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Nickel-Catalyzed Mizoroki-Heck-Type Reactions of Unactivated Alkyl Bromides

Megan R. Kwiatkowski and Prof. Erik J. Alexanian

Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599 (USA), eja@email.unc.edu

Abstract

The development of a general, nickel-catalyzed alkyl-Mizoroki-Heck reaction of unactivated alkyl bromides is described. The mild reaction proceeds efficiently using a wide range of primary and secondary alkyl bromides, and examples of intermolecular cross-couplings are provided. Reaction alkene regioselectivity is significantly enhanced over prior carbocyclizations using palladium catalysis. Mechanistic investigations are consistent with a direct carbocyclization in contrast to the auto-tandem atom-transfer cyclization and halide elimination previously observed with palladium catalysis.

Graphical Abstract

The development of a general, nickel-catalyzed alkyl-Mizoroki-Heck reaction of unactivated alkyl bromides is described. The mild reaction proceeds efficiently using a wide range of primary and secondary alkyl bromides, and examples of intermolecular cross-couplings are provided. Reaction alkene regioselectivity is significantly enhanced over prior carbocyclizations using palladium catalysis. Mechanistic investigations are consistent with a direct carbocyclization in contrast to the auto-tandem atom-transfer cyclization and halide elimination previously observed with palladium catalysis.

Keywords

radical reactions; cross-coupling; nickel; synthetic methods; alkyl halides

The Mizoroki-Heck reaction is an invaluable transformation for the construction of C–C bonds under mild conditions.^[1] While the use of aryl or vinyl electrophiles in these coupling reactions has been widely demonstrated, recent efforts have successfully extended the scope to include unactivated alkyl electrophiles.^[2] Owing to the general difficulty in activating alkyl electrophiles using transition metal catalysts, this has typically required either: 1) the use of alkyl iodides^[2e,g,k] or 2) the use of strongly reducing conditions (e.g., alkylmetal reductants).^[2a–d] Recent efforts in our group have led to the development of a general palladium-catalyzed carbocyclization of unactivated primary and secondary alkyl bromides

under mild conditions.^[3] While this work significantly increased the scope of catalytic carbocyclizations of unactivated alkyl electrophiles, control over the production of alkene regioisomers was poor, limiting the overall synthetic utility (Figure 1). Moreover, the development of a system using an inexpensive, first-row metal catalyst in lieu of palladium would be highly desirable.

Recent studies have established the utility of nickel catalysts in the activation of alkyl halides for a variety of useful C–C bond formations.^[4] The development of a nickel-catalyzed Mizoroki-Heck-type reaction of unactivated alkyl halides remains a major challenge, in part owing to the significantly higher energetic barrier to β -hydride elimination as compared to palladium systems.^[5] Previous work towards this goal was limited to the use of more reactive alkyl iodides, and generated both alkene regioisomers and reductive cyclization byproducts.^[2e] Herein, we report a general nickel-catalyzed Mizoroki-Heck-type reaction of unactivated alkyl bromides. This catalytic transformation proceeds under mild conditions with excellent alkene regioselectivity using an inexpensive first-row metal. We also demonstrate that intermolecular cross-couplings are possible using this simple catalytic system.

Our studies commenced with the carbocyclization of unactivated alkyl bromide **1** (Table 1). A catalytic system comprised of 10 mol % $\text{NiBr}_2\cdot\text{glyme}$ and 10 mol % bisphosphine ligand 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) provided the cyclized products **2** and **3** in excellent yield and alkene regioselectivity (entry 1). For comparison, the palladium-based catalytic system we previously reported^[3] proved inferior with respect to both reaction efficiency and especially alkene regioselectivity (entry 2). Substituting $\text{Ni}(\text{cod})_2$ as precatalyst gave **2** and **3** with comparable yield and selectivity relative to the standard conditions (entry 3). Notably, the use of air stable $\text{NiBr}_2\cdot\text{glyme}$ enables reaction setup without a glovebox with only a slight decrease in yield and selectivity (entry 4). Decreasing the catalyst loading to 5 mol % had a minor effect on chemical yield but significantly decreased alkene regioselectivity (entry 5). Substituting 1,10-phenanthroline or PPh_3 as ligand decreased reaction efficiency (entries 6–7), as did switching to Cs_2CO_3 as base (entry 8). No reaction occurred in the absence of Mn or the nickel precatalyst (entries 9–10).

