

Rh(I)-Catalyzed Direct *ortho*-Alkenylation of Aromatic Ketimines with Alkynes and Its Application to the Synthesis of Isoquinoline Derivatives

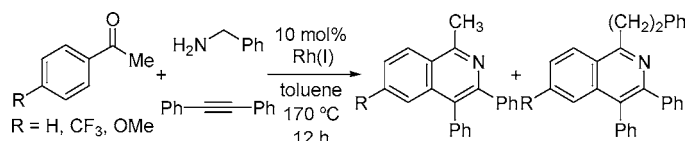
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ABSTRACT



Novel synthetic methods of both *ortho*-alkenylated aromatic ketones and isoquinoline derivatives have been developed through the Rh(I)-catalyzed direct *ortho*-alkenylation of common aromatic ketimines with alkynes. Furthermore, a highly efficient one-pot synthesis of isoquinoline derivatives was achieved by simply mixing aromatic ketone, benzylamine, and alkyne under a Rh(I) catalyst.

Since the pioneering work by Murai and co-workers in 1993,¹ the Ru-catalyzed *ortho*-alkylation of aromatic ketones and imines with olefins via C–H activation has been considered as one of the most useful and reliable synthetic methods for the preparation of 2-alkyl-substituted aromatic carbonyl compounds.² Recently, we reported the Rh(I)-catalyzed *ortho*-alkylation of aromatic ketones and imines with olefins.³ The reaction not only shows a high selectivity for monoalkylation with numerous 1-alkenes but can also be applied to various problematic olefins such as 1-alkenes with an allylic proton, α,ω -dienes, and internal olefins. However, for *ortho*-alkenylation of aromatic ketones, only a few examples of

Ru-catalyzed reactions of a specific ketone such as α -tetralone with internal alkynes have been reported.^{4–6} Herein, we report a Rh(I)-catalyzed direct *ortho*-alkenylation of common aromatic ketimines with 1-alkynes as well as internal alkynes and its application to a one-pot synthetic protocol of isoquinoline derivatives.⁷

The reactions of the benzylimine of acetophenone **1a** with some terminal alkynes were examined, and the results are summarized in Table 1. When **1a** (1.0 equiv) was treated with 1-hexyne (**2f**) or 1-octyne (**2g**) (1.2 equiv) in toluene at 130 °C for 2 h in the presence of Rh(PPh₃)₃Cl (**3**, 2 mol %), *ortho*-alkenylation of **1a** took place to produce **4af** or

(1) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, S. *Nature* **1993**, *366*, 529.

(2) (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62. (b) Murai, S.; Chatani, N.; Kakiuchi, F. *Pure Appl. Chem.* **1997**, *69*, 589. (c) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 3117. (d) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371. (e) Grigg, R.; Savic, V. *Tetrahedron Lett.* **1997**, *38*, 5737. (f) Dürr, U.; Kisch, H. *Synlett* **1997**, 1335. (g) Busch, S.; Leitner, W. *Chem. Commun.* **1999**, 2305. (h) Lim, Y.-G.; Han, J.-S.; Yang, S.-S.; Chun, J. H. *Tetrahedron Lett.* **2001**, *42*, 4853.

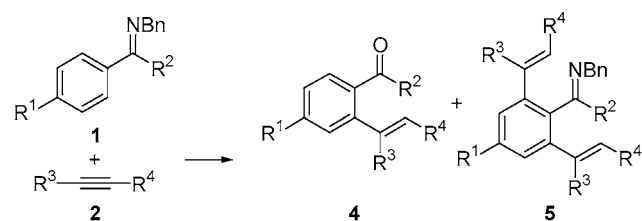
(3) (a) Jun, C.-H.; Moon, C. W.; Hong, J.-B.; Lim, S.-G.; Chung, K.-Y.; Kim, Y.-H. *Chem. Eur. J.* **2002**, *8*, 485. (b) Jun, C.-H.; Hong, J.-B.; Kim, Y.-H.; Chung, K.-Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440.

(4) (a) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681. For the site selective vinylation of aromatic compounds, see: (b) Kakiuchi, F.; Sato, T.; Tsujimoto, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1998**, 1053. (c) Harris, P. W. R.; Rickard, C. E. F.; Woodgate, P. D. *J. Organomet. Chem.* **1999**, *589*, 168. Also see: (d) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826.

