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Nickel-Catalyzed Heck-Type Reactions of Benzyl Chlorides and Simple Olefins

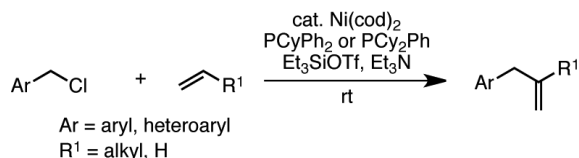
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Abstract

Nickel-catalyzed intermolecular benzylation and heterobenzylation of unactivated alkenes to provide functionalized allylbenzene derivatives is described. A wide range of both the benzyl chloride and alkene coupling partners are tolerated. In contrast to analogous palladium-catalyzed variants of this process, all reactions described herein employ electronically unbiased aliphatic olefins (including ethylene), proceed at room temperature and provide 1,1-disubstituted olefins over the more commonly observed 1,2-disubstituted olefins with very high selectivity.

The Heck-Mizoroki reaction¹ is a powerful carbon-carbon bond-forming process that couples alkenes with a wide scope of aryl, alkenyl, and alkyl halides.² When benzyl³ chlorides are employed, the coupling provides useful allylbenzene derivatives, a versatile functional group in organic synthesis. Despite the fact that the first coupling of methyl acrylate using benzyl chloride was described by Heck nearly 40 years ago,⁴ the intervening years have witnessed only sporadic reports of couplings with benzyl halides or related derivatives.^{5,6} Of these, the chief limitation is substrate scope; most examples utilize olefins bearing substituents that facilitate coupling electronically, such as acrylates, styrenes and N-vinyl amides. The benzylation of widely available aliphatic olefin feedstocks⁷ has not yet been realized. Moreover, the products obtained in these reactions are subject to olefin isomerization, and the previously reported examples generally afford a mixture of allylbenzene derivatives (kinetic products) and isomeric styrenes. This problem can be difficult to control at the high reaction temperatures (100–130 °C) employed. A further unsolved problem is regioselectivity; to the best of our knowledge no examples of Heck-type olefin couplings of simple alkenes that give 1,1-disubstituted products have been reported.⁸ While the ruthenium-catalyzed ene-yne coupling developed by Trost is a notable example,⁹ there are far fewer methods for the direct assembly of 1,1-disubstituted olefins compared to 1,2-disubstituted olefins, despite the fact that 1,1-disubstituted olefins are prevalent in many biologically active compounds¹⁰ and are very useful intermediates in target-oriented syntheses.¹¹



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 Supporting Information Available: Experimental procedures, spectral data for all unknown compounds and CIF file for complex 14. This material is available free of charge via the Internet at <http://pubs.acs.org>.

We address herein several of the aforementioned deficiencies. The nickel-catalyzed intermolecular benzylation of simple, unactivated olefins (eq 1) represents the first example of an alkene benzylation method that (a) utilizes α -olefins as substrates, including ethylene and propylene, (b) displays high selectivity for 1,1-disubstituted olefins, (c) avoids isomerization of the desired allylbenzene derivatives to the styrenyl products, and finally, (d) proceeds smoothly at room temperature.

We initially examined the nickel-catalyzed coupling reaction of ethylene (1 atm) and benzyl alcohol (1 equiv) in the presence of Et_3SiOTf (1.75 equiv) and triethylamine (6 equiv).¹² In stark contrast to our previously reported nickel-catalyzed olefin allylation,^{12d} methyl ether and methyl carbonate derivatives exhibited no conversion, indicating that they failed to undergo oxidative addition.¹³ Benzyl bromide afforded the product in poor yield and underwent undesired side reactions with the triethylamine.¹⁴ Ultimately, benzyl chloride (**1**) proved to be a suitable substrate.

For these initial studies with ethylene, PCyPh_2 provided superior reactivity and yields (entries 1 and 2). Only 1 mol % of the nickel complex derived from $\text{Ni}(\text{cod})_2$ and PCyPh_2 is required to catalyze the reaction, affording the product in quantitative yield. Using 5 mol % of the catalyst drastically increases the reaction rate, reducing the time required for complete conversion from 16 h to 2 h (entry 3). Decreasing the catalyst loading beyond 1 mol % significantly lowers the conversion (entry 4). No reaction took place with the exclusion of $\text{Ni}(\text{cod})_2$ and only a trace amount of the product was formed without addition of Et_3SiOTf (entry 5). In the latter case the consumption of benzyl chloride is believed to be caused by a change in mechanism from the desired manifold (*vide infra*) to one which favors homocoupling.

