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Rhodium-Catalyzed Domino Conjugate Addition−Cyclization Reactions for the Synthesis of a Variety of *N*- and *O*-Heterocycles: Arylboroxines as Effective Carbon Nucleophiles†

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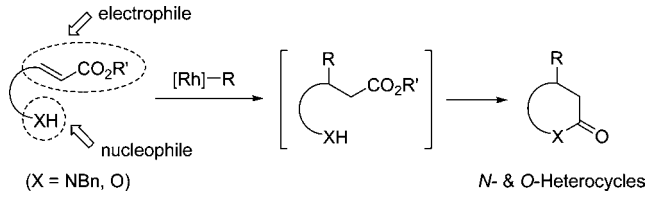
ABSTRACT



Facile and efficient Rh(I)-catalyzed domino conjugate addition−cyclization reactions of olefins bearing two electrophilic sites and a pendant nucleophile with organoboroxines have been developed to afford a variety of *N*- and *O*-heterocycles, such as 3,4-dihydroquinolin-2(1*H*)-ones, 3,4-dihydrocoumarins, and pyrrolidin-2-ones, which constitute important motifs in biologically active natural and synthetic organic compounds.

The conjugate addition of organometallic reagents to electron-deficient olefins is one of the most useful processes for carbon−carbon bond formation. Among many different procedures, the Rh(I)-catalyzed conjugate addition of organoboron reagents to α,β-unsaturated carbonyl compounds, known as the Hayashi−Miyaura reaction,[1] has attracted considerable attention as an important synthetic method for a variety of organic transformations.[2] This type of reaction is usually carried out in aqueous solvents and tolerates various functional groups. In recent years, there has been considerable research interest in Rh(I)-catalyzed tandem annulations in which the tandem cyclization was triggered by conjugate addition of organoborons to activated alkenes for the construction of carbocycles and heterocycles.[3]

Recently, we reported the Rh(I)-catalyzed tandem conjugate addition−Mannich cyclization reaction of imine-substituted electron-deficient alkenes with arylboronic acids to afford 2,3,4-trisubstituted 1,2,3,4-tetrahydroquinolines.[4] Our continued interest in Rh(I)-catalyzed tandem reactions prompted us to investigate the possibility of a domino conjugate addition−cyclization reaction of α,β-unsaturated esters bearing a nucleophile in the molecule. Since the Hayashi−Miyaura reaction is compatible with the presence of unprotected hydroxyl and amino groups,[2] we envisaged the Rh(I)-catalyzed domino conjugate addition−cyclization reaction of α,β-unsaturated esters bearing unprotected amino and hydroxyl moieties placed at an appropriate position for subsequent nucleophilic cyclization to afford *N*- and *O*-heterocycles, respectively (Scheme 1). In parallel with our efforts to develop efficient synthetic methods for heterocyclic

† Dedicated to the late Professor Chi Sun Hahn in admiration of his contributions to organic chemistry of Korea.

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(1) Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

(2) For reviews, see: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (d) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465. (e) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13. (f) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 3, p 55.

(3) For reviews, see: (a) Youn, S. W. *Eur. J. Org. Chem.* **2009**, 2597. (b) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217. (c) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354.

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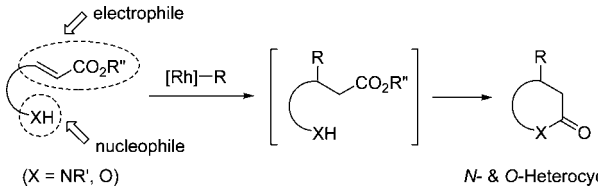
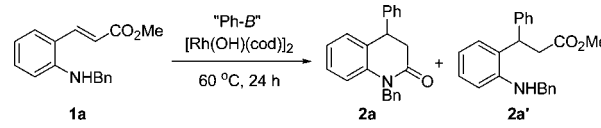
Scheme 1. Domino Conjugate Addition−Cyclization Reaction for the Synthesis of Heterocyclic Skeletons



