Synthetic Methods

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Asymmetric Synthesis of β-Alkynyl Aldehydes by Rhodium-Catalyzed Conjugate Alkynylation**

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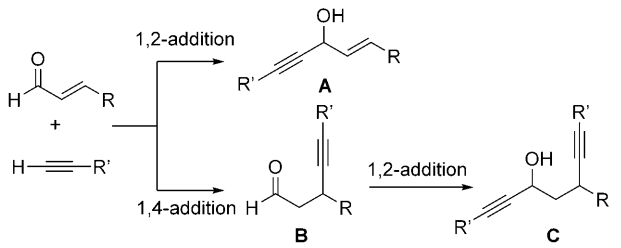
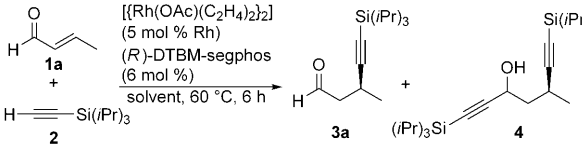
Catalytic asymmetric conjugate addition of terminal alkynes to α,β-unsaturated carbonyl compounds provides a powerful method to construct a chiral carbon center at the propargylic position, realizing high atom efficiency.[1] In 2006, Carreira and co-workers reported the first example of copper-catalyzed asymmetric conjugate addition of terminal alkynes to electron-deficient alkenes derived from Merdrum's acid, giving chiral β-alkynyl diesters with high enantioselectivity.[2] In contrast, we recently reported a rhodium-catalyzed reaction which realizes the asymmetric conjugate addition of a silylacetylene to α,β-unsaturated ketones giving chiral β-alkynyl ketones.[3–5] We next focused on the synthesis of a chiral β-alkynyl aldehyde, which is an important chiral building block in organic synthesis.[6] Diverse transformations of both the formyl group and the alkynyl group on β-alkynyl aldehydes offers access to useful compounds. For example, (+)-8-*epi*-xanthatin, which has promising biological activities, has been synthesized by way of (*S*)-3-methyl-5-(triisopropylsilyl)-4-pentynal (**3a**) derived from enantiopure methyl 3-hydroxy-2-methylpropanoate in six steps.[6] The asymmetric addition of terminal alkynes to α,β-unsaturated aldehydes is an ideal process for the synthesis of chiral β-alkynyl aldehydes, but it potentially includes several pathways leading to the 1,2-adduct **A**, the 1,4-adduct **B**, and the double-addition product **C** (Scheme 1).[7] In the rhodium-catalyzed addition of arylboronic acids to enals, Ueda and Miyaura reported in 2000 that high regioselectivity for the 1,4-addition product was accomplished by using a cationic rhodium complex in aqueous methanol.[8] Asymmetric variants of the 1,4-addition of arylboronic acids to enals have also been reported by Miyaura and co-workers,[9] Carreira and co-workers,[10] and our group.[11] In contrast, catalytic asymmetric conjugate alkynylation of enals has not been reported, to the best of our knowledge.[12] Herein we report the rhodium-catalyzed asymmetric conjugate alkynylation of enals, giving chiral β-alkynyl aldehydes in high yields with high enantioselectivity.



Scheme 1. Selectivity on an alkynylation of α,β-unsaturated aldehydes.

In the first set of experiments, addition of triisopropylsilyl acetylene (**2**) to 2-butenal (**1a**) was examined under several reaction conditions (Table 1). Treatment of **1a** with **2** (2.0 equiv) in 1,4-dioxane at 60 °C for six hours in the presence of in situ generated [Rh(OAc)((*R*)-DTBM-segphos)][13] (5 mol %), which is a standard set reaction conditions for the rhodium-catalyzed asymmetric alkynylation of enones,[3] gave a mixture of 1,4-addition product **3a** (21 %) and bis(alkynyl) alcohol **4** (48 %, d.r. = 1:1; Table 1, entry 1).[14] The chemoselectivity of the reaction was strongly dependent on the solvent. Thus, the use of a mixed solvent system composed of methanol and THF[11] furnished the 1,4-addition product **3a** in 71 % yield as the sole addition product (Table 1, entry 2). The reaction using 2-propanol or *tert*-butyl alcohol instead of methanol increased the yield of the bis(alkynyl) alcohol **4** (Table 1, entries 3 and 4). The reaction in methanol displayed the perfect selectivity for the 1,4-addition to give **3a** in 79 % yield (Table 1, entry 5). The

Table 1: Rhodium-catalyzed asymmetric conjugate alkynylation of enal **1a**.[a]