With optimized conditions in hand, we applied our catalytic system to the carbocyclizations of a range of substrates (Table 2). Reactions of primary alkyl bromides were successful with di- and trisubstituted alkenes (entries 1–6), styrenes (entry 7), and terminal alkenes (entry 8) to afford a variety of five-membered carbo- and heterocyclic products.^[6] Reactions proceeded with good to excellent levels of alkene regioselectivity, a distinct advantage over palladium-based systems. Efficient construction of bicyclic frameworks was also possible, as demonstrated by the reactions of cycloalkenyl substrates **18** and **20** (entries 9–10). Moreover, spirocycle **19** was inaccessible with palladium catalysis, further highlighting the utility of the present system.^[7] Secondary alkyl bromides were also viable substrates, as bis-tetrahydrofuran product **23** was formed from **22** with high diastereoselectivity (entry 11). Importantly, the reaction is not limited to five-membered ring synthesis; primary bromide **24** undergoes a 6-exo cyclization to afford piperidine derivative **25** in good yield and with excellent olefin regioselectivity (entry 12).^[8]

We continued by exploring the use of the nickel-based system in intermolecular cross-coupling. Despite the development of a number of intermolecular alkyl-Mizoroki-Heck-type cross-couplings using palladium catalysis,^[9] there are no general nickel-catalyzed variants available.^[10,11] We examined the cross-coupling of several alkyl bromides and alkene coupling partners (Table 3). Aryl-substituted acyclic bromide **26** delivered alkyl-Mizoroki-Heck-type products **27** and **28** in moderate yields in reactions with acrylonitrile and methyl acrylate, respectively (entries 1–2). The cross-coupling of the *N*-methylpyrrole derivative **29** proceeded with similar reaction efficiency (entry 3). Reactions involving the simple aliphatic substrate 2-bromooctane also produced cross-coupling products in moderate yield (entries 4–5). Cyclic bromides are also viable coupling partners, as demonstrated by the coupling of cycloheptyl bromide (entry 6).^[12] While the acrylate couplings in Table 3 solely delivered *E*-alkene products, the moderate *Z*-selectivity of couplings with acrylonitrile is consistent with our prior studies involving palladium-catalyzed couplings of alkyl iodides.^[9a]

We performed several experiments to shed light on the reaction mechanism, specifically to compare the nickel-catalyzed reaction to prior work involving palladium catalysis (eqs 1 and 2). The reaction of alkyl bromide **1** under standard conditions in the presence of 10 mol % of the single-electron transfer inhibitor 1,4-dinitrobenzene led to complete recovery of starting material, consistent with the presence of radical intermediates (eq 1). Furthermore, a reaction stopped at partial conversion did not yield any product of an atom-transfer radical cyclization, in contrast to the previously reported palladium-catalyzed carbocyclization which involved auto-tandem catalysis (eq 2).^[3] This experiment also suggests that alkene isomerization occurs over the course of the reaction; the regioisomeric ratio of the product at partial conversion (2.3:1 *rr*)

is much lower than that observed at completion (23:1 *rr*).^[13]

A plausible mechanism consistent with our observations is shown in Scheme 1. We hypothesize that activation of the alkyl bromide substrate by Ni(0) delivers a carbon-centered radical which undergoes C–C bond-forming alkene addition. Following cyclization, trapping of the newly generated carbon-centered radical by the nickel catalyst generates an alkylnickel(II) intermediate. β -Hydride elimination of this species then delivers the alkyl-Mizoroki-Heck-type carbocyclization product. As previously mentioned, alkene isomerization proceeds over the course of the reaction, likely via the $L_nNi^{II}(H)(Br)$ intermediate initially produced prior to a relatively slow catalytic turnover.

In conclusion, we have developed a general approach to the Mizoroki-Heck-type reaction of unactivated alkyl bromides using an inexpensive nickel catalyst under mild conditions. The reactions proceed in good yield and alkene regioselectivity across a range of substrates, and initial results involving cross-coupling have been demonstrated. We anticipate that the improved efficiency and selectivity of this process versus other protocols will prove valuable in implementing alkyl-Mizoroki-Heck-type reactions towards target-oriented synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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- [12]. Using the current conditions, reactions involving primary alkyl bromides proceed with lower yields.
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Figure 1.
Metal-catalyzed carbocyclizations of unactivated alkyl bromides with alkenes.

