Communication

Steric Tuning of Silylacetylenes and Chiral Phosphine Ligands for Rhodium-Catalyzed Asymmetric Conjugate Alkynylation of Enones

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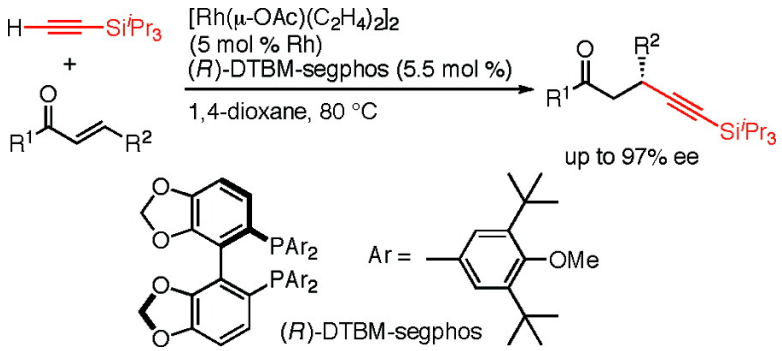

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Steric Tuning of Silylacetylenes and Chiral Phosphine Ligands for Rhodium-Catalyzed Asymmetric Conjugate Alkynylation of Enones

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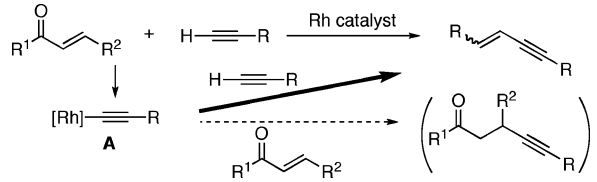
Rhodium-catalyzed asymmetric conjugate addition to α,β-unsaturated ketones and related compounds is now well-recognized to be one of the most efficient methods of introducing aryl and alkenyl groups with high enantioselectivity.[1] On the other hand, asymmetric conjugate addition of alkynyl groups has not been well-developed in spite of its high synthetic utility.[2] A most straightforward and convenient reaction scheme should be the addition of terminal acetylenes to enones, but it faces an inherent problem that terminal acetylene is more reactive than enone toward the alkynyl−rhodium intermediate, which results in the predominant formation of acetylene dimers rather than β-alkynylketones (Scheme 1).[3,4] One solution to this problem is the rhodium-catalyzed 1,3-rearrangement of an alkynyl group from alkynyl alkenyl carbinols, where the concentration of acetylene is kept minimal during the reaction, leading to high yields of the β-alkynylketones.[5] In this communication, we wish to report another solution to the rhodium-catalyzed asymmetric conjugate alkynylation, which is realized by use of (triisopropylsilyl)acetylene combined with DTBM-segphos[6] as a chiral phosphine ligand. The sterically bulky substituents on the silicon and phosphorus atoms should hinder the acetylene from approaching the alkynyl−rhodium intermediate (Figure 1).

Scheme 1.



The effects of the alkyl substituents on the silylacetylenes and chiral bisphosphine ligands were examined for the addition to 1-phenyl-2-buten-1-one (**1a**) (Table 1). In the presence of 5 mol % of a Rh/(*R*)-binap catalyst generated from $[Rh(\mu\text{-}OAc)(C_2H_4)_2]_2$[7] and (*R*)-binap,[8] the reaction of **1a** with 2 equiv of (*tert*-butyldimethylsilyl)acetylene at 80 °C for 12 h gave only 9% yield of β-alkynylketone **2a** (***Si*** = $SiMe_2{}^tBu$), where a major product was the dimer of the silylacetylene (entry 1).[9] Similarly, the reaction of (triethylsilyl)acetylene gave a low yield (10%) of β-alkynylketone **3a** (***Si*** = $SiEt_3$; entry 2). By use of sterically more bulky (triisopropylsilyl)acetylene, the yield of conjugate addition was increased to 35% (entry 3). This yield is still not satisfactory but substantially higher than that with other silylacetylenes. The results obtained for the reaction with binap, segphos, and their modified derivatives showed that the yield of **4a** (***Si*** = Si^iPr_3) is strongly dependent on the steric bulkiness of the diarylphosphino groups, with the more bulky aryl group giving the higher yield. The reaction with segphos[6] (Ar = Ph) resulted in the formation of **4a** in 36% yield (entry 4), which is comparable to that observed with binap. The yield of **4a** was increased to 49% by use of (*R*)-DMM-binap,[10] where the Ar on phosphorus is 3,5-Me_2-4-$MeOC_6H_2$ (entry 5), and the highest yield (87%) was obtained by use of (*R*)-DTBM-segphos, where Ar is very bulky 3,5-*t*-Bu_2-4-$MeOC_6H_2$ (entry 6). The reaction for a prolonged period of time (24 h) gave a quantitative yield of **4a**, whose enantiomeric excess was 91% (entry 7).