A particularly noteworthy feature of this method is the regioselectivity observed when 1-alkyl-substituted ($\text{R} \neq \text{H}$) alkenes are used. Excellent regioselectivity in favor of the unusual 1,1-over 1,2-disubstituted olefins (the exclusive regioisomer observed in *all* previously reported cases) is obtained under these nickel-catalyzed conditions. Furthermore, styrene and acrylate (excellent substrates in other Heck-type analogues) are poor substrates in this catalytic system, rendering this methodology complementary in both regioselectivity and reactivity to its palladium analogues. In contrast to ethylene, for the α -olefins, higher conversion (100%) was obtained with PCy_2Ph compared to PCyPh_2 (59% conversion, entries 6 and 7). A catalyst loading of 5 mol % was sufficient to catalyze the reaction, but improved yields were obtained when the loading was increased to 10 mol % (entries 7 and 8). The reactions with 1-octene proceeded readily at ambient temperature, albeit at a slower rate that was observed for ethylene. For 1-octene, 2 equivalents of olefin were required for complete conversion (entry 9), but with a slightly diminished yield compared to the reaction in which 5 equivalents were used (entry 7).

Given the rapid rate with which the coupling of ethylene proceeded, we used this simple olefin to examine the scope of the reaction with regard to the benzyl chloride partner. Gratifyingly, good to excellent yields were observed across a broad range of substrates under these optimized conditions (Table 2).¹⁵ Various benzyl chloride derivatives were tolerated, including those with para-(**2a-f**), meta-(**2g-l**), hetero-(**2m-r**) and ortho-substitution (**2s-t**). Both electron-rich and electron-deficient benzyl chlorides were coupled within 2 h at room temperature. High yields were also observed when halogen-substituted aromatic substrates were used. Even an ortho-iodo benzyl chloride was successfully employed, to afford the desired product (**2t**) in good yield. In this case, only 4% of the product derived from oxidative addition into the carbon-iodide bond was concomitantly formed. Cyano (**2c**) and ester (**2f**) functional groups on the aromatic rings were also tolerated, and α,α' -

dichloroxylenes (*meta* and *para*) were efficient substrates for the preparation of diallylbenzenes (**2b** and **2k**). It is noteworthy that nitrogen-protecting groups, Boc and Ts (**2n**, **2q** and **2r**), located β to the benzylic carbon, did not interfere with the reaction.

Having examined the substrate scope of functional groups on the benzyl chloride with ethylene, we next turned our attention to the substituted olefins. A variety of functionality on the α -olefin is tolerated, including silyl ethers (**3h** and **3k**), phthalimides (**3f** and **3l**) and alkyl groups with α -branching (**3d**). An alkene containing a pendant alkyl bromide underwent the coupling with no observable side reactions, furnishing **3i** in 97% yield and thereby demonstrating the excellent chemoselectivity of this reaction. Propylene, a gaseous olefin, afforded the desired product (**3j**) in excellent yield. Notably, α -olefins containing pendant olefins (**3b**) are also tolerated. As was observed for ethylene, aryl bromides are compatible with the reaction conditions (**3c**). A trifluoromethyl substituent was also tolerated under the reaction conditions. Despite the presence of three fluorine atoms at a benzylic position, no evidence of fluoride substitution was detected (entry **3l**).¹⁶

Attempts to employ more highly substituted benzyl chlorides revealed the limits of this reaction (Figure 1). No reaction was observed upon exposure of **5**, containing a methyl substituent at the benzylic position, to the reaction. Further examination of scope revealed that nitro-substituted aromatic groups were not compatible, despite the compatibility of nitrile- and ester-substituted benzyl chlorides. No conversion was observed when a pyridine was present (**7**) as the hetero-substituent, further revealing the limits of this catalyst system. We also examined the functional group tolerance with regard to the alkene partner. The steric limit is reached with *tert*-butyl ethylene **8**, for which no reaction was observed. While no reaction was observed for carbamate **9**, carbonate **10** formed an intractable mixture of products. To probe the compatibility of substrates containing enolizable protons, ester **11** was examined; the ester failed to undergo complete conversion even when more than 2 equivalents of Et₃SiOTf were used.

