishihara, Y.; Nakajima, K. *J. Am. Chem. Soc.* **1995**, *117*, 11039.
2. (a) Suzuki, K.; Hintermann, L.; Yamanoi, S. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 282–318; (b) Chinkov, N.; Marek, I. In *New Aspects of Zirconium Containing Organic Compounds*; Marek, I., Ed.; Springer Verlag: Berlin, Heidelberg, 2005; pp 133–166.
3. (a) Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1778; (b) Lipshutz, B. H.; Pfeiffer, S. S.; Noson, K.; Tomioka, T. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 110–148.
4. Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449–2452. and the references cited therein.
5. (a) Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2003**, *44*, 923; (b) Hanzawa, Y.; Takebe, Y.; Saito, A.; Kakuuchi, A.; Fukaya, H. *Tetrahedron Lett.* **2007**, *48*, 6471.
6. For the enantioselective addition of alkenylzirconocene chloride to imines through transmetallation: Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.
7. For review, see: Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341; Brossi, A.. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 50, pp 109–139; (a) Chrzanowska, M.; Sokolowska, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1435; (b) Cabello, N.; KIzirian, J.-C.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J.-C. *Eur. J. Org. Chem.* **2005**, 4835; (c) Alexakis, A.; Amiot, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2117; (d) Amiot, F.; Cointeaux, L.; Silve, E. J.; Alexakis, A. *Tetrahedron* **2004**, *60*, 8221; (e) Cointeaux, L.; Alexakis, A. *Tetrahedron: Asymmetry* **2005**, *16*, 925; (f) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646; (g) Sakamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 9646.
8. Rh(I)-catalyzed highly enantioselective 1,4-addition of organozirconocene chloride to α,β-enones has been reported: (a) Oi, S.; Sato, T.; Inoue, Y. *Tetrahedron Lett.* **2004**, *45*, 5051; (b) Nikolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874.
9. In the copper(I)-catalyzed reaction, the inevitable formation of 1,4-diphenylbutadiene (<10%) was observed. A similar observation has been made in the reaction of a Cu(I)-catalyzed conjugate addition of **1** to α,β-enones, see: Ref. 17a.
10. In the Pd-catalyzed nucleophilic addition of soft carbon nucleophiles to 3,4-dihydroisoquinoline in the presence of $[(Boc)_2]O$, the formation of *N*-acyl iminium salt via *N*,*O*-actal has been reported. See, Ref. 7g. For the in situ activation of C=N double bond with acid halide for the addition of alkynilides, see: (a) Fischer, C.; Carreria, E. M. *Org. Lett.* **2004**, *6*, 1497; (b) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.
11. Similar observation has been made in the Rh(I)-catalyzed reactions. See, Ref. 5.
12. (a) Shun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300; (b) Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143; Addition of alkenylzinc to 3,4-dihydroisoquinoline N-oxide: Wang, S.; Seto, C. T. *Org. Lett.* **2006**, *8*, 3979.
13. Examination of phosphine ligands (10 mol %) such as (*S*)-BINAP or (*R*)-QUINAP showed 3% or 10%ee, respectively.
14. Box ligands were purchased. Commercially unavailable Box ligands were prepared according to the procedure by the following papers: (a) Cornejo, A.; Fraile, J. M.; Garcia, J. I.; Gil, M. J.; Martinez-Merino, V.; Mayoral, J. A.; Pires, E.; Villalba, I. *Synlett* **2005**, 2321; (b) Itagaki, M.; Masumoto, K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3292; (c) Itagaki, M.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, *47*, 523.
15. Enantioselective alkylation by the reaction of organolithium and 3,4-dihydroisoquinoline derivatives using (−)-sparteine, see: Refs. 7a–c.
16. Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095.
17. We have no evidence for the generation of alkenyl copper species through transmetallation. Recently, it has been reported that copper(I)-catalyzed conjugate additions of alkenylzirconocene chloride to α,β-enone might proceed via a simultaneous three-component mechanism, which is proposed for the copper(I)-catalyzed addition of alkylzirconocene chloride to α,β-enone by Wipf et al. (a) El-Batta, A.; Hage, T. R.; Plotkin, S.; Bergdahl, M. *Org. Lett.* **2004**, *6*, 107; (b) Wipf, P.; Xu, W.; Smitrovich, J. H.; Lehmann, R.; Venanzi, L. M. *Tetrahedron* **1944**, *50*, 1935.