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Nickel-Catalyzed Allylic Substitution of Simple Alkenes

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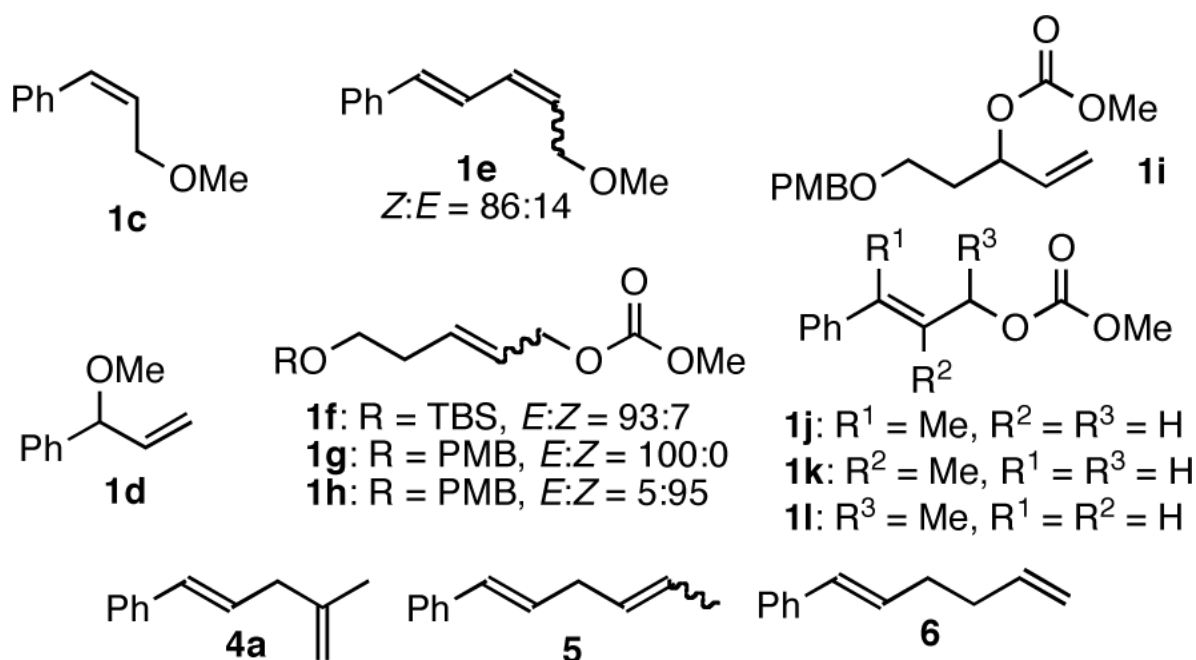
Transition metal-catalyzed allylic substitution reactions (ASR) have been widely applied in organic synthesis.¹ Many classes of carbon-centered nucleophiles can be employed, including active methylene compounds,² enolates,³ enamines⁴ and organometallic reagents.⁵ Oppolzer has also demonstrated that olefins 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).

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



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 ethylene (Table 2) afforded a mixture of **4a**, **5**, and **6** in an unselective manner (52:20:28). The use of PCy_2Ph in place of $\text{P}(o\text{-anisyl})_3$ 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 PCy_2Ph and $\text{P}(\text{O}i\text{Pr})_3$, 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.

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 $\text{Ni}(0)$ complex reacts with **1b** without the assistance of Et_3SiOTf ,¹³ affording allyl nickel complex **8**. The methoxy group is removed upon reaction with Et_3SiOTf , generating cationic allylnickel complex **9**, poised for olefin coordination. Migratory insertion (giving **10**) orients the alkene substituent R away from the Ni, and $(\text{PhO})_3\text{P}$ -facilitated^{10d} 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.