We propose the reaction mechanism shown in Scheme 1. Nickel(0) complex **12**, possibly in equilibrium with alkene (substrate or cyclooctadiene) complex **13**, adds oxidatively to benzyl chloride without mediation of Et₃SiOTf, affording a mixture of nickel(II) complex **14**, bearing an η^3 -benzyl ligand and one phosphine, and **15** bearing an η^1 -benzyl ligand and two phosphines.¹⁷ In solution at room temperature, a rapid equilibrium exists between complexes **14** and **15**, but favors complex **14**.¹⁸ As depicted, Ni(η^3 -CH₂C₆H₅)(PCy₂Ph)Cl (**14**) has been characterized by X-ray crystallography. Counteranion exchange from Cl⁻ to TfO⁻ mediated by Et₃SiOTf provides cationic nickel complex **16**,¹⁹ which then undergoes olefin coordination. Subsequent migratory insertion, the carbon-carbon bond-forming step in which the regioselectivity is determined, gives alkyl-nickel species **17**. This is followed by β -hydride elimination, affording the 1,1-disubstituted olefin product and nickel complex **18**. Nickel(0) complex **12** is then regenerated by triethylamine, completing the catalytic cycle.

In Heck reactions catalyzed by palladium, the selectivity of the olefin insertion step is governed by a combination of electrostatic and frontier orbital effects, yet which effect is dominant in this reaction is unclear at this time. In the proposed mechanism, the productive pathway is the one that places the metal on the less substituted olefinic carbon. Given the relatively shorter nickel-carbon bond lengths (compared to the analogous palladium system), it is conceivable that steric effects are the dominant factor in this reaction. The ease with which ethylene undergoes the reaction compared to substituted olefins (2 h versus 16 h), despite its significantly lower relative concentration (1 atm in 0.2M toluene versus neat in 5 equiv olefin), lends support to this argument. However, the most sterically demanding olefin tolerated by the reaction—vinyl cyclohexane—was also the only substrate that afforded any of the linear adduct.

The observation that 36% of the benzyl chloride is converted to the homo dimer in the absence of Et_3SiOTf (Table 1, entry 5) can also be rationalized using this mechanism. Unable to form allyl complex **16**, it is likely that two molecules of the nickel chloride (**14**, **15**) undergo disproportionation to the catalytically incompetent Ni(II)Cl_2 and a Ni(II)Bn_2 intermediate. The latter would then afford the self-coupled product (dihydrostilbene) via reductive elimination.

In conclusion, we have described a novel nickel-catalyzed intermolecular benzylation of simple, widely available α -olefins and ethylene. The functional group tolerance seen across the broad range of substrates studied rivals that observed for analogous reported palladiumcatalyzed methods. The observed selectivity favoring 1,1-versus 1,2-disubstituted olefins is a unique and significant feature of this methodology. Additionally, the relatively low temperature at which these reactions proceed (room temperature) is unique. The above study represents an important advance in catalytic reactions using simple olefins as substrates. We are currently investigating Et_3SiOTf -free processes as well as other types of catalytic reactions using simple olefins as nucleophiles in carbon-carbon bond-forming reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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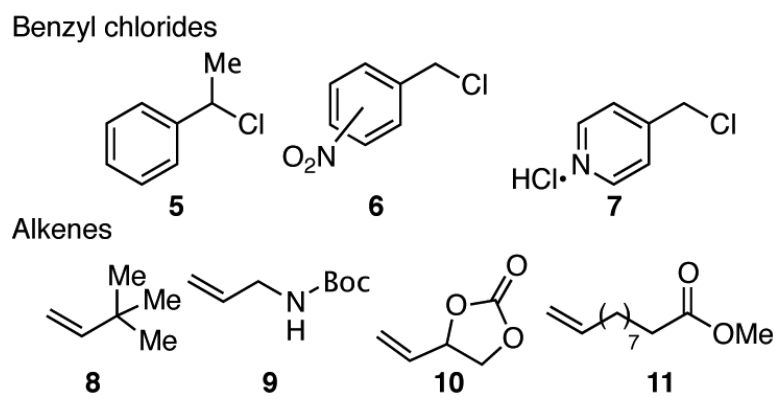
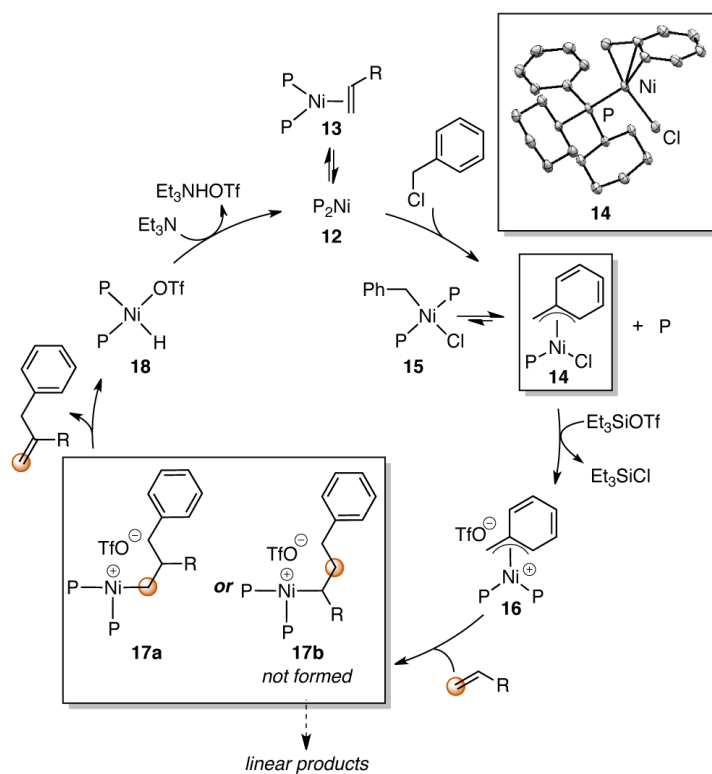


