

Nickel-Catalyzed Allylic Substitution of Simple Alkenes

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Transition metal-catalyzed allylic substitution reactions (ASR) have been widely applied in organic synthesis.¹ Many classes of carbon-centered nucleophiles can be employed, including active methylene compounds,² enolates,³ enamines,⁴ and organometallic reagents.⁵ Oppolzer has also demonstrated that olefins may be used as nucleophile equivalents in catalytic intramolecular ASR.⁶ However, catalytic intermolecular allylic substitution of simple alkenes has not been extensively investigated.⁷ Such a transformation would enable the construction of 1,4-dienes (“skipped” dienes) prevalent in natural compounds.⁸ Moreover, many simple alkenes, e.g., alpha olefins, are inexpensive feedstock chemicals and, as compared to enolates and other organometallic reagents, are generally easier to synthesize and compatible with a greater range of reaction conditions. Herein we report the first examples of catalytic intermolecular allylic substitution of unactivated, simple alkenes. Catalyst loadings as low as 2.5 mol % Ni afford the desired product in high yield in both gram-scale and smaller scale coupling reactions.

In the course of investigating nickel-catalyzed carbon–carbon bond-forming reactions in which alkenes serve as nucleophiles,^{9,10} we observed the ASR of ethylene (1 atm) by cinnamyl methyl ether (**1a**). Catalyzed by Ni(cod)₂ and P(*o*-anisyl)₃ in the presence of triethylsilyl trifluoromethanesulfonate (Et₃SiOTf) and triethylamine at room temperature, this reaction afforded linear 1,4-diene **2a** in 91% yield (Table 1, entry 1), along with a small amount of conjugated 1,3-diene **3a** (5%), yet no detectable 1,4-diene isomers of **2a**. Ethylene also undergoes substitution with a wide range of allylating reagents, including electrophiles bearing classically poor leaving groups, such as alkyl ethers, Me₃Si ethers, and even allylic alcohols (entries 1–4). Cinnamyl derivatives with classical leaving groups (acetate, chloride, and methyl carbonate (**1b**), entries 5–7) also performed well in this transformation. In the case of **1b**, a catalyst loading of 2.5 mol % Ni provided a 91% yield of **2a** (entry 7).

An examination of the scope of the ethylene ASR revealed that both *Z*-cinnamyl methyl ether (**1c**) and the corresponding branched

isomer **1d** provided linear product **2a** in good yield with complete *E* selectivity (Table 2, entries 2–3). A broad range of allylic alcohol derivatives functioned well (entries 4–8), with a small amount of branched product observed with substrates bearing alkyl substituents (entries 5–8). Generally, substituents at any position of the allyl carbonate were tolerated (entries 9–11).

Table 2. Ni-Catalyzed Allylic Substitution of H₂C=CH₂^a

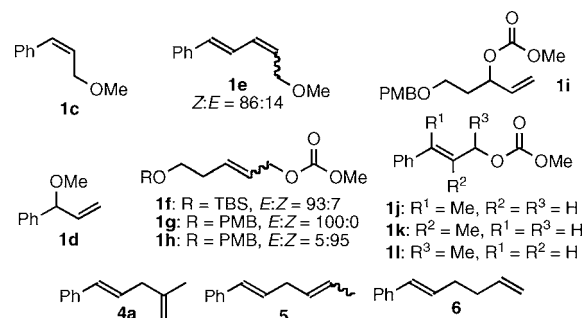
Entry	Substrate	Product	Yield ^b	l:b ^c	<i>E:Z</i> ^d
1	1a		75%	>99:1	>99:1
2	1c	2a	83%	>99:1	>99:1
3	1d	2a	74%	>99:1	>99:1
4	1e		84%	>99:1	83:17
5	1f		97%	95:5	94:6
6	1g		73%	98:2	92:8
7	1h	2d	82%	98:2	92:8
8	1i	2d	76%	98:2	92:8
9	1j		57%	>99:1	94:6
10	1k		81%	>99:1	88:12
11	1l		71% ^e	>99:1	>99:1

^a See Supporting Information. ^b Isolated yield. ^c Linear/branched product. ^d Ratio of geometric isomers of linear products. ^e Approx. 15% yield of 1-phenylbutadiene also obtained; see Supporting Information.

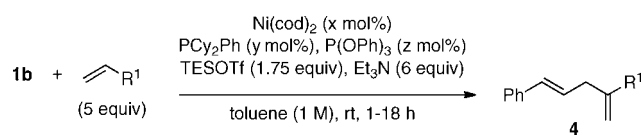
Table 1. Scope of Leaving Group in Ni-Catalyzed ASR

Entry	X	y	yield of 2a ^a	yield of 3a ^{a,b}
1	OMe (1a)	10	91	5
2	OEt	10	85	4
3 ^c	OTMS	10	75	trace
4 ^d	OH	20	56	<5
5	OAc	10	86	10
6	Cl	10	63	20
7 ^e	OCO ₂ Me (1b)	2.5	91	7

^a Determined by ¹H NMR. ^b For **3a** byproduct *E/Z* = approx 3:1 in all cases. ^c Me₃SiOTf (1.75 equiv) used in place of Et₃SiOTf, 4 h. ^d Me₃SiOTf (3 equiv) used instead of Et₃SiOTf. ^e 10 mol % P(*o*-anisyl)₃ used, 3 h.



