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Rhodium-Catalyzed Asymmetric Conjugate Alkynylation of Enones with Alkynylsilanols

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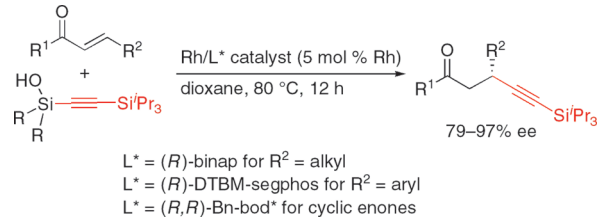
ABSTRACT



Asymmetric conjugate alkynylation of α,β-unsaturated ketones with (triisopropylsilyl)ethynylsilanols giving β-alkynylketones took place in high yields with high enantioselectivity in the presence of chiral rhodium catalysts.

Catalytic asymmetric conjugate alkynylation of α,β-unsaturated carbonyl compounds is one of the significant challenges in asymmetric carbon−carbon bond formation.[1] Despite the recent progress of transition metal-catalyzed asymmetric conjugate alkylation, arylation, and alkenylation,[2] asymmetric conjugate addition of alkynyl groups has not been well developed. There have been a few reports on catalytic asymmetric alkynyl conjugate addition by Carreira (Cu),[3] Corey (Ni),[4] and Chong (chiral 1,1′-binapthols).[5−7] Recently, we reported a rhodium-catalyzed reaction that realizes the asymmetric conjugate addition of terminal alkynes to α,β-unsaturated ketones by use of a bulky silylacetylene in the presence of a bulky bisphosphine−rhodium complex as a catalyst (Scheme 1).[8,9] Although high yields and high enantioselectivities were obtained in the rhodium-catalyzed

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(2) For reviews, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13. (c) Hayashi, T. *Pure Appl. Chem.* **2004**, *76*, 465. (d) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (e) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (f) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (g) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179. (h) Harutynyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824.

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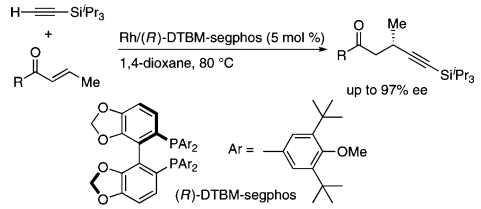
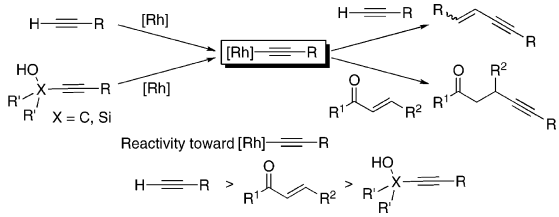
Scheme 1



asymmetric addition,[8] the reaction has the drawback that the scope of the enone substrates is rather narrow. Thus the yields of the β-alkynylation products are low for the conjugate enones substituted with aryl groups at the β-position and cyclic enones. This is mainly due to the low reactivity of such enones, resulting in the predominant formation of acetylene dimers rather than β-alkynylketones. To realize the alkynylation of less reactive enones, more effective suppression of the dimerization of terminal alkynes is important. One solution of the problem is to use internal alkynes bearing bulky substituents, which can provide the alkynylrhodium intermediates, because the bulky internal alkynes are expected to be less reactive than enones toward the alkynylrhodium species (Scheme 2). Here, we report the

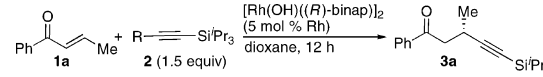
Scheme 2



use of alkynylsilanols for the asymmetric conjugate alkynylation of enones. The reaction is applicable to a wide scope of enones including β-aryl-substituted ones and cyclic enones.[10,11]