(5) For β -vinylation of α,β -unsaturated ketone with internal alkynes, see: Kakiuchi, F.; Uetsuhara, T.; Tanaka, Y.; Chatani, N.; Murai, S. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 511.

(6) *ortho*-Arylation of aromatic ketones using arylboronates also has been reported very recently: Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698.

(7) Rh(I)-catalyzed *ortho*-vinylation of some 2-phenylpyridine derivatives with only internal alkynes has been reported: Lim, Y.-G.; Lee, K.-H.; Koo, B. T.; Kang, J.-B. *Tetrahedron Lett.* **2001**, *42*, 7609.

Table 1. Rh(I)-Catalyzed *ortho*-Vinylolation of Ketimines (**1**)^a

entry	1 (R ¹ , R ²)	2 (R ³ , R ⁴)	ratio (4/5) ^b	yield (%) ^c
1	1a (H, Me)	2f (H, ⁿ Bu)	100:0 (4af/5af)	88
2		2g (H, ⁿ Hex)	100:0 (4ag/5ag)	85
3		2h (H, ^t Bu)	86:14 (4ah/5ah)	96
4		2i (Ph, Ph)	100:0 (4ai/5ai)	93
5	1b (CF ₃ , Me)	2h (H, ^t Bu)	65:35 (4bh/5bh)	95
6 ^d			82:18 (4bh/5bh)	81
7	1c (OMe, Me)		52:48 (4ch/5ch)	92
8 ^d			76:24 (4ch/5ch)	41
9 ^e	1d (H, Et)		86:14 (4dh/5dh)	72
10 ^e	1e (H, ⁿ Pent)		100:0 (4eh/5eh)	60

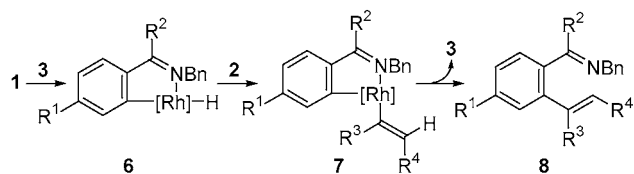
^a Reagent and conditions: (1) **1** (1.0 equiv), **2** (1.2 equiv), Rh(PPh₃)₃Cl (**3**, 2 mol %), toluene, 130 °C, 2 h. (2) 1 N HCl, room temperature, 12 h. ^b Determined by GC. ^c Isolated yield. ^d Carried out at 100 °C for 30 min. ^e Carried out using 4 mol % of **3**.

4ag in 88% and 85% isolated yields, respectively, after hydrolysis (Table 1, entries 1 and 2). Under the above reaction conditions, the reaction of **1a** with 3,3-dimethyl-1-butyne (**2h**) gave a 86:14 mixture of monoalkenylated ketone **4ah** and dialkenylated ketimine **5ah** in an almost quantitative yield (entry 3).⁸ An internal alkyne, diphenylacetylene **2i**, was also reacted with **1a** smoothly to afford **4ai** in a 93% yield (entry 4). To compare the reactivities of aromatic ketimines bearing different *para*-substituents, we examined the reaction of **1b** or **1c** with **2h** under mild reaction conditions. When the reaction was carried out at 100 °C for 30 min, the electron-withdrawing group (CF₃) containing compound **1b** displayed much better reactivity than the electron-donating group (OCH₃) containing compound **1c** (entries 6 and 8). This result is identical to that observed for the *ortho*-alkylation of aromatic ketimines with alkenes.³ Other aromatic ketimines possessing longer alkyl chain on the imino moiety were also examined and showed somewhat low reactivities under similar reaction conditions (entries 9 and 10).