The scope with respect to the alkene was also investigated (Table 3). The ASR of propylene by **1b** under the same conditions as were used for

Table 3. Ni-Catalyzed Allylic Substitution of Alkenes^a


entry	x	y	z	R ¹ (product)	yield (%) ^a
1 ^b	10	20	0	Me (4a)	77 (71) ^c
2	10	10	10	<i>n</i> -hexyl (4b)	79
3	20	20	20	CH ₂ OTES (4c)	73
4	10	10	10	(CH ₂) ₂ OTBS (4d)	83 ^d
5	20	20	20	CH ₂ CHMe ₂ (4e)	87
6 ^e	20	40	0	cyclohexyl (4f)	64 ^f
7	20	40	0	Ph-CH=CH-CH=CH-Ph (7)	25

^a Isolated yield; *E/Z* selectivity >98:2 in all cases. ^b Propylene pressure 1 atm (balloon); toluene (0.2 M). ^c 5 mol % Ni(cod)₂, 10 mol % PCy₂Ph. ^d Yield of free alcohol after treatment with 1 N HCl. ^e Et₃SiOTf added over 4 h. ^f Yield includes trace amounts of regioisomers (total <8%).

ethylene (Table 2) afforded a mixture of **4a**, **5**, and **6** in an unselective manner (52:20:28). The use of PCy₂Ph in place of P(*o*-anisyl)₃ dramatically improved the selectivity for the 1,1-disubstituted product (**4a**, Table 3, entry 1, 77% yield, >98% selectivity), but higher boiling (i.e., not a gas at STP) monosubstituted alkenes (alpha olefins) such as 1-octene gave the corresponding product in low yield (approx 20%) under the same conditions. A solution to this problem was ultimately found by changing three reaction parameters: Increasing the initial substrate concentration, using a combination of PCy₂Ph and P(OPh)₃, and mixing **1b** with the nickel complex prior to addition of alkene. Under these conditions, many alpha olefins gave the coupling products **4** in good yield and with excellent selectivity, including the more sterically demanding vinylcyclohexane (Table 3, entries 2–6).¹¹ The opposite regioselectivity was observed in the case of styrene, with **7** being a sole coupling product (entry 7). It is worthy of note that, in the case of all aliphatic olefins, C–C bond formation occurs at the more substituted position of the alkene.

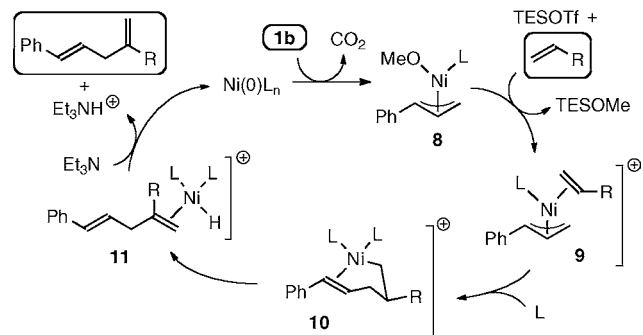


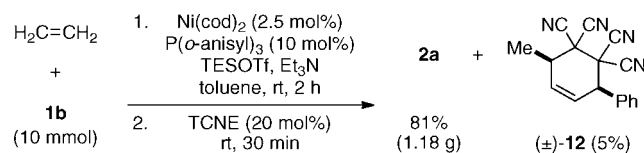
Figure 1. Proposed mechanism of Ni-catalyzed allylic substitution of olefins (L = organophosphine; triflate (TfO⁻) omitted for clarity).

Although more detailed studies are required, we propose the mechanism delineated in Figure 1, in which methyl carbonate **1b** is used as a representative substrate.¹² The Ni(0) complex reacts with **1b** without the assistance of Et₃SiOTf,¹³ affording allyl nickel complex **8**. The methoxy group is removed upon reaction with Et₃SiOTf, generating cationic allylnickel complex **9**, poised for olefin coordination. Migratory insertion (giving **10**) orients the alkene substituent R away from the Ni, and (PhO)₃P-facilitated^{10a} β-H elimination and reductive elimination provide the 1,4-diene product and regenerate the catalyst.

As a demonstration of the scalability of this transformation, the ASR of ethylene was conducted on 10-mmol scale. Filtration of the reaction

mixture through a pad of silica gel and treatment with tetracyanoethylene (TCNE) cleanly and completely removed the major 1,3-diene byproduct (**E-3a**) via [4+2] cycloaddition (giving **12**). The desired coupling product (**2a**) was not affected by TCNE treatment and was isolated in 81% yield (1.18 g) in >98% purity.

Scheme 1. Gram-Scale Allylic Substitution Reaction of Ethylene



In summary, we report the first examples of catalytic allylic substitution of simple alkenes. This method accommodates a wide range of allylic alcohol derivatives and nonactivated terminal alkenes, such as ethylene and propylene, affording synthetically valuable 1,4-dienes. High selectivity for substitution at the 2-position of alpha olefins is generally observed, favoring 1,4-diene products with a 1,1-disubstituted alkene. Further investigation of the reaction mechanism and the development of a mediator-free (i.e., without Et₃SiOTf) process are underway.

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Supporting Information Available: Experimental procedures and data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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