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Asymmetric Catalytic Reductive Coupling of 1,3-Enynes and Aromatic Aldehydes

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Dedicated to Professor Günther Wilke on the occasion of his 80th birthday.

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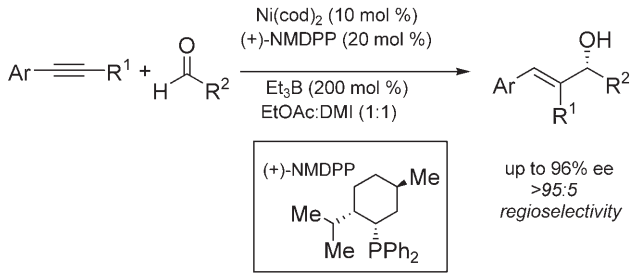
Abstract: Nickel-catalyzed reductive coupling reactions of 1,3-enynes and aromatic aldehydes efficiently afford conjugated dienols in excellent regioselectivity and modest enantioselectivity when conducted in the presence of catalytic amounts of a monodentate, *P*-chiral ferrocenyl phosphine ligand. 1-(Trimethylsilyl)-substituted enynes are shown to be effective coupling partners in these reactions, and the dienol products thus formed readily undergo protiodesilylation under mild conditions.

Keywords: allylic alcohols; asymmetric catalysis; C–C bond formation; nickel; reductive coupling

1,3-Dienes are important and versatile intermediates in organic synthesis. They are able participants in an array of cycloaddition reactions, most notably the Diels–Alder reaction,[1–3] and there are a variety of efficient methods for preparing them.[4] Many of these, such as olefination reactions,[5,6] cross-couplings,[7,8] alkene/enyne metathesis,[9] and other transformations,[10] facilitate convergent synthesis because they simultaneously construct a new carbon-carbon bond. Recently, our laboratory[11] and others[12] reported a new strategy for the synthesis of 1,3-dienes *via* transition metal-catalyzed reductive coupling reactions of 1,3-enynes and aldehydes. In addition to forming a new carbon-carbon bond, these methods also generate a stereogenic center,[13] allowing for efficient construction of chiral 1,3-dienes that have been widely employed in diastereoselective Diels–Alder reactions.[14,15] We now report the first enantioselective examples of catalytic reductive coupling reactions of 1,3-enynes, promoted by sub-stoichiometric amounts of a monodentate, *P*-chiral ferrocenyl phosphine ligand.

Previous work from our laboratory has shown that nickel-catalyzed reductive couplings of aryl-substituted alkynes (Ar–C≡C–R) and aldehydes are highly enantioselective when (+)-neomenthyldiphenylphosphine (NMDPP) is employed as a chiral ligand (Scheme 1).[16] We have also described a class of *P*-chiral, monodentate ferrocenyl phosphines (e.g., **1a**, **1b**; Figure 1) that are efficient promoters of related couplings of aliphatic internal alkynes (Alkyl–C≡C–Alkyl′) and aldehydes,[17] and of multi-component coupling reactions of alkynes, imines, and organoboron reagents.[18]

Reductive coupling reactions of 2-methyl-1-hexen-3-yne and benzaldehyde in the presence of catalytic amounts of $Ni(cod)_2$ and (+)-NMDPP, and a stoichiometric quantity of triethylborane (Et_3B), afforded dienol **2a** in low yield and low enantioselectivity, but with high regioselectivity (Table 1, entry 1). Ferrocenylphosphine **1a** maintained this high regioselectivity but enhanced both the efficacy and enantioselectivity of the transformation (entry 2). *ortho*-Isopropylphenyl-substi-



Scheme 1. Asymmetric, nickel-catalyzed reductive coupling of arylalkynes and aldehydes.

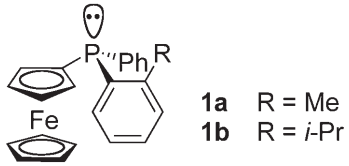
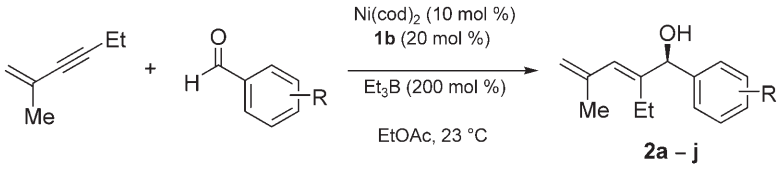


Figure 1.