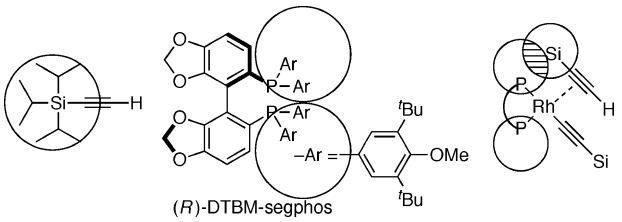
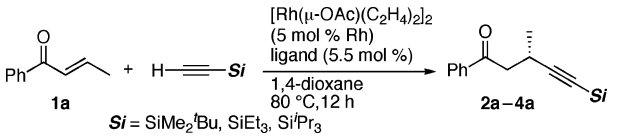


Figure 1.

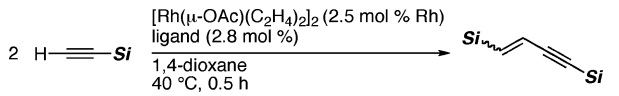
Table 1. Rhodium-Catalyzed Asymmetric Conjugate Addition of Silylacetylenes to Enone **1a**[a]



entry	ligand	***Si***	product	yield (%)[b]
1	(*R*)-binap	$SiMe_2{}^tBu$	**2a**	9
2	(*R*)-binap	$SiEt_3$	**3a**	10
3	(*R*)-binap	Si^iPr_3	**4a**	35
4	(*R*)-segphos	Si^iPr_3	**4a**	36
5	(*R*)-DMM-binap	Si^iPr_3	**4a**	49
6	(*R*)-DTBM-segphos	Si^iPr_3	**4a**	87
7[c]	(*R*)-DTBM-segphos	Si^iPr_3	**4a**	99 (91)[d]

[a] Reaction conditions: enone **1a** (0.20 mmol), silylacetylene (0.40 mmol), $[Rh(\mu\text{-}OAc)(C_2H_4)_2]_2$ (5 mol % of Rh), ligand (5.5 mol %), 1,4-dioxane (0.4 mL) at 80 °C for 12 h. [b] NMR yield. [c] For 24 h. [d] Enantiomeric excess (%) determined by HPLC analysis with a chiral stationary phase column: Chiralcel OJ-H.

Table 2. Rhodium-Catalyzed Dimerization of Silylacetylenes[a]



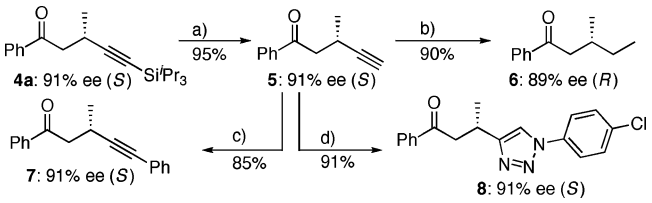
entry	ligand	***Si***	conversion (%)[b]
1	(*R*)-binap	$SiEt_3$	95
2	(*R*)-binap	Si^iPr_3	86
3	(*R*)-DTBM-segphos	$SiEt_3$	25
4	(*R*)-DTBM-segphos	Si^iPr_3	4

[a] Reaction conditions: silylacetylene (0.40 mmol), $[Rh(\mu\text{-}OAc)(C_2H_4)_2]_2$ (2.5 mol % of Rh), ligand (2.8 mol %), 1,4-dioxane (0.8 mL) at 40 °C for 0.5 h. [b] Determined by GC.

The high yield of β-alkynylketone **4a** obtained by the combination of (triisopropylsilyl)acetylene and DTBM-segphos ligand is caused by effective suppression of the dimerization of silylacetylene, which is demonstrated by reference experiments of alkyne dimerization carried out in the absence of enones (Table 2). The Rh/binap catalyst was very active for the dimerization, especially for (triethylsilyl)acetylene, giving high yields of the acetylene dimers

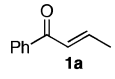
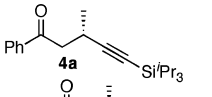
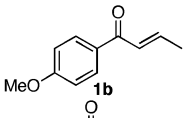
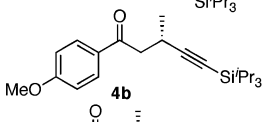
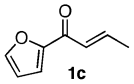
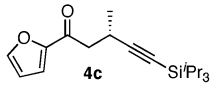
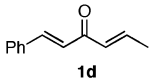
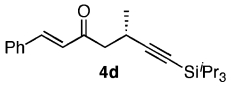
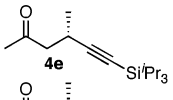
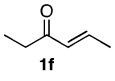
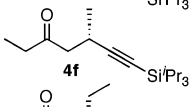
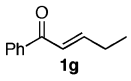
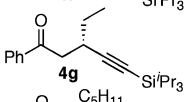
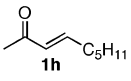
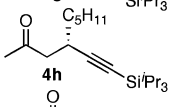
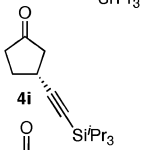
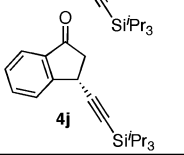
10.1021/ja710540s CCC: $40.75

