Asymmetric C–H Addition

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Nickel-Catalyzed Asymmetric Addition of Alkyne C–H Bonds across 1,3-Dienes Using Taddol-Based Chiral Phosphoramidite Ligands**

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Much interest has been focused on the catalytic, direct conversion of alkyne C–H bonds through C–C bond-forming reactions without the stoichiometric generation of acetylides.[1] One of the most widely used procedures for such an atom-economical process is the nucleophilic alkynylation of carbonyl compounds, α,β-unsaturated carbonyl compounds, or related electrophiles, in which catalytically generated metal acetylides often play a key role.[2,3] Recent attention has focused on the development of asymmetric variants of these nucleophilic alkynylation reactions for the synthesis of highly functionalized chiral alkyne derivatives.[4,5]

Besides these nucleophilic alkynylation reactions, hydroalkynylation, i.e. the addition of alkyne C–H bonds, across unactivated carbon–carbon multiple bonds has attracted increasing attention.[1b] After extensive studies on the homo- and cross-dimerization reactions of alkynes using rhodium, palladium, and nickel catalysts,[6] hydroalkynylation has been extended to carbon–carbon double bonds, such as those in allenes and cyclopropenes.[7,8] However, the scope of the hydroalkynylation reaction is still significantly limited.[9,10] As a consequence, no successful catalytic asymmetric hydroalkynylation reactions have been established, except for the rhodium-catalyzed hydroalkynylation of allenes.[10]

We recently showed that bulky triisopropylsilylacetylene underwent addition to C=C bonds in 1,3-dienes, norbornene, styrenes, and methylenecyclopropanes in the presence of nickel triorganophosphine catalysts.[9] The relatively narrow scope for the choice of phosphine ligands in these reactions could be a major difficulty in applying this system to asymmetric synthesis. Herein, we report the nickel-catalyzed asymmetric hydroalkynylation reactions of 1-aryl-1,3-butadienes involving the essential use of taddol-derived phosphoramidite ligands (taddol = 2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol). In addition to the significance of the chiral ligands, the use of a terminal alkyne that contains an α-siloxy-*sec*-alkyl group on the alkynyl carbon is important to achieve sufficient reaction efficiency.

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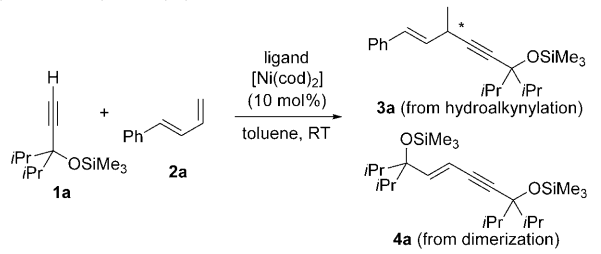
The reaction of alkyne **1a** with *trans*-1-phenyl-1,3-butadiene (**2a**) was carried out in the presence of [Ni(cod)$_2$] (cod = cycloocta-1,5-diene) with various chiral monodentate phosphorus ligands (Table 1). The reactions afforded various ratios of the desired diene–alkyne coupling product **3a** along with alkyne dimerization product **4a**. Use of H-mop[11] and binol (binol = 1,1′-binaphthol)-derived phosphoramidite ligands[12] resulted in low to moderate enantiomeric excess values (Table 1, entries 1–4). In particular, the binol-derived phosphoramidite ligands that have a bulky amino group showed significantly lower selectivities for the desired hydroalkynylation product **3a** (Table 1, entries 3 and 4). We found that the product selectivity (**3a**/**4a**) was highly sensitive to the chiral ligand that was utilized in the reaction, with some dependence upon bulkiness of the ligand. Taddol-derived phosphorus ligands[13] afford higher product selectivity and acceptably high enantioselectivity for the formation of **3**. Examination of a series of chiral ligands that were derived from 3,5-xylyl-taddol showed that the enantioselectivities increased on changing the N substituents from ethyl to benzyl, and then to phenyl (Table 1, entries 5–8). The highest enantioselectivity (91–92% *ee*) was obtained using NPh_2 derivative (*R*,*R*)-**9** with a phosphorus/nickel ratio of 2:1 to 1.2:1 (Table 1, entry 9). No further improvement in product selectivity or enantioselectivity could be achieved using other taddol-derived NPh_2 phosphoramidite ligands **10**–**13** (Table 1, entries 10–13).