Figure 1.
Substrates that did not undergo the desired benzylation.



Scheme 1. Proposed Catalytic Cycle and ORTEP Drawing of η^3 -Nickel Complex 14^a
^a P = PR₃.

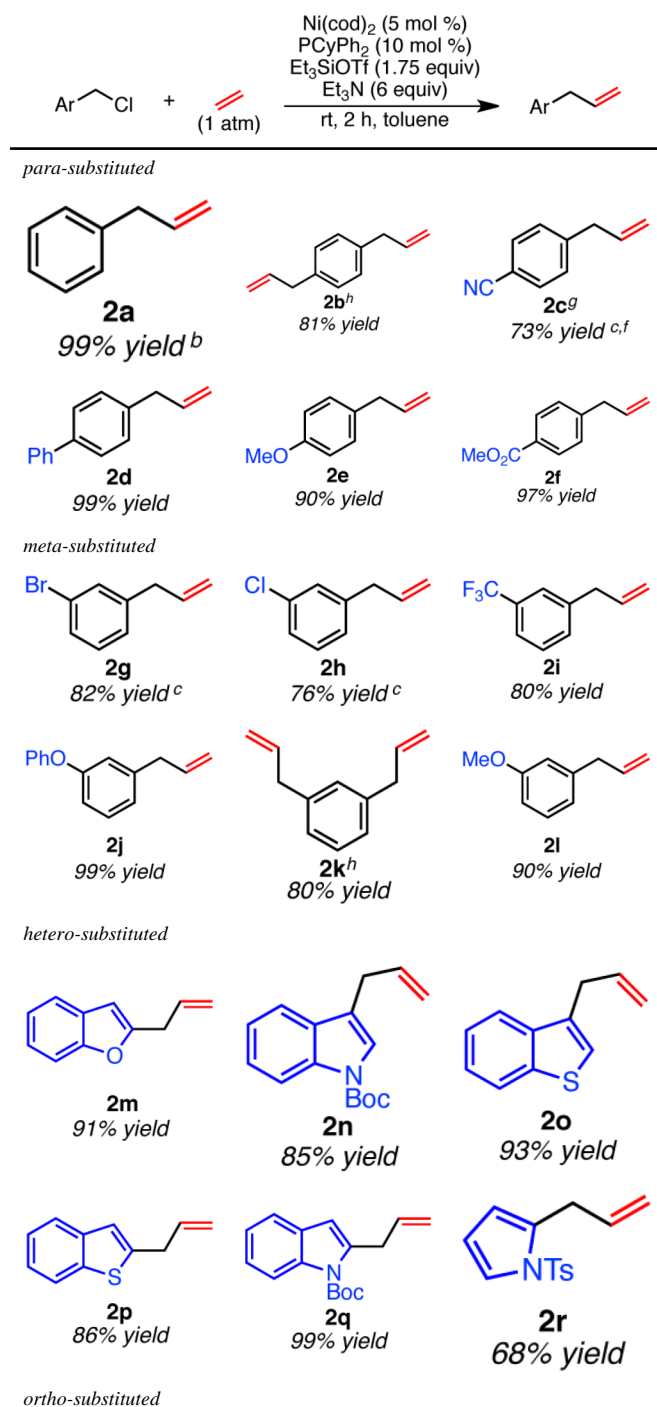
Table 1

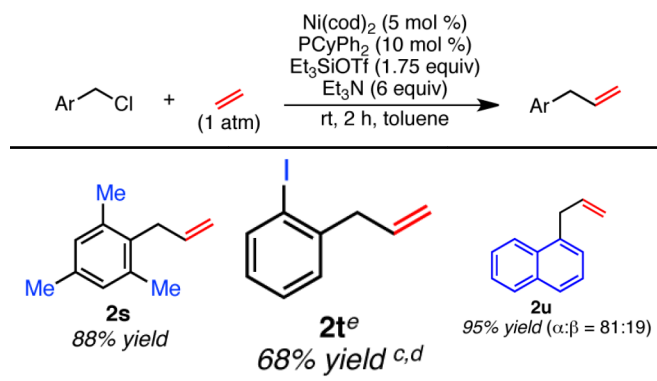
Optimization of Olefin Benzoylation Conditions