synthesis,[4,5] we were interested in developing a one-pot synthesis of various heterocycles, involving sequential C−C and C−heteroatom bond formations in an efficient manner. Herein we disclose the realization of this propasal, together with an in depth investigation of reaction parameters and optimization of reaction conditions,[6,7] which ultimately led to the construction of a diverse range of 3,4-dihydroquinolin-2(1*H*)-ones,[8] 3,4-dihydrocoumarins,[9] and pyrrolidin-2-ones.[10] In view of the prevalence of these structural motifs in a number of natural and designed bioactive compounds or precursors thereof, such a synthetic methodology is particularly valuable. It also has been found that arylboroxines act as effective nucleophiles in this reaction system.

In light of our recent success in Rh(I)-catalyzed tandem conjugate addition−Mannich cyclization reactions,[4] we began our studies on the proposed domino conjugate addition−cyclization reaction using *o*-benzylamino methyl cinnamate (**1a**)[11] as the test substrate. The results of our reaction optimizations are summarized in Table 1. In the presence of base (Table 1, entries 1−3), $[Rh(OH)(cod)]_2$-catalyzed reaction of **1a** with $PhB(OH)_2$ in dioxane, dioxane/H_2O (10/1) or THF afforded predominantly the 1,4-addition product (**2a′**, 0−50%) with only trace amounts of desired product (**2a**, 0−10%). In the absence of base, reactions proceeded with an appreciable increase in the formation of **2a** (Table 1, entry 4), in particular, with THF as solvent giving **2a** as the sole product (35% yield, Table 1, entry 5). The use of phosphine ligands (Table 1, entry 6) proved counterproductive for the reaction, where only the recovery of starting material (**1a**) was observed. The source of organoboron reagent was also investigated (Table 1, entries 7 and 8), where the use of $(PhBO)_3$ gave a yield comparable to that of $PhB(OH)_2$ (Table 1, entry 7 vs entry 5).[12] The combination of base or phosphine additives with $(PhBO)_3$ led to a notable increase in the formation of **2a**, but still accompanied with significant amounts of 1,4-addition product

Table 1. Optimization Studies for the Domino Conjugate Addition−Cyclization Reaction of **1a**



1a **2a** **2a′**

entry	conditions	**2a** (%)[a]	**2a′** (%)[a]
1	$PhB(OH)_2$ with base[b] in dioxane	0−5	0
2	$PhB(OH)_2$ with base[b] in dioxane/H_2O (10:1)	0−10	0−40
3	$PhB(OH)_2$ with base[b] in THF	0−10	0−50
4	$PhB(OH)_2$ in solvent[c]	0−20	0−70
5	$PhB(OH)_2$ in THF	35	0
6	$PhB(OH)_2$ with ligand[d] in THF	0	0
7	$(PhBO)_3$ in THF	40	0
8	$NaBPh_4$ or $PhBF_3K$ in THF	0−10	0−10
9	$(PhBO)_3$ with base[b] (except NEt_3) or ligand[d] in THF	5−70	0−50
10	**$(PhBO)_3$ with NEt_3 in THF**	**90 (95)[e]**	**trace**
11	$(PhBO)_3$ with NEt_3 in solvent[c]	0−80	0−70
12	$(PhBO)_3$ with NEt_3 and ligand[d] in THF	50−80	0−10
13	$(PhBO)_3$ with other metal catalyst[f] and NEt_3 in THF	0	0

[a] Yields were determined by ^1H NMR using trichloroethylene as an internal standard. [b] Base: Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4, KOH, NaOH, NEt_3. [c] Solvent: THF/H_2O (10:1), dioxane/H_2O (10:1), dioxane, MeOH, toluene, MeCN, DMF. [d] Ligand: PPh_3, P(*o*-Tol)$_3$, $P(C_6F_5)_3$, dppp, BIPHEP, BINAP. [e] Performed at 100 °C for 1 h. [f] For other Rh, Pd, Ir, Cu catalysts, see Supporting Information.

