

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

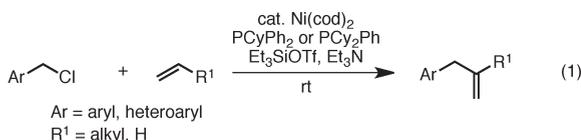
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Supporting Information

ABSTRACT: Nickel-catalyzed intermolecular benzylation and heterobenzylation of unactivated alkenes to provide functionalized allylbenzene derivatives are 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



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 Et₃SiOTf (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 (Table 1).

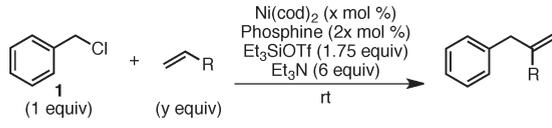
For these initial studies with ethylene, PCyPh₂ provided superior reactivity and yields (entries 1 and 2). Only 1 mol % of the nickel complex derived from Ni(cod)₂ and PCyPh₂ is required to catalyze the reaction, affording the product in quantitative yield. Using 5 mol % of the catalyst drastically increases the reaction rate, reducing the time required for complete conversion from 16 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 Ni(cod)₂ and only a trace amount of the product was formed without addition of Et₃SiOTf (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 (R ≠ 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 PCy₂Ph compared to PCyPh₂ (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

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Table 1. Optimization of Olefin Benzylation Conditions



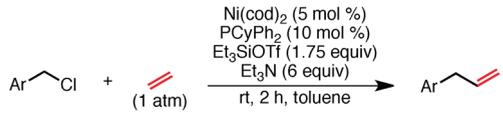
entry	R	PR ₃	y	x	time (h)	conv (%) ^a	yield (%) ^a
1	H	P(<i>o</i> -anis) ₃	1 atm	20	23	76	73
2	H	PCyPh ₂	1 atm	1	13	100	100
3	H	PCyPh ₂	1 atm	5	2	100	100
4	H	PCyPh ₂	1 atm	0.5	16	17	17
5 ^b	H	PCyPh ₂	1 atm	20	2	36	1
6	<i>n</i> -hex	PCyPh ₂	5	10	16	59	28
7	<i>n</i> -hex	PCy ₂ Ph	5	10	16	100	90
8	<i>n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

with 1-octene proceeded readily at ambient temperature, albeit at a slower rate that was observed for ethylene. For 1-octene, 2 equiv of olefin was required for complete conversion (entry 9), but with a slightly diminished yield compared to the reaction in which 5 equiv was 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- (2 m–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) (Table 3). 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)

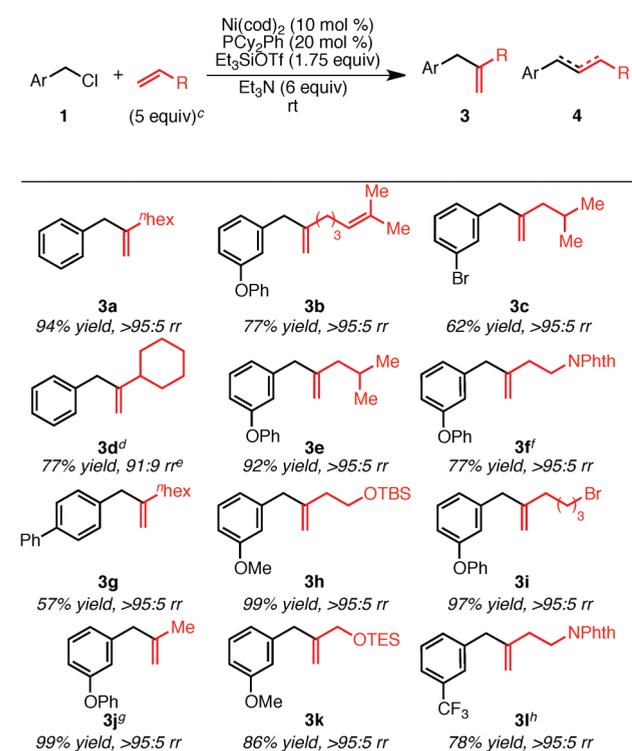
Table 2. Nickel-Catalyzed Benzylation of Ethylene^a