entry	R	PR ₃	y (equiv)	x	time (h)	conv (%) ^a	yield (%) ^a
1	H	P(<i>o</i> -anis) ₃	1 atm	20	23	76	73
2	H	PCyPh ₂	1 atm	1	13	100	100
3	H	PCyPh ₂	1 atm	5	2	100	100
4	H	PCyPh ₂	1 atm	0.5	16	17	17
5 ^b	H	PCyPh ₂	1 atm	20	2	36	1
6	<i>n</i> -hex	PCyPh ₂	5	10	16	59	28
7	<i>n</i> -hex	PCy ₂ Ph	5	10	16	100	90
8	<i>n</i> -hex	PCy ₂ Ph	5	5	16	100	80
9	<i>n</i> -hex	PCy ₂ Ph	2	10	16	100	78
10	<i>n</i> -hex	PCy ₂ Ph	1	10	16	86	54

^a Determined by GC.^b Et₃SiOTf not used.

Table 2
Nickel-Catalyzed Benzylolation of Ethylene^a





^a Isolated yield unless otherwise noted.

^b Determined by GC (internal standard).

^c Determined by ¹H NMR spectroscopy (internal standard).

^d Yield obtained with 10 mol % catalyst.

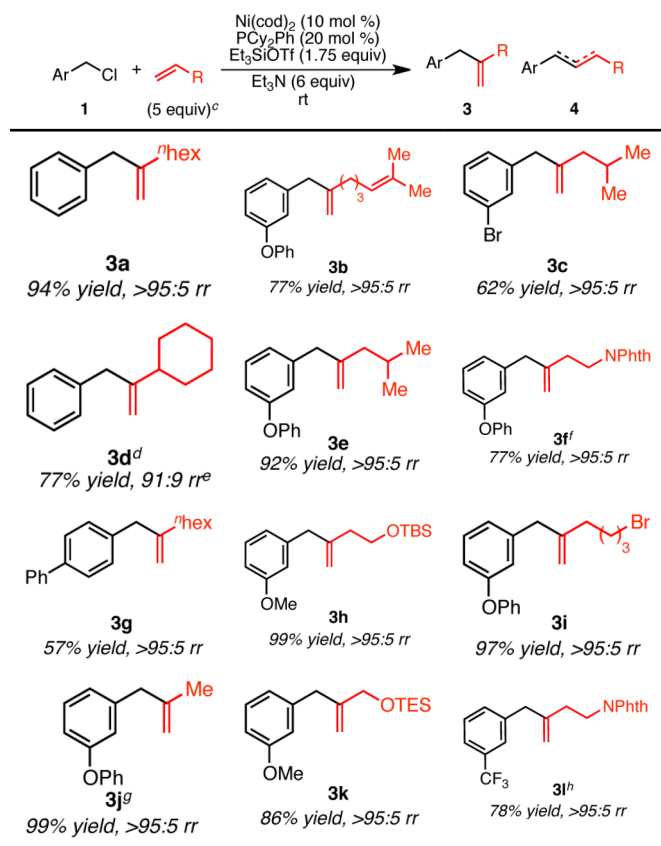
^e 2,3-Dihydro-1*H*-indene (4%) observed as inseparable byproduct.

^f Yield obtained with 20 mol % catalyst loading.

^g 4-Cyano- β -methylstyrene (5%) obtained as an inseparable byproduct.

^h Obtained with 2.5 equiv Et₃SiOTf.

Table 3
Nickel-Catalyzed Benzoylation of 1-Substituted Olefins^{a,b}



^a All yields are isolated yields.

^b rr = Regioisomeric ratio (3/4).

^c Reactions carried out neat in olefin (5 equiv) except for the examples that employ a gaseous or solid olefin; for these entries, toluene was used as a solvent.

^d 20 mol % of the catalyst.

^e Total yield of 3 and 4.

^f Toluene (1.4 M) used as solvent; 1.5 equiv of olefin.

^g Propylene introduced via balloon (1 atm); toluene (0.2 M) used as solvent.

^h Toluene (1.2 M) used as solvent.