(4) Youn, S. W.; Song, J.-H.; Jung, D.-I. *J. Org. Chem.* **2008**, *73*, 5658.

(5) (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859. (c) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581. (d) Youn, S. W.; Eom, J. I. *Org. Lett.* **2005**, *7*, 3355. (e) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521. (f) Youn, S. W. *Org. Prep. Proced. Int.* **2006**, *38*, 505. (g) Youn, S. W.; Eom, J. I. *J. Org. Chem.* **2006**, *71*, 6705. (h) Youn, S. W. *Synlett* **2007**, 3050. (i) Youn, S. W.; Bihn, J. H. *Tetrahedron Lett.* **2009**, *50*, 4598. (j) Ock, S. K.; Youn, S. W. *Bull. Korean Chem. Soc.* **2010**, *31*, 704.

(6) For related examples of Rh(I)-catalyzed conjugate addition of organoboronic acids to α,*β*-unsaturated carbonyl compounds, however, requiring a discrete extra step such as deprotection, hydrogenation, oxidation, etc. for the following cyclization reaction to afford heterocyclic compounds, see the following. Deprotection: (a) Becht, J.-M.; Meyer, O.; Helmchen, G. *Synthesis* **2003**, 2805. (b) Zoute, L.; Kociok-Köhn, G.; Frost, C. G. *Org. Lett.* **2009**, *11*, 2491. Hydrogenation: (c) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821. For related Pd-catalyzed reactions followed by oxidation, see: (d) Kobayashi, K.; Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1019. (e) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal.* **2007**, *349*, 1759. For examples of similar reactions for the synthesis of *γ*-lactones, see: (f) Segura, A.; Csákÿ, A. G. *Org. Lett.* **2007**, *9*, 3667. (g) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Sferrazza, A. *Synlett* **2009**, 1277.

(7) For Rh(I)-catalyzed conjugate addition of arylboronic acids to coumarins, see: Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285.

(8) (a) Jones, G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, U.K., 1996; p 167. (b) Zhou, W.; Zhang, L.; Jiao, N. *Tetrahedron* **2009**, *65*, 1982, and references therein.

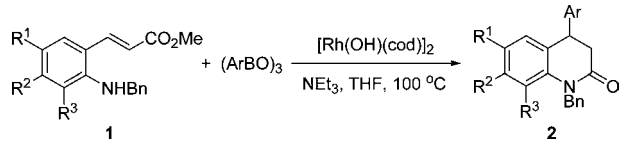
(9) (a) Donnelly, D. M. X.; Boland, G. M. In *The Flavonoids. Advances in Research Since 1986*; Harborne, J. B., Ed.; Chapman and Hall: London, 1993; p 239. (b) Semeniuchenko, V.; Groth, U.; Khilya, V. *Synthesis* **2009**, 3533, and references therein.

(10) For a review, see: Shorvon, S. *Lancet* **2001**, *358*, 1885.

(11) Various protecting groups such as Bn, Ts, Ac, and Boc for amine moieties and free amines have been examined, and benzyl appeared preferable as an effective protecting group among them for this reaction. For further details, see Supporting Information.

(12) Selected examples of successful Rh(I)-catalyzed reactions involving other organoborons in place of organoboronic acids. Arylboroxines: (a) Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 595. (b) Chen, F.-X.; Kina, A.; Hayashi, T. *Org. Lett.* **2006**, *8*, 341. (c) Goossen, L. J.; Paetzold, J. *Adv. Synth. Catal.* **2004**, *346*, 1665. (d) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. $NaBPh_4$: (e) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588. Examples of successful use of arylboroxines in other transition metal-catalyzed reactions. Pd catalysis: (f) Perkins, J. R.; Carter, R. G. *J. Am. Chem. Soc.* **2008**, *130*, 3290. Ni catalysis: (g) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750.