In these reactions, the use of *trans* diene was found to be crucial for obtaining high enantioselectivity and reactivity. In contrast, the reaction of *cis*-1-phenyl-1,3-butadiene with alkyne **1a** under the optimized reaction conditions afforded **3a** in only 8% yield with 18% *ee*, along with the alkyne dimerization product **4a** as the major product. Furthermore, the structure of the terminal alkyne was also crucially important. In contrast to alkyne **1a**, dimethyl derivative 3-trimethylsiloxy-3-methyl-1-butyne and triisopropylsilylacetylene completely failed to give the corresponding diene–alkyne coupling product, but gave the corresponding alkyne dimerization and oligomerization products. Alkyne **1b**, which carries a dimethylphenylsilyl group instead of a trimethylsilyl group on the oxygen atom, gave comparable product selectivity (57:31) with high enantioselectivity (92% *ee*).

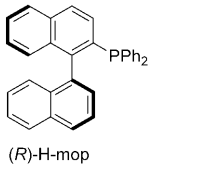
Various *trans*-1-aryl-1,3-butadienes were subjected to the asymmetric hydroalkynylation reaction (Table 2).[14] Importantly, in this investigation, the diene was used as the yield-limiting component, and alkyne **1** was added slowly using a syringe pump over 80–90 hours. The slow-addition method minimized the formation of dimer **4**, thus leading to higher yields of hydroalkynylation products **3**. Besides 1-phenyl- and 1-*para*-tolyl-1,3-butadiene (Table 2, entries 1–3), *para*-tri-

Table 1: Screening of chiral phosphine ligands in nickel-catalyzed asymmetric hydroalkynylation of **2a** with **1a**.[a]

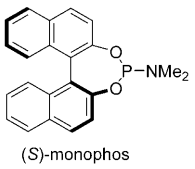


Entry	Ligand	*t* [h]	Yield **3a**/**4a** [%][b]	*ee* **3a** [%][c]
1	(*R*)-H-mop	22	30:68	20 (*R*)
2	(*S*)-monophos	180	46:36	49 (*R*)
3	(*S*,*S*,*S*)-**5**	180	10:85	15 (*S*)
4	(*R*,*S*,*S*)-**5**	180	11:87	35 (*R*)
5	(*R*,*R*)-**6**	180	39:49	24 (*S*)
6	(*R*,*R*)-**7**	20	43:46	57 (*S*)
7	(*R*,*R*)-**8**	90	52:32	79 (*S*)
8	(*R*,*R*)-**9**	48	53:47	92 (*S*)
9[d]	(*R*,*R*)-**9**	48	51:33	91 (*S*)
10	(*R*,*R*)-**10**	33	33:66	69 (*S*)
11	(*R*,*R*)-**11**	33	33:64	70 (*S*)
12	(*R*,*R*)-**12**	17	33:66	62 (*S*)
13	(*R*,*R*)-**13**	180	12:78	78 (*S*)

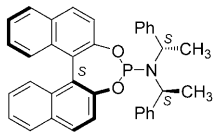
[a] Reaction conditions: **1a** (0.050 mmol), **2a** (0.15 mmol), $[Ni(cod)_2]$ (0.005 mmol), and ligand (0.010 mmol) were stirred in toluene (0.05 mL) at room temperature. [b] Yield determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase. [d] 0.006 mmol ligand was used.



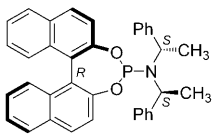
(*R*)-H-mop



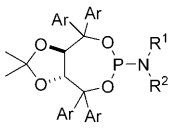
(*S*)-monophos



(*S*,*S*,*S*)-**5**



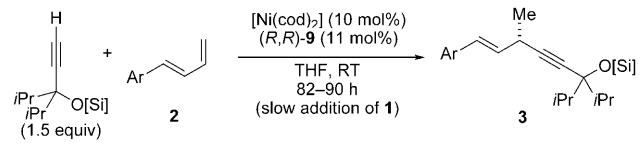
(*R*,*S*,*S*)-**5**



Ligand	Ar	NR^1R^2
(*R*,*R*)-**6**	3,5-Xy	NEt_2
(*R*,*R*)-**7**	3,5-Xy	NBn_2
(*R*,*R*)-**8**	3,5-Xy	NPhBn
(*R*,*R*)-**9**	3,5-Xy	NPh_2
(*R*,*R*)-**10**	Ph	NPh_2
(*R*,*R*)-**11**	*p*-tol	NPh_2
(*R*,*R*)-**12**	*p*-$CF_3C_6H_4$	NPh_2
(*R*,*R*)-**13**	3,5-$(CF_3)_2C_6H_3$	NPh_2

fluoromethyl- and *para*-chloro-substituted 1-phenyl-1,3-butadienes afforded their corresponding hydroalkynylation products with high enantioselectivities (Table 2, entries 4 and 5). *meta*- and *ortho*-methoxyphenyl derivatives also gave the desired products in high enantioselectivity (Table 2, entries 6–8). As with the reaction of the 1-naphthyl derivative, high *ee* values were obtained with moderate reaction yield (Table 2, entry 9).