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 non-activated 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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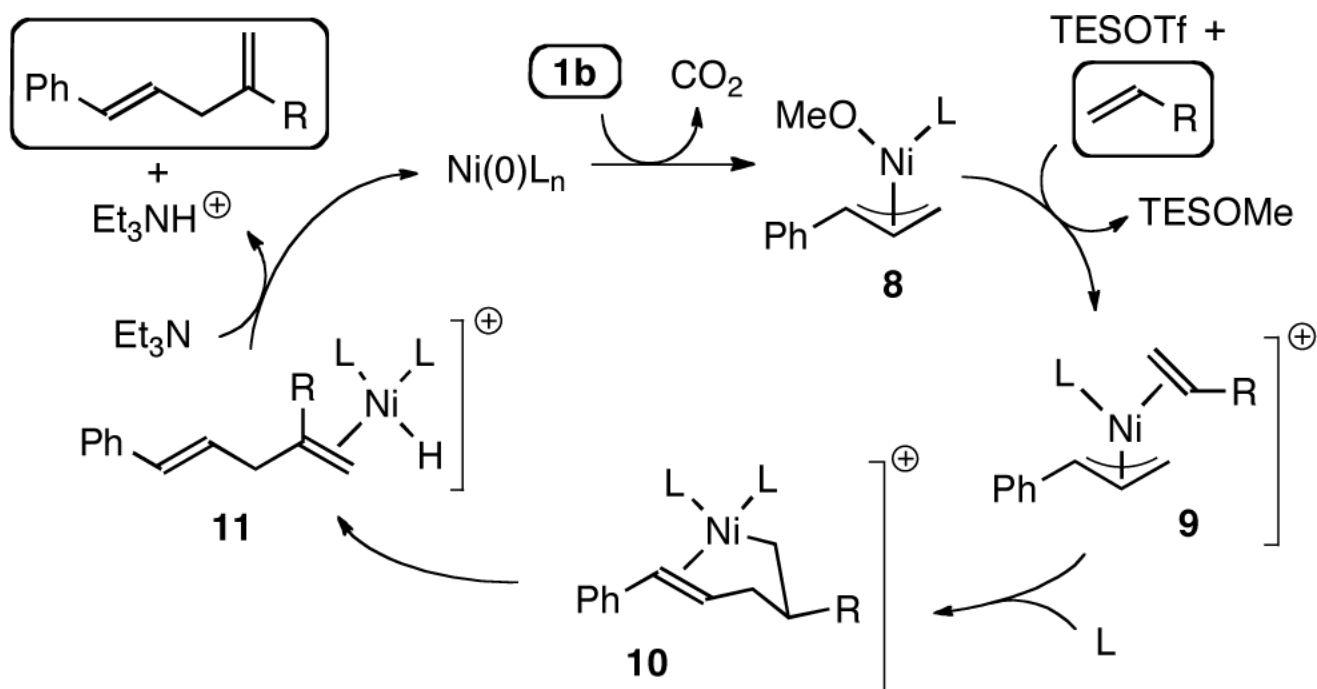
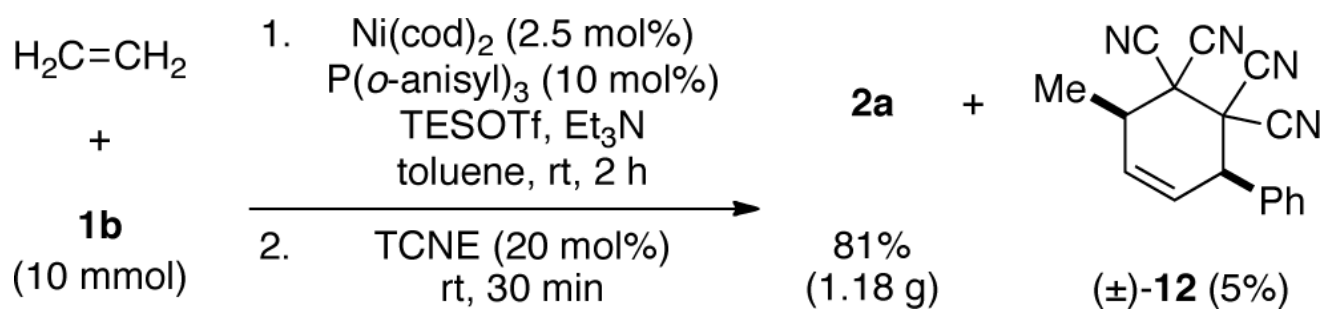


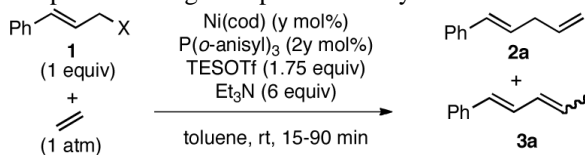
Figure 1. Proposed Mechanism of Ni-Catalyzed Allylic Substitution of Olefins (L = organophosphine; triflate (TfO⁻) omitted for clarity).