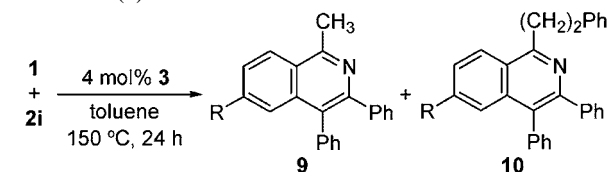
The proposed mechanism for the Rh(I)-catalyzed *ortho*-alkenylation is as follows: (1) Precoordination of ketimine **1** to the rhodium catalyst **3** followed by the insertion of the Rh into an *ortho* C–H bond affords rhodium hydride **6**. (2) Anti-Markovnikov *syn*-addition of the Rh–H bond into the coordinated **2** and the prompt reductive elimination of the resulting Rh(III) intermediate **7** generates the *ortho*-alkenylated ketimine **8**, which is transformed into **4** by hydrolysis (Figure 1).⁹

During the course of optimization of the reaction variables, we found that two isoquinoline derivatives were formed

(8) Attempts to hydrolyze the 2,4-dialkenylated ketimines **5** failed.

**Figure 1.** Mechanism for Rh(I)-catalyzed *ortho*-alkenylation.

unexpectedly from the reaction of **1a** with **2i** under more vigorous reaction conditions.¹⁰ For example, when a mixture of **1a** (1.0 equiv) and **2i** (1.2 equiv) was heated at 150 °C for 24 h in the presence of 4 mol % of **3**, a mixture of **9a** and **10a** was isolated in 73% yield with a 53:47 ratio (Table 2, entry 1). We postulate that ketimine **8ai** (R¹ = H, R³ =

Table 2. Tandem *ortho*-Alkenylation–Cyclization of Ketimines (**1**)^a

entry	1 (R)	ratio (9/10) ^b	yield(%) ^c
1	1a (H)	53:47 (9a/10a)	73 (82)
2	1b (CF ₃)	33:67 (9b/10b)	55 (67)
3	1c (OMe)	41:59 (9c/10c)	71 (82)

^a Reagent and conditions: **1** (1.0 equiv), **2i** (1.2 equiv), **3** (4 mol %), toluene, 150 °C, 24 h. ^b Determined by GC. ^c Isolated yield. GC yields are given in parentheses.

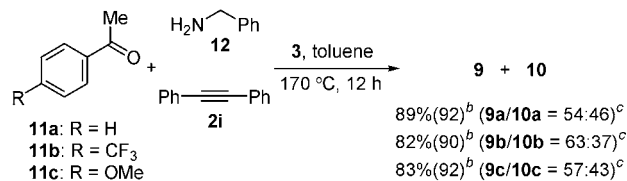
R⁴ = Ph), generated from **1a** and **2i** by direct *ortho*-alkenylation, might be a key intermediate for this tandem *ortho*-alkenylation–cyclization process. The phenethyl group (CH₂CH₂Ph) of **10a** seems to be introduced by the migration of the benzyl group of **8ai** into the benzylic position of another **8ai**.¹¹ Other ketimines were also examined in this tandem reaction, and the results are depicted in Table 2.

Next, we were intrigued by the possibility of developing a more convenient one-pot synthetic method of isoquinoline derivatives by simply mixing aromatic ketone, primary amine, and alkyne under Rh(I) catalyst without the prior preparation of the corresponding ketimines (Scheme 1). As was expected, a mixture of two isoquinolines, **9a** and **10a**,

(9) The stereochemistry of **4** and **5** was deduced from the proposed mechanism (Figure 1) and confirmed to be all-*trans* by measuring the coupling constant between two olefinic protons of the products only except for **4ai**.

(10) Recently, Larock and co-workers ingeniously utilized Pd-catalyzed tandem cross coupling of the *tert*-butylimine of *o*-iodobenzaldehyde with alkynes-iminoannulation sequence to synthesize a variety of 3,4-disubstituted isoquinoline derivatives: (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. Also see: (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437 and references therein.

Scheme 1. One-Pot Tandem Reaction of Aromatic Ketones (**11**)^a

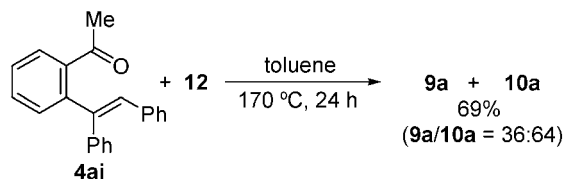


^a Reagent and conditions: **11** (1.0 equiv), **12** (3.0 equiv), **2i** (3.0 equiv), **3** (10 mol %), toluene, 170 °C, 12 h. ^b Isolated yield. GC yields are given in parentheses. ^c The ratio of **9:10** was determined by GC.

was obtained in 89% isolated yield with a 54:46 ratio directly from the reaction of acetophenone (**11a**, 1 equiv) with **2i** (3.0 equiv) and benzylamine **12** (3.0 equiv) at 170 °C for 12 h under **3** (10 mol %) (Scheme 1). Other substituted acetophenones, **11b** and **11c**, also showed a good reactivity in this one-pot tandem process.