Treatment of 1-pheny-2-buten-1-one (**1a**) with (triisopropylsilyl)acetylene (**2m**; 1.5 equiv) in the presence of [Rh(OH)((*R*)-binap)]$_2$[12] (5 mol % of Rh) at 80 °C for 12 h gave β-alkynylketone **3a** in 26% yield with the formation of a large amount of 1,4-bis(triisopropylsilyl)-1-buten-3-yne, which is a head-to-head dimer of **2m** (Table 1, entry 1).[13]

Table 1. Rhodium-Catalyzed Conjugate Alkynylation of Enone **1a**[a]



entry	R	temp (°C)	yield (%)[b]	ee (%)[c]
1	H (**2m**)	80	26	90
2	$CMe_2(OH)$ (**2n**)	80	27	88
3[d]	$CMe_2(OH)$ (**2n**)	80	78	88
4	$SiMe_2(OH)$ (**2o**)	60	73	95
5[e]	$SiMe_2(OH)$ (**2o**)	60	93	96
6[e,f]	$SiMe_2(OH)$ (**2o**)	60	89	96

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.30 mmol), [Rh(OH)((*R*)-binap)]$_2$ (5 mol % of Rh) in 1,4-dioxane (0.4 mL). [b] Isolated yield. [c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H). [d] Reaction time 63 h. [e] Performed in dioxane/H_2O (10:1). [f] The reaction of enone **1a** (1.0 mmol)) and **2o** (1.5 mmol).

This result clearly indicates that the dimerization of **2m** catalyzed by the rhodium/binap complex is a major problem even in the use of the terminal alkyne bearing a bulky triisopropylsilyl group. We next focused on the propargylic alcohol **2n**, whose analogues are known to provide alkynylrhodium species by reaction with a hydroxorhodium complex,[9,10a,14] but the reactivity of **2n** as an alkynylating reagent was low under the reaction conditions (entries 2 and 3). Alkynylsilanols[15] are another synthetic equivalent to terminal alkynes in the palladium-catalyzed coupling reactions.[16] A unique feature of organosilanols is their high ability of transmetalation to late transition metals.[17] An alkynylsilanol was successfully applied to the rhodium-catalyzed asymmetric conjugate alkynylation of enones. Thus, the use of alkynyl(dimethyl)silanol **2o** in the reaction of **1a** gave **3a** in 73% yield with 95% ee (entry 4). The reaction in aqueous dioxane gave higher yield (93%) of **3a** with 96% ee (entry 5).

Table 2 summarizes the results obtained for the reaction of several enones **1** with alkynylsilanols **2**. The reaction of 1-propenyl ketones **1a**−**1d**, substituted with aryl or alkenyl groups on the carbonyl, proceeded well to give the corresponding β-alkynylketones **3a**−**3d** in high yields, the enantioselectivity ranging between 94% and 97% ee (entries

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(9) As an alternative method, rhodium-catalyzed asymmetric 1,3-rearrangement of alkynyl group from alkynyl alkenyl carbinols has been also reported: Nishimura, T.; Katoh, T.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 14158.

(10) For examples of our recent studies of rhodium-catalyzed alkynylations, see: (a) Nishimura, T.; Guo, X.-X.; Ohnishi, K.; Hayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 2669. (b) Shintani, R.; Takatsu, K.; Katoh, T.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1447. (c) Nishimura, T.; Guo, X.-X.; Hayashi, T. *Chem. Asian J.* **2008**, *3*, 1505. (d) Nishimura, T.; Tsurumaki, E.; Kawamoto, T.; Guo, X.-X.; Hayashi, T. *Org. Lett.* **2008**, *10*, 4057.