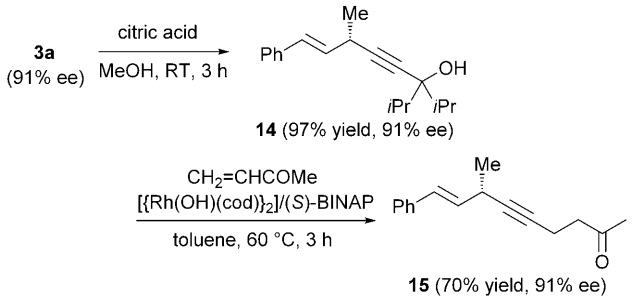
Table 2: Nickel-catalyzed asymmetric hydroalkynylation of 1-aryl-1,3-butadienes.[a]



Entry	**1**	**2** (Ar)	Prod.	Yield [%][b]	*ee* [%][c]
1	**1a**	**2a** (Ph)	**3a**	63	91
2	**1b**	**2a**	**3a′**	60	91
3	**1b**	**2b** (*p*-tol)	**3b′**	57	91
4	**1b**	**2c** (*p*-$CF_3C_6H_4$)	**3c′**	59	90
5	**1a**	**2d** (*p*-ClC_6H_4)	**3d**	55	90
6	**1b**	**2e** (*m*-$MeOC_6H_4$)	**3e′**	68	93
7	**1a**	**2f** (*o*-$MeOC_6H_4$)	**3f**	52	92
8	**1b**	**2f**	**3f′**	58	92
9	**1b**	**2g** (1-naphthyl)	**3g′**	41	92

[a] Reaction conditions: **1** (0.45 mmol) and **2** (0.30 mmol) in THF (0.1 mL) were stirred at room temperature in the presence of $[Ni(cod)_2]$ (30 μmol) and (*R*,*R*)-**9** (33 μmol). [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phas.

The enantioenriched products are useful building blocks in asymmetric organic synthesis. One example is the conversion of the siloxyalkyl group, which is often utilized as a protecting group for a terminal alkyne,[15] into other organic groups by catalytic transformation. The silyl moiety of the siloxyalkyl group is removed by treatment with citric acid (Scheme 1). The hydroxyalkyl group at the *sp* carbon atom



Scheme 1. Desilylation of hydroalkynylation product **3a** followed by rhodium-catalyzed conjugate addition to MVK. MVK = methyl vinyl ketone.

was directly converted into the 3-oxobutyl group by rhodium-catalyzed conjugate addition to methyl vinyl ketone (MVK), which proceeded through C–C bond cleavage at the alkynyl carbon atom.[16] The enantiomeric purity was conserved throughout the transformation, resulting in the isolation of functionalized alkyne **15** with 91 % *ee*. The two C(*sp*)–C(sp^3) bonds in **15** were formed by two different catalytic C–C bond-forming reactions. This demonstrates the potential applicability of the enantioselective catalytic hydroalkynylation reactions in asymmetric organic synthesis.

Further improvement of the new catalytic asymmetric process, mechanistic studies, and synthetic applications are underway.

Experimental Section

General procedure for hydroalkynylation of **2** with **1**: $[Ni(cod)_2]$ (8.3 mg, 0.030 mmol) and (*R*,*R*)-**9** (25.6 mg, 0.033 mmol) were placed in a reaction vessel under a nitrogen atmosphere. *trans*-1,3-Diene (0.30 mmol) and THF (0.10 mL) were added successively, and the reaction mixture was stirred under a nitrogen atmosphere at room temperature. Alkyne **1a** or **1b** (0.45 mmol) was added to the solution using a syringe pump over 82–90 hours. The reaction mixture was passed through a short pad of silica gel (hexanes/EtOAc = 400:1). After the evaporation of volatile materials, the residue was purified further by preparative GPC and/or HPLC (hexane/EtOAc = 400:1).

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[14] Tetrahydrofuran was used in the reactions shown in Table 2 on the basis of our investigation into the effect of solvent on the reaction yield and enantioselectivity. Nonpolar solvents, such as toluene, 1,2-dimethoxyethane, tetrahydrofuran, and dioxane gave almost identical results in terms of yield and enantioselectivity, whilst the use of acetonitrile afforded slightly lower enantioselectivity (88% *ee*) and lower yield (33% yield, determined by NMR analysis, under the reaction conditions used in Table 1).

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