Table 2. Rh(I)-Catalyzed Domino Conjugate Addition−Cyclization Reaction for the Synthesis of 3,4-Dihydroquinolin-2(1*H*)-ones



entry	substrate	Ar	catalyst (mol %)	time (h)	product	yield (%)[a]
1	$R^1 = R^2 = R^3 = H$ (**1a**)	Ph	2.5	1	**2a**	88
2	$R^1 = R^2 = R^3 = H$ (**1a**)	4-MeC_6H_4	2.5	1	**2b**	84
3	$R^1 = R^2 = R^3 = H$ (**1a**)	3-$MeOC_6H_4$	2	1	**2c**	81
4	$R^1 = R^2 = R^3 = H$ (**1a**)	4-$MeOC_6H_4$	2	1	**2d**	80
5	$R^1 = R^2 = R^3 = H$ (**1a**)	4-HOC_6H_4	2	7	**2e**	49
6	$R^1 = R^2 = R^3 = H$ (**1a**)	2-naphthyl	2	1	**2f**	83
7	$R^1 = R^2 = R^3 = H$ (**1a**)	3-$O_2NC_6H_4$	5	1	**2g**	80
8	$R^1 = R^2 = R^3 = H$ (**1a**)	4-FC_6H_4	5	1	**2h**	88
9	$R^1 = R^2 = R^3 = H$ (**1a**)	4-ClC_6H_4	5	3	**2i**	77
10	$R^1 = R^2 = R^3 = H$ (**1a**)	3-ClC_6H_4	5	3	**2j**	54
11	$R^1 = R^2 = R^3 = H$ (**1a**)	4-$CH_3COC_6H_4$	7	5	**2k**	53
12	$R^1 = R^2 = R^3 = H$ (**1a**)	β-styryl	5	24	**2l**	37
13	$R^1 = Me$, $R^2 = R^3 = H$ (**1b**)	Ph	3	1	**2m**	82
14	$R^1 = R^3 = Me$, $R^2 = H$ (**1c**)	Ph	3	20	**2n**	67
15	$R^2 = MeO$, $R^1 = R^3 = H$ (**1d**)	Ph	3	3	**2o**	73
16	$R^1 = CF_3$, $R^2 = R^3 = H$ (**1e**)	Ph	2.5	7	**2p**	61
17	$R^2 = NO_2$, $R^1 = R^3 = H$ (**1f**)	Ph	2.5	7	**2q**	76

[a] Isolated yields.

2a′ (Table 1, entry 9). Ultimately, we were delighted to find that the use of NEt_3 as a base in THF gave full conversion of **1a**, furnishing **2a** in 90% yield with only trace amounts of 1,4-addition product **2a′** (Table 1, entry 10). Performing the reaction at elevated temperature (100 °C) further improved the reaction yield to 95% (Table 1, entry 10). Having identified NEt_3 as the crucial ingredient, the beneficial effect by varying the solvent or the use of phosphine ligand as additive was reinvestigated but proved insignificant (Table 1, entries 11 and 12). Finally, $[Rh(OH)(cod)]_2$ proved unique for the success of this reaction, where a variety of other Rh-, Pd-, Ir-, and Cu-based catalysts were found to be totally ineffective (Table 1, entry 13). It is noteworthy that, in contrast to the conventional reaction conditions employed in the Rh(I)-catalyzed conjugate additions and related domino processes (e.g., entries 1−3, Table 1), the reagent system and reaction conditions developed herein proved uniquely successful for substrate **1a** leading to domino product **2a**.