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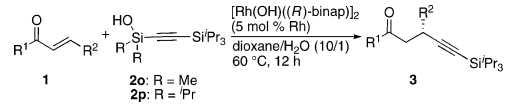
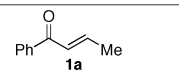
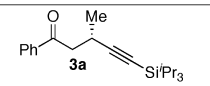
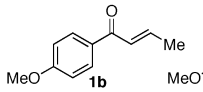
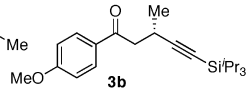
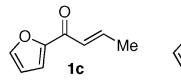
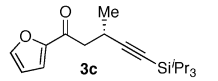
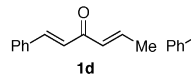
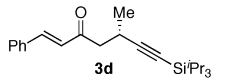
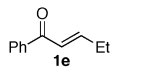
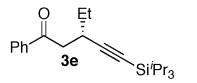
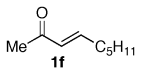
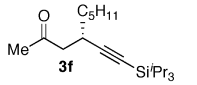
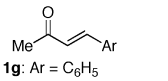
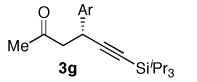
Table 2. Asymmetric Conjugate Alkynylation of Enones[a]



1 2o: R = Me 2p: R = ^{i}Pr 3

entry	enone	product	isolated yield and ee[b]
1	 1a	 3a	93%, 96% ee
2	 1b	 3b	92%, 97% ee
3	 1c	 3c	97%, 95% ee
4	 1d	 3d	94%, 94% ee
5	 1e	 3e	94%, 97% ee
6	 1f	 3f	91%, 90% ee
7	 1g: Ar = C_6H_5	 3g	10%[c]
8[d]			82%, 96% ee
9[d]	1h: Ar = 4-MeOC_6H_4	3h	73%, 98% ee

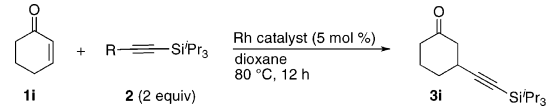
[a] Reaction conditions: **1** (0.20 mmol), **2o** (0.30 mmol), [Rh(OH)((*R*)-binap)]$_2$ (5 mol % of Rh) in 1,4-dioxane/H_2O (10:1, 0.4 mL). [b] Determined by chiral HPLC analysis. [c] ee was not determined. [d] Performed with **2p** (0.4 mmol) in 1,4-dioxane (0.4 mL) at 80 °C for 24 h in the presence of [Rh(OH)(cod)]$_2$ (5 mol % of Rh) and (*R*)-DTBM-segphos (6 mol %).

1−4). Linear enones **1e** and **1f**, bearing a longer alkyl chain at the β position, are also good substrates (entries 5 and 6). On the other hand, the yield of β-alkynylation product was low for the enone **1g**, which is substituted with a phenyl group at the β-position (entry 7). The alkynylation of β-arylenones was greatly improved by use of (*R*)-DTBM-segphos[18] as a ligand and more bulky silanol **2p** having two isopropyl groups. Thus, the reaction of β-arylenones **1g** and **1h** with alkynylsilanol **2p** gave β-alkynylketones **3g** and **3h**, respectively, in good yields (82% and 73%) with high enantioselectivity (96% and 98% ee; entries 8 and 9).[19]

(17) For examples of transition-metal-catalyzed coupling reactions using organosilanols, see: (a) Hirabayashi, K.; Nishihara, Y.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 7893. (b) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299. (c) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342. (d) Hirabayashi, K.; Ando, J.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1409. (e) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K.; Osakada, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774. (f) Fujii, T.; Koike, T.; Mori, A.; Osakada, K. *Synlett* **2002**, 295. (g) Fujii, T.; Koike, T.; Mori, A.; Osakada, K. *Synlett* **2002**, 298. (h) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 565. (i) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 3221. (j) Demmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876. (k) Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486. (l) Denmark, S. E. *J. Org. Chem.* **2009**, *74*, 2915.