entry	Substrate	Yield (%)
2a	<i>para</i> -substituted (H)	99% yield ^b
2b ^h	<i>para</i> -substituted (Cl)	81% yield
2c ^g	<i>para</i> -substituted (CN)	73% yield ^{c,f}
2d	<i>para</i> -substituted (Ph)	99% yield
2e	<i>para</i> -substituted (MeO)	90% yield
2f	<i>para</i> -substituted (MeO ₂ C)	97% yield
2g	<i>meta</i> -substituted (Br)	82% yield ^c
2h	<i>meta</i> -substituted (Cl)	76% yield ^c
2i	<i>meta</i> -substituted (F ₃ C)	80% yield
2j	<i>meta</i> -substituted (PhO)	99% yield
2k ^h	<i>meta</i> -substituted (Cl, Cl)	80% yield
2l	<i>meta</i> -substituted (MeO)	90% yield
2m	hetero-substituted (indole)	91% yield
2n	hetero-substituted (indole, Boc)	85% yield
2o	hetero-substituted (indole)	93% yield
2p	hetero-substituted (thiophene)	86% yield
2q	hetero-substituted (thiophene, Boc)	99% yield
2r	hetero-substituted (thiophene, NTs)	68% yield
2s	<i>ortho</i> -substituted (Me, Me)	88% yield
2t ^e	<i>ortho</i> -substituted (I)	68% yield ^{c,d}
2u	<i>ortho</i> -substituted (naphthalene)	95% yield ($\alpha:\beta = 81:19$)

^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.

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

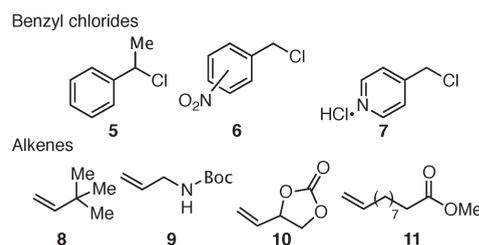
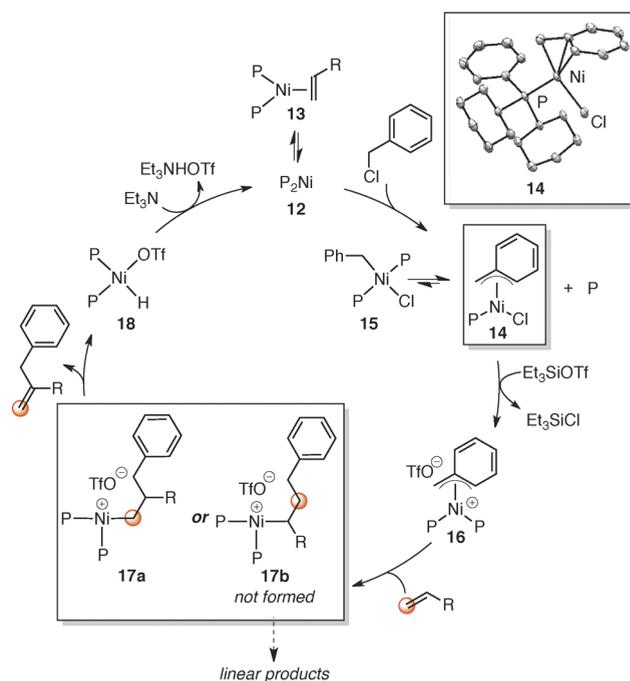
Attempts to employ more highly substituted benzyl chlorides revealed the limits of this reaction (Figure 1). No reaction was observed upon exposure of 5, containing a methyl substituent at the benzylic position, to the reaction. Further examination of scope revealed that nitro-substituted aromatic groups 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 heterosubstituent, further revealing the limits

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 Twenty mole percent 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.

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 equiv of Et₃SiOTf was 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 η³-benzyl ligand and one phosphine, and 15 bearing an η¹-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(η³-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

**Figure 1. Substrates that did not undergo the desired benzoylation.****Scheme 1. Proposed Catalytic Cycle and ORTEP Drawing of η³-Nickel Complex 14^a**

^a P = PR₃.

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 vs 16 h), despite its significantly lower relative concentration (1 atm in 0.2 M toluene vs 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 Et₃SiOTf (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)Cl₂ and a Ni(II)Bn₂ 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 palladium-catalyzed 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 Et₃SiOTf-free processes as well as other types of catalytic reactions using simple olefins as nucleophiles in carbon–carbon bond-forming reactions.

■ ASSOCIATED CONTENT

S Supporting Information. 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>.

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(13) See Supporting Information for details.

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(15) GC or NMR yields are given for cases where product volatility made isolation difficult.

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