Table 1. Catalytic, asymmetric reductive coupling of 2-methyl-1-hexen-3-yne and aromatic aldehydes.[a]



2a – j

Entry	R	Ligand	Yield [%],[b] Regioselectivity[c]	ee [%][d]
1	Ph	NMDPP	16 (>95:5)	8
2	"	**1a**	61 (>95:5)	36
3	"	**1b**	66 (>95:5)	56[e]
4	*o*-Me	"	71 (>95:5)	54
5	*p*-Me	"	73 (>95:5)	56
6	*p*-OMe	"	66 (>95:5)	56
7[f]	*p*-Cl	"	54 (>95:5)	55
8[f]	*p*-CF_3	"	62 (>95:5)	50
9[f]	*p*-(COMe)	"	55 (>95:5)	56
10[f]	*p*-(CO_2Me)	"	65 (>95:5)	53
11	1-naphthyl	"	52 (>95:5)	48
12	2-naphthyl	"	47 (>95:5)	58

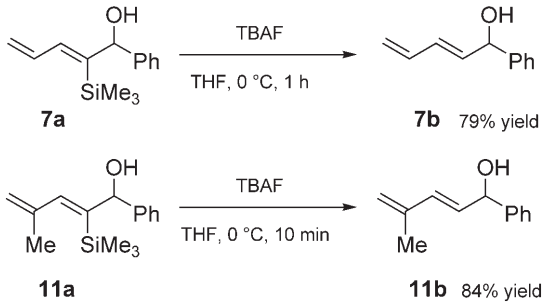
[a] *Experimental conditions:* To $Ni(cod)_2$ (0.05 mmol) and **1b** (0.1 mmol) at room temperature were added EtOAc (0.5 mL), Et_3B (1.0 mmol), the aldehyde (1.0 mmol), and 2-methyl-1-hexen-3-yne (0.5 mmol). The reaction mixture was stirred for 3 h at room temperature unless otherwise noted.
[b] Yield of isolated product.
[c] Determined by ^1H NMR.
[d] Determined by HPLC analysis using Chiralcel OJ or Chiralpak AD-H column.
[e] Absolute configuration of the major enantiomer determined to be (*R*) *via* Mosher's ester analysis.
[f] Reaction was conducted at 35 °C.[19]

tuted-ferrocenylphosphine **1b** provided even higher levels of both reactivity and enantioselectivity (entry 3). A variety of aromatic aldehydes undergo reductive coupling with 2-methyl-1-hexen-3-yne under these conditions in excellent regioselectivity and modest enantioselectivity. Both electron-donating (entries 4–6, 11–12) and electron-withdrawing[19] (entries 7–10) substituents are tolerated, and aromatic ketones and esters are also compatible (entries 9 and 10).

In our previously reported investigations,[11] we found that related coupling reactions of 1,3-enynes proceeded in excellent regioselectivity, regardless of the substitution pattern on the alkene or the size or nature of the other alkyne substituent. The same was found to be true in reactions promoted by ferrocenylphosphine **1b**, and a variety of vinyl-substituted enynes provided a single dienol regioisomer with moderate enantioselectivity (Table 2, entries 1–5), even when this required C–C bond formation to occur adjacent to sterically-demanding *tert*-butyl[20] (entry 4) and trimethylsilyl (entry 5) groups.

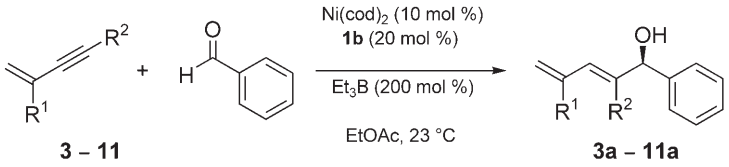
To further investigate this pronounced directing effect, we synthesized a series of isopropenyl-substituted alkynes that we had not previously investigated in nickel-catalyzed reductive coupling reactions. As in the case of their vinyl-substituted counterparts, all coupling reactions of these enynes proceeded in excellent regioselectivity (entries 6–9), and in every case the enantioselectivity surpassed that of the corresponding vinyl-substituted enyne (entries 2–5).