To get more insight into this tandem process, the following one-pot experiment was performed. The reaction of 1-[2-(1,2-diphenylvinyl)phenyl]ethanone (**4ai**, 1.0 equiv), prepared separately through direct *ortho*-alkenylation, with an excess of **12** (3.0 equiv) was carried out in the absence of both **2i** and **3** in toluene at 170 °C. After 24 h, a mixture of **9a** and **10a** was obtained in a 69% isolated yield in a 36:64 ratio (Scheme 2). This result implies that the formation of the

Scheme 2. Reaction of Enone (**11**) with Benzylamine (**12**)



isoquinolines **9a** and **10a** must be a thermal process through the key intermediate **8ai** (R¹ = H, R² = Me, R³ = R⁴ = Ph; Figure 1).

At the present time the mechanism for the formation of **9** and **10** from the reaction of **1** with **2i** is unclear. One plausible explanation is shown in Figure 2. Electrocyclic reaction of **8i** might give the unstable bicyclic intermediate **13**, which could abstract an acidic α -hydrogen from another

(11) The structure of **10a** has been confirmed undoubtedly by the independent synthesis of **10a** from **9a**. See Supporting Information.

8i to afford an ion pair consisting of iminium **14** and enamide **15**. Nucleophilic attack on the benzylic position of **14** by **15** generates 3,4-dihydroisoquinoline **16** and imine **17**. Similarly, another 3,4-dihydroisoquinoline **18** could be formed from **17**.¹² Finally, both **16** and **18** can be easily oxidized into the stable aromatic isoquinolines **9** and **10** (Figure 2).

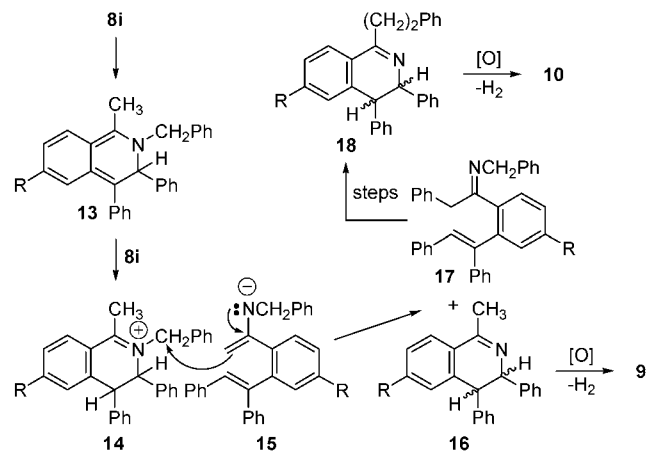


Figure 2. Plausible explanation for the formation of **9** and **10**.

In summary, we have developed novel synthetic methods for both *ortho*-alkenylated aromatic ketones and isoquinoline derivatives under different reaction conditions through the Rh(I)-catalyzed direct *ortho*-alkenylation of common aromatic ketimines with alkynes. Furthermore, the highly efficient single-step synthesis of isoquinoline derivatives was achieved by the three-component reaction of aromatic ketone with benzylamine and alkyne without any use of *ortho*-functionalized aromatic compounds. Extension of the scope of these synthetic methods and mechanistic studies are currently under investigation.

Acknowledgment. This work was supported by the National Research Laboratory (NRL) (2000-N-NL-01-C-271) and Koren Science and Engineering Foundation (20004010). High resolution mass spectra were provided by the Korea Basic Science Institute.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) When the reaction of **1a** with **2i** was performed for a short period of reaction time (e.g., for 2 h), a small amount of **16a** and **18a** (R = H) was isolated and characterized spectroscopically. See Supporting Information.