Entry	Solvent	Yield of **3a** [%][b]	Yield of **4** [%][b]
1	1,4-dioxane	21	48
2	MeOH/THF (4:1)	71	0
3	*i*PrOH/THF (4:1)	63	17
4	*t*BuOH/THF (4:1)	10	55
5	MeOH	79	0
6[c]	MeOH	93 (96 % *ee* (*S*))[d]	0

[a] Reaction conditions: enal **1a** (0.20 mmol), alkyne **2** (0.40 mmol), [{Rh(OAc)$(C_2H_4)_2$}$_2$] (5 mol % of Rh), (*R*)-DTBM-segphos (6 mol %), solvent (0.4 mL) at 60 °C for 6 h. [b] Determined by ^{1}H NMR analysis. [c] Performed at 40 °C for 24 h. [d] Determined by HPLC analysis of 3-methyl-5-(triisopropylsilyl)-4-pentynyl benzoate derived from **3a**.

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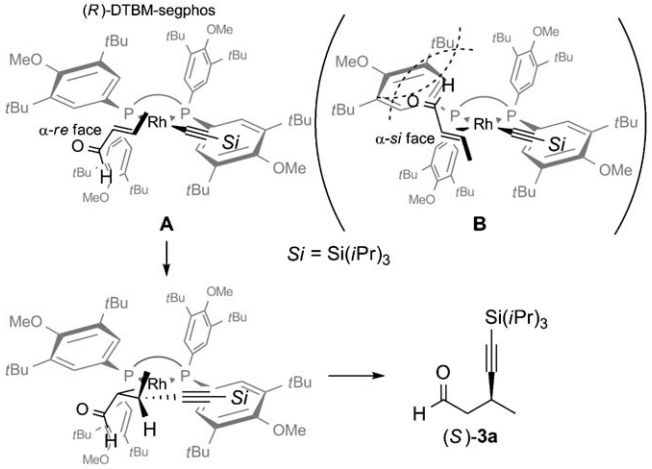
reaction under milder reaction conditions (40 °C for 24 h) proceeded to give **3a** in 93 % yield with an enantiomeric excess (*ee*) of 96 % (Table 1, entry 6).[15] The absolute configuration of **3a** was determined to be *S*-(+) by correlation with terminal alkyne **5** [$[\alpha]_D^{20} = +53$ ($c = 1.05$, $CHCl_3$) for 96 % *ee* (*S*); lit. $[\alpha]_D^{26} = -51.2$ ($c = 1.14$, $CHCl_3$) for (*R*)-**5**],[16] which was derived from **3a** in three steps (see Scheme 3). The absolute configuration of (*S*)-**3a** is in good agreement with the stereochemical pathway shown in Scheme 2, the enal intermediate **A** being attacked by the alkynylrhodium on its α-*re* face in the present reaction.



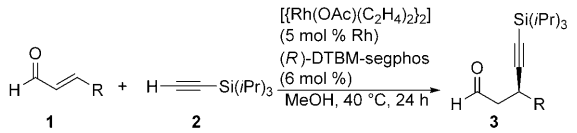
Scheme 2. Stereochemical pathway.

The present rhodium-catalyzed asymmetric alkynylation displayed tolerance to a wide range of functional groups (Table 2). The reaction of alkyne **2** with β-substituted enals having alkyl (**1a**–**1d**) and alkenyl groups (**1e**) proceeded well to give the corresponding β-alkynyl aldehydes **3a**–**3e** in good yields with the enantioselectivity ranging between 95 and 99 % *ee* (Table 2, entries 1–6). The alkynylation of enals having bromo (**1f**), hydroxy (**1g**), ether (**1h**), ester (**1i**), keto (**1j**), nitro (**1k**), and sulphonyl (**1l**) groups gave the corresponding β-alkynyl aldehydes in good yields with high enantioselectivity (Table 2, entries 7–13).

The β-alkynyl aldehydes obtained here with high enantioselectivity are readily converted into functionalized compounds without loss of enantiomeric purity (Scheme 3 and 4). For example, the reduction of the formyl group on **3a**, then etheration of the resulting alcohol, and final desilylation by treatment with tetrabutylammonium fluoride gave terminal alkyne **5**, which is one of the key intermediates for the syntheses of natural products, ciguatoxin,[16] frondosin B,[17] and goniodomin A[18,19] (Scheme 3). As another example of a synthetic application, the Pinnic oxidation[20] of **3b**, and then esterification of the resulting carboxylic acid with Me_3SiCHN_2 gave β-alkynyl ester **6** in 77 % yield (Scheme 4). The Wittig olefination of **3b** gave δ-alkynyl-α,β-unsaturated ester in 86 % yield (98 % *ee*).