Scheme 1.

Plausible catalytic cycle for the nickel-catalyzed alkyl-Mizoroki-Heck-type carbocyclization.

Table 1.Catalyst system development for the nickel-catalyzed alkyl-Mizoroki-Heck-type carbocyclizations.^[a,b]

entry	variation from standard conditions above	combined yield (%)	ratio 2:3
1	none	97	23:1
2	5 mol % [Pd(allyl)Cl] ₂ , 20 mol % dtbpf, 2 equiv Et ₃ N, PhCF ₃ , 100 °C	74	1:4.7
3	10 mol % Ni(cod) ₂ instead of NiBr ₂ •glyme	88	>25:1
4	no glovebox	86	21:1
5	5 mol % instead of 10 mol % NiBr ₂ •glyme/xantphos	85	8.4:1
6	10 mol % 1,10-phenanthroline instead of xantphos	<5	-
7	20 mol % PPh ₃ instead of xantphos	25	1.8:1
8	3 equiv Cs ₂ CO ₃ instead of Et ₃ N	0	-
9	no Mn	0	-
10	no NiBr ₂ •glyme	0	-

^[a] Reactions were performed with [1]₀ = 0.25 M.^[b] Yield and alkene regioisomeric ratio determined by ¹H NMR spectroscopy of crude reaction mixture using an internal standard. Product 2 formed as a mixture of alkene *E* and *Z* isomers, see Supporting Information for details.

Table 2.Scope of nickel-catalyzed Mizoroki-Heck-type carbocyclizations of diverse unactivated alkyl bromides.^[a]

entry	substrate	product	yield (%) ^[b]
1			94 23:1 rr (1.4:1 <i>E:Z</i>)
2			86 (1.1:1 <i>E:Z</i>)
3 ^[c]			84
4			84 >25:1 rr
5 ^[c]			46 ^[e]
6			82 ^[d] 15:1 rr

entry	substrate	product	yield (%) ^[b]
7			86 (1.6:1 <i>E:Z</i>)
8			70 >25:1 rr
9 ^[c]			80 3.1:1 rr
10			88 14:1.7:1 rr
11			73 ^[d] (>95:5 dr)
12 ^[c]			64 >25:1 rr

[a] Reactions were performed with [substrate]₀ = 0.25 M in MeCN at 80 °C with 10 mol % NiBr₂•glyme, 10 mol % xantphos, 3 equiv Mn, and 3 equiv Et₃N as base.

[b] Isolated yield, rr = regioisomeric ratio, see Supporting Information for details regarding minor alkene regioisomers.

[c] Reactions were performed with [substrate]₀ = 0.25 M in DMSO.

[d] Yield determined by ¹H NMR spectroscopy of crude reaction mixture using an internal standard.

[e] Yield of major alkene regioisomer, see Supporting Information for details.

Table 3.

Nickel-catalyzed Mizoroki-Heck-type cross-couplings of alkyl bromides with acrylonitrile and methyl acrylate.^[a]

entry	substrate	product	yield (%) ^[b]
1			64 (5.7:1 <i>Z:E</i>)
2 ^[c,d]			36 ^[e]
3 ^[c]			57 (5.7:1 <i>Z:E</i>)
4			50 (7.3:1 <i>Z:E</i>)
5 ^[c,d]			31 ^[e]
6			47 (5.6:1 <i>Z:E</i>)

^[a] Reactions performed with [substrate]₀ = 0.5 M in DMF at 70 °C with 10 mol % Ni(cod)₂, 10 mol % xantphos, 3 equiv alkene, 3 equiv Mn, and 3 equiv Et₃N as base.

^[b] Isolated yield.

^[c] Na₂CO₃ used as base instead of Et₃N.

^[d] Reactions were performed with [substrate]₀ = 0.5 M in MeCN.

^[e] Yield determined by ¹H NMR spectroscopy of crude reaction mixture using an internal standard.