The reactivity of 2-cyclohexen-1-one (**1i**) in the present rhodium-catalyzed alkynylation is very different from that of linear enones (Table 3). Thus, the reaction of enone **1i**

Table 3. Conjugate Alkynylation of 2-Cyclohexen-1-one (**1i**)[a]



1i 2 (2 equiv) 3i

entry	catalyst	R	yield (%)[b]
1	[Rh(OH)((*R*)-binap)]$_2$	$SiMe_2$(OH) (**2o**)	2
2	[Rh(OH)((*R*)-DTBM-segphos)]$_2$[c]	Si^iPr_2(OH) (**2p**)	22
3	[Rh(OH)(cod)]$_2$	$SiMe_2$(OH) (**2o**)	69
4	[Rh(OH)(cod)]$_2$	Si^iPr_2(OH) (**2p**)	83
5	[Rh(OH)(cod)]$_2$	H (**2m**)	5

[a] Reaction conditions: **1i** (0.20 mmol), **2** (0.40 mmol), Rh catalyst (5 mol % of Rh) in 1,4-dioxane (0.4 mL) at 80 °C for 12 h. [b] Determined by ^{1}H NMR. [c] In situ generated from [Rh(OH)(cod)]$_2$ (5 mol % of Rh) and (*R*)-DTBM-segphos (6 mol %).

with alkynylsilanol **2o** in the presence of [Rh(OH)(binap)]$_2$ at 80 °C for 12 h gave only 2% of β-alkynylketone **3i** (entry 1). The reaction with bulky silanol **2p** in the presence of the rhodium/DTBM-segphos catalyst also gave a low yield of **3i** (22%) (entry 2). On the other hand, it was found that the rhodium complex bearing a diene as a ligand was effective in the alkynylation of **1i**. The use of [Rh(OH)(cod)]$_2$ (cod = 1,5-cyclooctadiene) gave **3i** in 69% yield (entry 3). Higher yield of **3i** was obtained by use of silanol **2p** as an alkynylating reagent (entry 4). The use of terminal alkyne **2m** resulted in a low yield of **3i** here again (entry 5).

On the basis of the high catalytic activity of cod complex [Rh(OH)(cod)]$_2$ as demonstrated in Table 3, chiral diene ligands[20] were tested for the asymmetric alkynylation of cyclic enones. The use of (*R*,*R*)-Bn-bod*[20c,d] enabled the alkynylation to proceed with high enantioselectivity. Thus, the reaction of cyclic enones **1i**−**1k** with alkynylsilanol **2p** in the presence of Cs_2CO_3 (10 mol %) and a chiral diene-rhodium catalyst, in situ generated from [RhCl(C_2H_4)$_2$]$_2$ (5

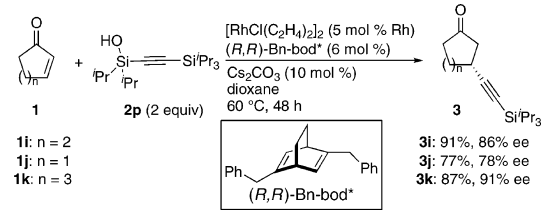
(18) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(19) The reaction of **1g** with **2p** in the presence of [Rh(OH)((*R*)-binap)]$_2$ at 80 °C for 24 h gave **3g** in 52% yield with 8% ee. On the other hand, the reaction of **1g** with **2o** catalyzed by in situ generated [Rh(OH)((*R*)-DTBM-segphos)]$_2$ gave **3g** in 14% yield.

(20) For a review of chiral diene ligands, see: (a) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482 For selected examples of the asymmetric reactions using chiral diene ligands, see: (b) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (c) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (d) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503. (e) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (f) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (g) Läng, F.; Breher, F.; Stein, D.; Grützmacher, H. *Organometallics* **2005**, *24*, 2997. (h) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331. (i) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (j) Noël, T.; Vandyck, K.; Van der Eycken, J. *Tetrahedron* **2007**, *63*, 12961. (k) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669.

mol % of Rh) and (*R*,*R*)-Bn-bod*, at 60 °C for 48 h gave the corresponding 1,4-addition products **3i**−**3k** in 77−91% yield with 78−91% ee (Scheme 3).

Scheme 3. Asymmetric Conjugate Alkynylation of Cyclic Enones



In summary, we have developed a rhodium-catalyzed asymmetric conjugate alkynylation of enones with alkynylsilanols giving β-alkynylketones with high enantioselectivity.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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