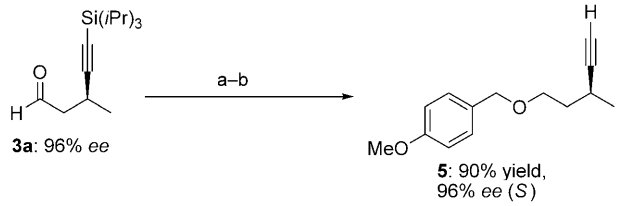
In summary, we have developed a rhodium-catalyzed conjugate alkynylation of α,β-unsaturated aldehydes giving enantioenriched β-alkynyl aldehydes, which are useful chiral building blocks. The chemoselectivity of the product was strongly dependent on the solvent, and the reaction in methanol displayed perfect selectivity for the formation of 1,4-addition products of enals.

Table 2: Rhodium-catalyzed asymmetric conjugate alkynylation of enals.[a]

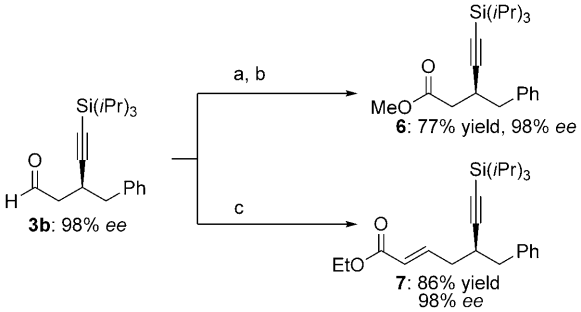


Entry	R	Yield [%][b]	*ee* [%][c]
1	CH_3 (**1a**)	91 (**3a**)	96 (*S*)
2[d]	CH_3 (**1a**)	84 (**3a**)	96 (*S*)
3	CH_2Ph (**1b**)	90 (**3b**)	98 (*S*)
4	C_5H_{11} (**1c**)	86 (**3c**)	98 (*S*)
5	$CH(CH_3)_2$ (**1d**)	88 (**3d**)	99 (*R*)
6	(*Z*)-$(CH_2)_2CH{=}CHC_2H_5$ (**1e**)	93 (**3e**)	95 (*S*)
7	$(CH_2)_2CH_2Br$ (**1f**)	61 (**3f**)	94 (*S*)
8	$(CH_2)_8CH_2OH$ (**1g**)	92 (**3g**)	96 (*S*)
9	CH_2OCH_3 (**1h**)	85 (**3h**)	93 (*S*)
10	$(CH_2)_2CH_2OC(O)Ph$ (**1i**)	79 (**3i**)	95 (*S*)
11	$(CH_2)_3C(O)Ph$ (**1j**)	74 (**3j**)	97 (*S*)
12	$(CH_2)_2CH_2NO_2$ (**1k**)	83 (**3k**)	93 (*S*)
13	$(CH_2)_2CH_2SO_2Ph$ (**1l**)	83 (**3l**)	96 (*S*)

[a] Reaction conditions: enal **1** (0.20 mmol), alkyne **2** (0.40 mmol), [{Rh(OAc)(C2H4)2}2] (5 mol % of Rh), MeOH (0.4 mL) at 40 °C for 24 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis. The absolute configurations of **3b**–**3l** were assigned by analogy to product in entry 1. [d] The reaction of **1a** (2.0 mmol) with **2** (4.0 mmol).



Scheme 3. a) $NaBH_4$, EtOH, RT, 1 h. b) *p*-Methoxybenzyl chloride, NaH, Bu_4NI, DMF, RT, 2 h. c) Bu_4NF, THF, RT, 2 h (90 % in three steps). DMF = *N*,*N*-dimethylformamide.



Scheme 4. a) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene, *t*BuOH/H_2O, RT, 1 h. b) Me_3SiCHN_2, benzene/EtOH, 0 °C, 15 min. c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, 40 °C, 13 h.

Experimental Section

A mixture of [{Rh(OAc)(C_2H_4)$_2$}$_2$] (2.2 mg, 5 μmol, 10 μmol of Rh) and (*R*)-DTBM-segphos (14.2 mg, 12 μmol) in methanol (0.4 mL) was stirred at room temperature for 15 min. Then α,β-unsaturated aldehyde **1** (0.20 mmol) and (triisopropylsilyl)acetylene (73.0 mg, 0.40 mmol) were added to the solution, which was then stirred at 40 °C for 24 h. The mixture was passed through a short column of silica gel with diethyl ether as the eluent. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel with hexane/ethyl acetate to give compound **3**.

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[14] The formation of 1,2-addition product was not observed.

[15] The reaction of **1a** with *tert*-butyldimethylsilyl acetylene, triethylsilyl acetylene, phenylacetylene, and 1-octyne under the same conditions gave the corresponding β-alkynyl aldehydes in 25, 8, 5, and 1% yield, respectively.

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