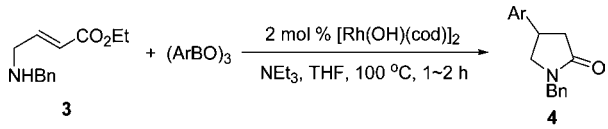
Having established the optimal reaction conditions, we set out to explore the scope of this domino process. As shown in Table 2, reaction of *o*-benzylamino methyl cinnamate (represented by generic structure **1**) with arylboroxines [$(ArBO)_3$] gave 3,4-dihydroquinolin-2(1*H*)-one **2** in moderate to good yields. Arylboroxines bearing electron-donating (Table 2, entries 2−5) or electron-withdrawing (Table 2, entries 7−11) groups were well tolerated, and the reaction conditions were compatible with a variety of functional groups. In some cases, more catalysts were required to drive the reactions to completion in acceptable time periods, giving products in good yields. Generally, electron-rich arylboroxines required lower catalyst loadings than their electron-deficient counterparts (Table 2, entries 2−5 vs 7−11). 2-Naphthylboroxine also reacted with **1a** to give the corresponding dihydroquinolinone **2f** (Table 2, entry 6). Alkenylboroxine (Table 2, entry 12) and hydroxyl- or acetyl-substituted phenylboroxine (Table 2, entries 5 and 11) afforded the corresponding products in moderate yields. In stark contrast, this domino cyclization reaction failed with sterically hindered aryl- (2-$MeOC_6H_4$), heteroaryl- (2-thienyl, 2-furanyl), and formyl-substituted aryl- (3-$CHOC_6H_4$) boroxines to give the desired products in significantly lower yields (0−30%). On the other hand, the size of the ester group also appeared to influence the reactivity. Reactions of substrates with large ester groups such as cyclohexyl or *tert*-butyl gave low (30% by ^1H NMR) or no conversions, respectively.[13] Subsequently, we explored the effects of substituents at the aryl moiety of **1**. The yields remained equally good with both electron-donating and electron-withdrawing substituents on the phenyl ring (Table 2, entries 13−17).

We proceeded to extend the application of this reaction system to the formation of pyrrolidin-2-ones **4** from (*E*)-ethyl 4-benzylamino-2-butenoate **3** (Scheme 2). Linear aliphatic α,β-unsaturated esters bearing an amino group also proved to be good substrates, giving the corresponding five-membered *N*-heterocyles, pyrrolidin-2-ones in good yields, irrespective of the arylboroxines used.

Encouraged by the successful synthesis of *N*-heterocycles, we then turned our attention to the synthesis of *O*-heterocycles. α,β-Unsaturated carbonyl compounds with an OH

(13) (a) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (b) Sukuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951.

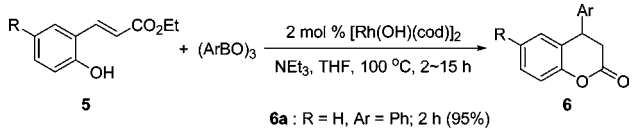
Scheme 2. Rh(I)-Catalyzed Domino Conjugate Addition−Cyclization Reaction for the Synthesis of Pyrrolidin-2-ones



4a : Ar = Ph; 1 h (84%)
4b : Ar = 4-MeC_6H_4; 2 h (74%)
4c : Ar = 4-FC_6H_4; 2 h (73%)

group are interesting bifunctional substrates with regard to the possibility of this domino process to afford *O*-heterocycles such as 3,4-dihydrocoumarins. To our delight, reaction of **5** with various arylboroxines proceeded smoothly as well to form the corresponding 3,4-dihydrocoumarins in good yields (Scheme 3). Compared to the amino-substituted

Scheme 3. Rh(I)-Catalyzed Domino Conjugate Addition−Cyclization Reaction for the Synthesis of 3,4-Dihydrocoumarins