While the 1-(trimethylsilyl)-substituted enynes investigated underwent coupling in low enantioselectivity (Table 2, entries 5 and 10), they are nevertheless worthy of note as they provide access to synthetically-versatile silyl-substituted conjugated dienes.[21] We have found that alkenylsilanes **7a** and **11a** are readily protiodesilylated under mild conditions to afford dienols **7b** and **11b**, respectively (Scheme 2). This two-step sequence affords an efficient route to functionalized 1,3-butadiene and isoprene units, respectively.[22] These products also correspond to the dienols expected from reductive coupling reactions of terminal enynes (H–C≡



Scheme 2. Protiodesilylation of alkenylsilanes.

Table 2. Catalytic, asymmetric reductive coupling reactions of 1,3-enynes with benzaldehyde.[a]



3 – 11 3a – 11a

Entry	R^1	R^2	Yield [%],[b] Regioselectivity[c]	ee [%][d]
1[e]	H	*n*-hex	66 (>95:5)	32
2	"	Cy	70 (>95:5)	42
3	"	Ph	58 (>95:5)	44
4[f]	"	*t*-Bu	66 (>95:5)	33
5[e]	"	$SiMe_3$	53 (>95:5)	14
6[g]	Me	Cy	77 (>95:5)	55[h]
7	"	Ph	42 (>95:5)	54
8[f]	"	*t*-Bu	64 (>95:5)	52
9	"	$SiMe_3$	69 (>95:5)	28

[a] *Experimental conditions:* To $Ni(cod)_2$ (0.05 mmol) and **1b** (0.1 mmol) at room temperature were added EtOAc (0.5 mL), Et_3B (1.0 mmol), benzaldehyde (1.0 mmol), and the enyne (0.5 mmol). The reaction mixture was stirred for 3 h at room temperature unless otherwise noted.
[b] Yield of isolated product.
[c] Determined by ^1H NMR.
[d] Determined by HPLC analysis using Chiralcel OJ, OD, or Chiralpak AD-H column.
[e] Reaction was conducted at 0 °C.
[f] Reaction was conducted at 65 °C.[19]
[g] Reaction was conducted at 38 °C.[19]
[h] Absolute configuration of the major enantiomer determined to be (*R*) *via* Mosher's ester analysis.

$C{-}CR_2{=}CR_2$), which are typically not effective coupling partners.

In summary, we have described a catalytic, enantioselective reductive coupling of 1,3-enynes and aldehydes promoted by a *P*-chiral ferrocenyl monophosphine ligand that affords conjugated dienols in very high regioselectivity and modest enantioselectivity. A variety of aromatic aldehydes serve as coupling partners, and novel enyne substitution was investigated. Trimethylsilyl-substituted dienols obtained *via* reductive coupling undergo protiodesilylation under mild conditions, increasing the scope of synthetically-useful 1,3-dienes that can be accessed using this methodology.

Experimental Section

Standard Procedure for the Catalytic Asymmetric Reductive Coupling of 1,3-Enynes and Aldehydes

In a glovebox, $Ni(cod)_2$ (14 mg, 0.5 mmol), and **1b** (42 mg, 0.1 mmol) were placed into a 10 mL oven-dried, single-necked, round-bottom flask, which was then sealed with a rubber septum. The flask was removed from the glovebox, placed under argon, and ethyl acetate (0.5 mL) was added *via* syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). The resulting solution was stirred 5 min at ambient temperature, and then the aldehyde (1.0 mmol) was added dropwise *via* microsyringe. After stirring an additional 5 min, the enyne (0.5 mmol) was added. The reaction mixture was stirred for 3 h at room temperature, at which point the septum was removed and the mixture was stirred for 30 min open to air to promote oxidation of the catalyst. The crude mixture was purified by flash chromatography on silica gel using a solvent gradient (hexanes:ethyl acetate; 50:1 to 10:1).

Standard Procedure for the Protiodesilylation of Dienyl Alcohols 3a and 4a

A solution of the dienol (0.3 mmol) in THF (3 mL) was cooled to 0 °C. Tetrabutylammonium fluoride (1–2.5 equivs.) was added dropwise *via* syringe and the solution was stirred at 0 °C until consumption of the alkenylsilane was evident by TLC analysis (0.2–1.0 h). H_2O was added (2 mL) and the mixture was partitioned between EtOAc (15 mL) and brine (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (1 × 30 mL), dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel using a solvent gradient (hexanes:ethyl acetate; 93:7 to 90:10).

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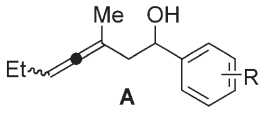
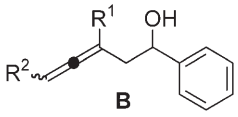


A



B

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