Scheme 1.
Gram-Scale Allylic Substitution Reaction of Ethylene

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.

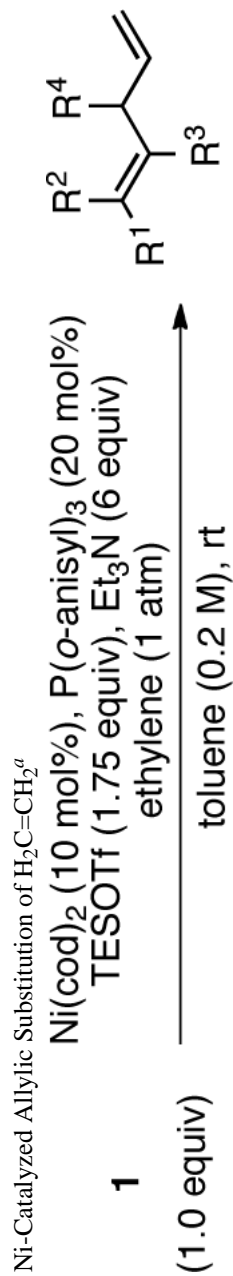
^b For **3a** byproduct *E:Z* = approx 3:1 in all cases.

^c Me₃SiOTf (1.75 equiv) used in place of Et₃SiOTf, 4h.

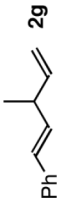
^d Me₃SiOTf (3 equiv) used instead of Et₃SiOTf.

^e 10 mol% P(*o*-anisyl)₃ used, 3 h.

Table 2



Entry	Substrate	Product	Yield ^b	I:b ^c	E:Z ^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	2b	84%	>99:1	83:17
5	1f		97%	95:5	94:6
6	1g	2d	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	2f	81%	>99:1	88:12

Entry	Substrate	Product	Yield ^b	I:B ^c	E:Z ^d
11	11		71% ^e	>99:1	>99:1

^aSee Supporting Information.

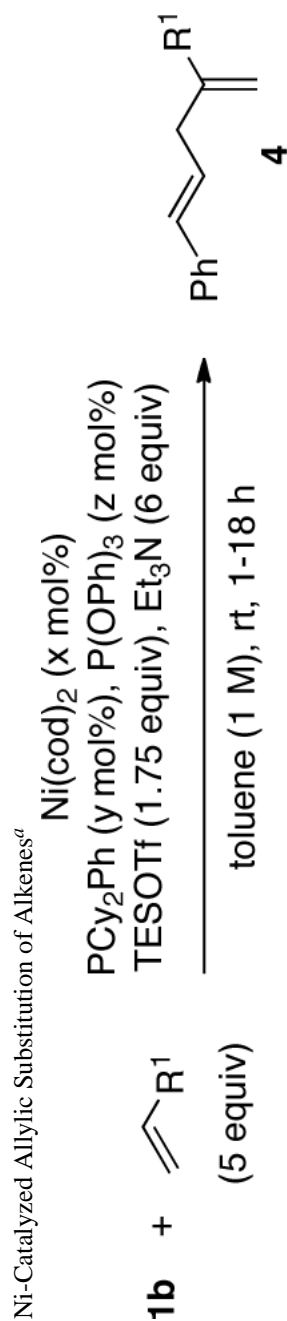
^bIsolated yield.

^cLinear:branched product.

^dRatio of geometric isomers of linear products.

^eApprox. 15% yield of 1-phenylbutadiene also obtained; see Supporting Information.

Table 3



entry	x	y	z	R ¹ (product)	yield (%) ^a
1 ^b	10	20	0	Me (4a)	77 (71) ^c
2	10	10	10	n-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 (7)	25

^aIsolated yield, *E/Z* selectivity >98:2 in all cases.

^bPropylene pressure 1 atm (balloon); toluene (0.2 M).

^c5 mol% Ni(cod)₂, 10 mol% PCy₂Ph.

^dYield of free alcohol after treatment with 1N HCl.

^eEt₃SiOTf added over 4 h.

^fYield includes trace amounts of regioisomers (total < 8%).