Rhodium-catalyzed asymmetric conjugate alkynylation of nitroalkenes†

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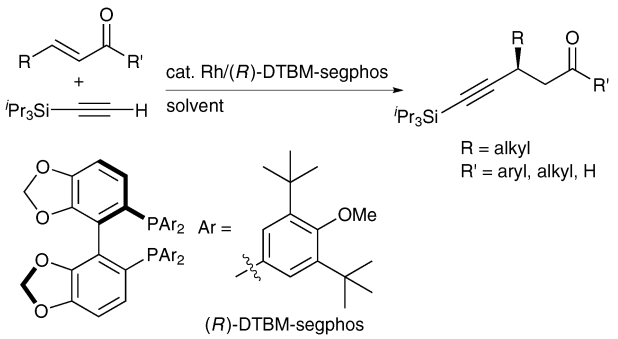
Asymmetric addition of (triisopropylsilyl)acetylene to nitroalkenes took place in the presence of a rhodium/chiral bisphosphine catalyst to give β-alkynylated nitroalkanes in high yields with high enantioselectivity.

Transition metal-catalyzed asymmetric addition of terminal alkynes to unsaturated bonds has substantial merit for the synthesis of chiral internal alkynes in view of atom efficiency.[1,2] An ideal process is the reaction of terminal alkynes in the presence of a truly catalytic amount of a catalyst without using a stoichiometric amount of pre-prepared alkynylmetal reagents. The catalytic conjugate addition of terminal alkynes to α,β-unsaturated carbonyl compounds is a challenging reaction realizing high atom efficiency, and there have been several reports on the addition to β-unsubstituted enones and enoates.[3] In contrast, asymmetric conjugate alkynylation of enones and related compounds bearing β-substituents,[4] which is essential for the creation of new stereogenic carbon centers at β-position, has remained to be developed.[5,6] In 2005, Carreira *et al.* reported the first example of a catalytic asymmetric conjugate addition of terminal alkynes using a chiral copper catalyst, where the Michael acceptors are those derived from Meldrum's acid.[7] In this context, we recently reported rhodium-catalyzed asymmetric addition of (triisopropylsilyl)acetylene to conjugated enones and enals, which requires only a rhodium complex coordinated with a chiral bisphosphine ligand, (*R*)-DTBM-segphos (Scheme 1).[8,9] Here we report that nitroalkenes are another class of Michael acceptors suitable for the rhodium-catalyzed asymmetric alkynylation.

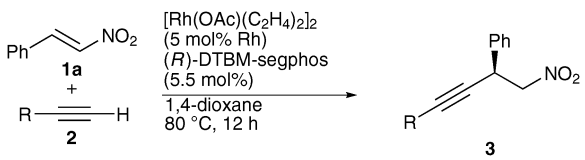


Scheme 1 Asymmetric conjugate alkynylation of enones and enals.

Nitroalkenes are known to be more reactive than enones toward the conjugate addition,[10] and successful examples of the asymmetric addition have been reported for arylation[11] and alkylation.[12,13] Nevertheless, there has been only one report on the asymmetric alkynylation of nitroalkenes to the best of our knowledge. Thus, Tomioka *et al.* reported[14] the asymmetric addition of alkynylzinc reagents in the presence of a stoichiometric amount of a chiral amino alcohol.

A nitroalkene substituted with a phenyl group at the β-position was found to be highly reactive toward the rhodium-catalyzed alkynylation. The high reactivity is in remarkable contrast to the low reactivity of β-phenyl-substituted conjugated enones.[15] As shown in Table 1, the reaction of β-nitrostyrene (**1a**) with (triisopropylsilyl)acetylene (**2o**, 2 equiv.) in 1,4-dioxane in the presence of Rh(OAc)((*R*)-DTBM-segphos) (5 mol% of Rh), *in situ* generated from $[Rh(OAc)(C_2H_4)_2]_2$ and (*R*)-DTBM-segphos,[16] at 80 °C for 12 h gave the addition product **3ao** in 94% yield with 97% ee (*R*)[17] (entry 1). The yield of **3ao** was kept high (88%) in the alkynylation with a reduced amount (1.2 equiv.) of **2o** (entry 2). The reaction with a lower catalyst loading (2 mol% of Rh) for a prolonged reaction time gave the addition product in high yield (89%) with high enantioselectivity (entry 3). A substituent on the terminal alkyne had a great influence on the yield of the addition product in the alkynylation of nitroalkenes, as it has been already observed in the alkynylation of enones.[8a] Thus, the addition of (*tert*-butyldimethylsilyl)acetylene (**2p**) and (triethylsilyl)acetylene (**2q**) resulted in very low yields of the corresponding addition products due to the alkyne

Table 1 Asymmetric addition of alkynes **2** to nitrostyrene (**1a**)[a]



Entry	R	Yield[b] (%)	ee[c] (%)
1	^{i}Pr$_3$Si (**2o**)	94 (**3ao**)	97 (*R*)
2[d]	^{i}Pr$_3$Si (**2o**)	88 (**3ao**)	97 (*R*)
3[e]	^{i}Pr$_3$Si (**2o**)	89 (**3ao**)	97 (*R*)
4	^{t}BuMe$_2$Si (**2p**)	5 (**3ap**)[f]	—[g]
5	Et$_3$Si (**2q**)	5 (**3aq**)[f]	—[g]
6	Ph (**2r**)	0 (**3ar**)	—

[a] Reaction conditions: $[Rh(OAc)(C_2H_4)_2]_2$ (5 mol% of Rh), (*R*)-DTBM-segphos (5.5 mol%), **1a** (0.20 mmol), **2** (0.40 mmol), 1,4-dioxane (0.4 mL) at 80 °C for 12 h. [b] Isolated yield. [c] Determined by HPLC analysis with a chiral stationary phase column: Chiralcel OD-H. [d] Reaction with 1.2 equiv. of **2o**. [e] The reaction of **1a** (1.0 mmol) with **2o** (2.0 mmol) in presence of the rhodium catalyst (2 mol% of Rh) in 1,4-dioxane (0.5 mL) for 24 h. [f] Determined by ^{1}H NMR. [g] Not determined.