Scheme 2. [a]



[a] Conditions: (a) TBAF, THF; (b) cat. $RhCl(PPh_3)_3$, EtOH, H_2 (1 atm); (c) iodobenzene, cat. $Pd(PPh_3)_4$, cat. CuI, Et_3N, 60 °C; (d) 1-azido-4-chlorobenzene, cat. $CuSO_4 \cdot 5H_2O$, Na-ascorbate, CH_3CN, H_2O.

Table 3. Asymmetric Conjugate Addition of (Triisopropylsilyl)acetylene to Enones[a]

entry	enone	product	isolated yield and ee[b]
1	 **1a**	 **4a**	99%, 91% ee (*S*)
2	 **1b**	 **4b**	88%, 91% ee (*S*)
3	 **1c**	 **4c**	99%, 93% ee (*S*)
4	 **1d**	 **4d**	78%, 95% ee (*S*)
5	 **1e**	 **4e**	90%, 95% ee (*S*)
6	 **1f**	 **4f**	92%, 92% ee (*S*)
7	 **1g**	 **4g**	80%, 89% ee (*S*)
8	 **1h**	 **4h**	90%, 97% ee (*S*)
9[c]	 **1i**	 **4i**	67%, 88% ee (*R*)
10	 **1j**	 **4j**	54%, 95% ee (*S*)

[a] Reaction conditions: enone **1** (0.20 mmol), (triisopropylsilyl)acetylene (0.40 mmol), $[Rh(\mu\text{-}OAc)(C_2H_4)_2]_2$ (5 mol % of Rh), (*R*)-DTBM-segphos (5.5 mol %), 1,4-dioxane (0.4 mL) at 80 °C for 24 h. [b] Enantiomeric excess values were determined by HPLC. The absolute configurations of **4b**−**4j** were assigned by consideration of the stereochemical pathway. [c] For 42 h.

at the reaction temperature of 40 °C (entries 1 and 2). The dimerization was much slower with the Rh/DTBM-segphos catalyst, the conversion of (triisopropylsilyl)acetylene being only 4% under the same reaction conditions (entries 3 and 4).

The silyl group of **4a** obtained here with 91% ee was readily removed by treatment with tetrabutylammonium fluoride (TBAF) to give alkynylketone **5** without loss of enantiomeric purity (Scheme 2, a). The absolute configuration of **4a** was determined to be *S*-(−) by correlation with saturated ketone **6** (Scheme 2; b).[11] As examples of the synthetic application, the terminal acetylene on **5** was subjected to Sonogashira coupling[12] with iodobenzene and a copper-catalyzed cycloaddition[13] with 1-azido-4-chlorobenzene, both of which gave the target compounds in high yields (Scheme 2, c and d).

The present rhodium-catalyzed asymmetric alkynylation using (triisopropylsilyl)acetylene and DTBM-segphos was successfully applied to several types of α,β-unsaturated ketones (Table 3). The reaction of 1-propenyl ketones **1a**−**1f** bearing aryl, alkenyl, or alkyl substituents on the carbonyl all proceeded well under standard conditions to give the corresponding β-alkynylketones **4a**−**4f** in high yields, the enantioselectivity ranging between 91 and 95% ee (entries 1−6). Linear enones **1g** and **1h**, which are substituted with a longer alkyl chain at the β-position, are also good substrates (entries 7 and 8). Although their reactivity is somewhat lower toward the present alkynylation, cyclic enones **1i** and **1j** gave the corresponding β-alkynylketones **4i** and **4j** with high ee (entries 9 and 10).

In summary, we have succeeded in a conjugate addition of (triisopropylsilyl)acetylene to α,β-unsaturated ketones with high enantioselectivity by use of a rhodium/(*R*)-DTBM-segphos catalyst, where the sterically bulky substituents on the silicon and phosphorus atoms suppress the alkyne dimerization.

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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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(8) Binap; 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

(9) The formation of 1,4-bis(*tert*-butyldimethylsilyl)-1-buten-3-yne (*E* and *Z* isomers) with the complete conversion of the silylacetylene was observed by ^1H NMR of the crude reaction mixture.

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