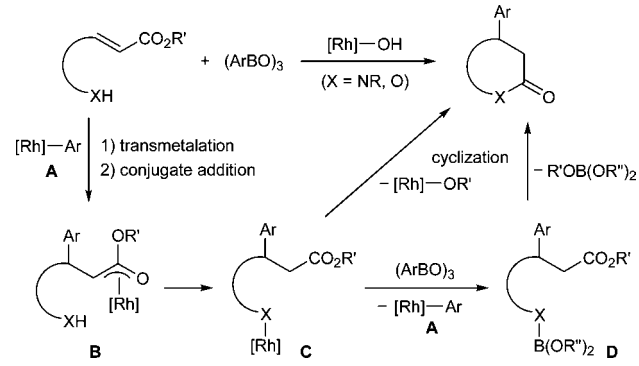
6a : R = H, Ar = Ph; 2 h (95%)
6b : R = H, Ar = 4-MeC_6H_4; 3 h (79%)
6c : R = H, Ar = 3-$MeOC_6H_4$; 14 h (94%)
6d : R = H, Ar = 2-naphthyl; 3 h (82%)
6e : R = H, Ar = 4-FC_6H_4; 4 h (65%)
6f : R = H, Ar = 3-$O_2NC_6H_4$; 14 h (51%)
6g : R = Me, Ar = Ph; 15 h (93%)
6h : R = F, Ar = Ph; 15 h (81%)

substrates, hydroxyl-containing substrates required rather longer reaction times to complete the second cyclization step of the conjugate addition intermediate, which could be observed on TLC during the reaction progress and isolated if the reaction was stopped midway, probably due to the lower nucleophilicity of the OH group.

A plausible mechanism for the Rh-catalyzed domino conjugate addition−cyclization presented herein is outlined in Scheme 4.[2,3,14] Initially, an organorhodium(I) species (**A**) is generated by transmetalation of hydroxorhodium(I) with arylboroxine. Then, conjugate addition of the arylrhodium(I) species (**A**) to α,*β*-unsaturated ester occurs to afford the (oxa-*π*-allyl)rhodium(I) intermediate (**B**),[15] which undergoes intramolecular proton exchange between Rh^I-enolate and the XH (X = N, O) group, forming *X*-rhodium(I) species (**C**).

(14) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

Scheme 4. Proposed Mechanism for the Rh(I)-Catalyzed Domino Conjugate Addition−Cyclization Reaction



Subsequently, either direct cyclization of **C** or cyclization of *X*-boryl species (**D**) via transmetalation of **C** with arylboroxine produces the cyclized product along with **A** to promote the next catalytic cycle. The reluctance of uncyclized 1,4-addition product **2a′** to undergo cyclization under the same or similar related reaction conditions is suggesting an activated species **C** or **D** (see Supporting Information). Furthermore, conducting the reaction in protic solvents also led to predominant formation of 1,4-addition product **2a′** (see Supporting Information), suggesting the competing protonation of activated species **C** or **D** in favor of the desired cyclization.

In summary, we have developed a Rh(I)-catalyzed domino conjugate addition−cyclization reaction to construct a wide range of *N*- and *O*-heterocycles, including but not limited to 3,4-dihydroquinolin-2(1*H*)-ones, 3,4-dihydrocoumarins, and pyrrolidin-2-ones. Furthermore, a variety of functional groups could be tolerated under the reaction conditions, and circumvent the use of protecting groups in contrast to related processes. This method should find wide scope applications in chemical and biological investigations, and the studies in these areas are currently underway in our laboratory.

Acknowledgment. This work was supported by National Research Foundation of Korea Grant funded by the Korean Government (Nos. R01-2008-000-20332-0 and 2009-0063856).

Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) It cannot be excluded that conjugate addition of **A** to α,*β*-unsaturated ester may take place by chelation of **A** with XH group or X^- under the basic conditions. For an example of a Rh(I)-catalyzed conjugate addition under chelation or nonchelation conditions by OH group, see: de la Herrán, G.; Mba, M.; Murcia, M. C.; Plumet, J.; Csákÿ, A. G. *Org. Lett.* **2005**, *7*, 1669.