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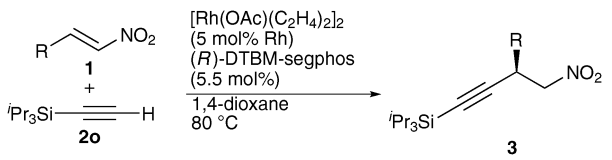
Table 2 Asymmetric addition of (triisopropylsilyl)acetylene (**2o**) to nitroalkenes **1**[a]



Entry	R	Time/h	Yield[b] (%)	ee[c] (%)
1	Ph (**1a**)	12	94 (**3ao**)	97 (*R*)
2	4-MeC_6H_4 (**1b**)	24	91 (**3bo**)	98 (*R*)
3	3-MeC_6H_4 (**1c**)	24	95 (**3co**)	97 (*R*)
4	2-MeC_6H_4 (**1d**)	24	95 (**3do**)	97 (*R*)
5	4-MeOC_6H_4 (**1e**)	24	70 (**3eo**)	95 (*R*)
6	4-AcOC_6H_4 (**1f**)	24	92 (**3fo**)	97 (*R*)
7	4-ClC_6H_4 (**1g**)	24	95 (**3go**)	97 (*R*)
8	4-$CF_3C_6H_4$ (**1h**)	24	88 (**3ho**)	98 (*R*)
9	2-Naphthyl (**1i**)	24	99 (**3io**)	97 (*R*)
10	Me (**1j**)	48	80 (**3jo**)	92 (*R*)
11	Et (**1k**)	48	83 (**3ko**)	94 (*R*)
12	^{i}Pr (**1l**)	48	96 (**3lo**)	99 (*R*)
13	Cyclohexyl (**1m**)	48	91 (**3mo**)	97 (*R*)
14	4-MeO$C_6H_4CH_2OCH_2$ (**1n**)	48	88 (**3no**)	92 (*R*)

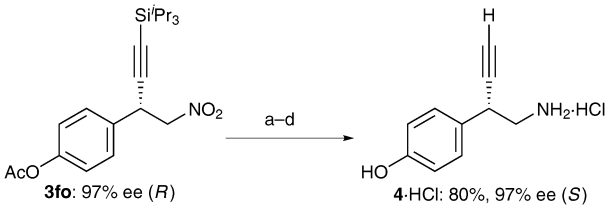
[a] Reaction conditions: $[Rh(OAc)(C_2H_4)_2]_2$ (5 mol% of Rh), (*R*)-DTBM-segphos (5.5 mol%), **1** (0.20 mmol), **2o** (0.40 mmol), 1,4-dioxane (0.4 mL) at 80 °C. [b] Isolated yield. [c] Determined by HPLC analysis. The absolute configuration of **3fo** was determined to be *R* (Scheme 2). For others, they were assigned by analogy with entry 6.

dimerization (entries 4 and 5). In the reaction of phenylacetylene (**2r**), the formation of the corresponding addition product was not observed (entry 6).

Table 2 summarizes the results obtained for the reactions of several nitroalkenes **1** with (triisopropylsilyl)acetylene (**2o**). The addition to β-nitrostyrenes substituted with a methyl group at *para*- (**1b**), *meta*- (**1c**), and *ortho*-position (**1d**) on the benzene ring all gave the corresponding addition products with high enantioselectivities (entries 2–4). The present catalytic asymmetric alkynylation was also successful for nitroalkenes substituted with aromatic groups bearing methoxy (**1e**), acetoxy (**1f**), chloro (**1g**), and trifluoromethyl (**1h**), and with 2-naphthyl group (**1i**) giving the corresponding addition products (**3eo–3io**) with over 95% ee (entries 5–9). Nitroalkenes substituted with primary alkyl groups, methyl (**1j**) and ethyl (**1k**), secondary alkyl groups, isopropyl (**1l**) and cyclohexyl (**1m**), and a functionalized alkyl group (**1n**) are also good substrates to give the corresponding addition products **3jo–3no** in high yields with high enantioselectivity (entries 10–14).[18]

The β-alkynylated nitroalkanes obtained here with high enantioselectivity are readily converted into β-ethynyl alkylamines without loss of enantiomeric purity (Scheme 2). For example, deacetylation of **3fo** followed by reduction of the nitro group into amino by treatment with $Zn/ClSiMe_3$ in ethanol,[19] and desilylation gave β-ethynyltyramine **4** (80% yield as **4**·HCl),[20] which is an inhibitor of dopamine β-hydroxylase.[21] The absolute configuration of **3fo** was determined to be *R*-(−) by correlation with (*S*)-**4**·HCl ($[\alpha]_D^{20}$ −15.3 (*c* 1.00, DMF) for 97% ee (*S*); lit.[21b] $[\alpha]_D^{25}$ −17.1 (*c* 1.5, DMF) for (*S*)-**4**·HCl).

In summary, we have succeeded in a conjugate addition of (triisopropylsilyl)acetylene to nitroalkenes by use of a rhodium/(*R*)-DTBM-segphos catalyst giving the addition products in high yields with high enantioselectivity.



Scheme 2 Transformation of **3fo** into **4**·HCl. *Reagents and conditions*: (a) TsOH·H_2O, EtOH, 70 °C; (b) Zn, Me_3SiCl, EtOH, rt; (c) Bu_4NF, THF, rt; (d) HCl in Et_2O.

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