Letter

Migratory Reductive Acylation between Alkyl Halides or Alkenes and Alkyl Carboxylic Acids by Nickel Catalysis

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Migratory Reductive Acylation between Alkyl Halides or Alkenes and Alkyl Carboxylic Acids by Nickel Catalysis

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ABSTRACT: A mild migratory reductive acyl cross-coupling has been achieved through NiH-catalyzed chainwalking and subsequent cross-coupling from two abundant starting materials, alkyl bromides and carboxylic acids. This strategy allows the direct acylation of the benzylic sp^3 C–H bond with high yield as a single regioisomer. As an alternative, the alkyl bromide could be replaced by the proposed olefin intermediate and commercially available *n*-PrBr to achieve a remote hydroacylation process.

KEYWORDS: *acylation, C–H activation, isomerization, migration, nickel, reductive cross-coupling*

Reductive cross-electrophile coupling,[1-3] direct coupling of two shelf-stable electrophiles, typically involving the abundant alkyl halides[4], has received considerable attention in recent years owing to the benefit of circumventing the synthesis of organometallic reagents which have limited stability and commercial availability. This attractive strategy allows direct formation of C–C bonds at the halogen-bearing carbon of alkyl halides – the *ipso* carbon; thus, new bonds that can be introduced are limited to the position of the halogen. Hence, site-selective cross-coupling at different positions other than this carbon along the hydrocarbon chain of alkyl halides would have considerable synthetic potential and would be complementary to the current coupling strategy. The recently emerging sp^3 C–H functionalization,[5] would undoubtedly be an ideal alternative solution. However, to ensure good reactivity and regioselectivity, most of these processes need a polar directing group in the proximity and this limits their application in organic synthesis. A synergistic combination of metal-hydride[6] catalyzed chainwalking and transition-metal-catalyzed cross-coupling provides an attractive approach to this goal.[7-11]

Catalytic reductive acyl cross-coupling from carboxylic acid derivatives is an efficient approach for ketone synthesis. Previously, Mukaiyama,[3a] Weix,[3b,3h] Gong,[3c-3f] and Reisman[3g] reported elegant work concerning nickel-catalyzed[12] reductive acylation reactions from two abundant feedstock chemicals, alkyl halides and carboxylic acid derivatives (Figure 1a, top). This conventional strategy requires the regio-specific starting material of alkyl halide. In contrast, unrefined alkyl halides or olefins are generally more widely available than the region-specific ones[13] (some activated halides, such as benzylic halides, are not stable enough and have the issue of chemoselective control in reductive cross-coupling (homo- vs cross-coupling)), strategy to produce the same site-specific ketone from any isomer of alkyl halides or olefins (or isomeric mixtures) turns out to be attractive in organic synthesis (Figure 1a, bottom). If chainwalking, enabled by NiH generated *in situ* through β-hydride elimination of an alkylnickel species derived from the alkyl halide starting material, could take place before the selective acyl cross-coupling, migratory acylation could happen potentially at a distal, inert sp^3 C–H position and the sensitive ketone group could be preserved under these mild reaction conditions (Figure 1b). Here we describe our development of such an acylation reaction based on a migratory reductive cross-electrophile coupling strategy.

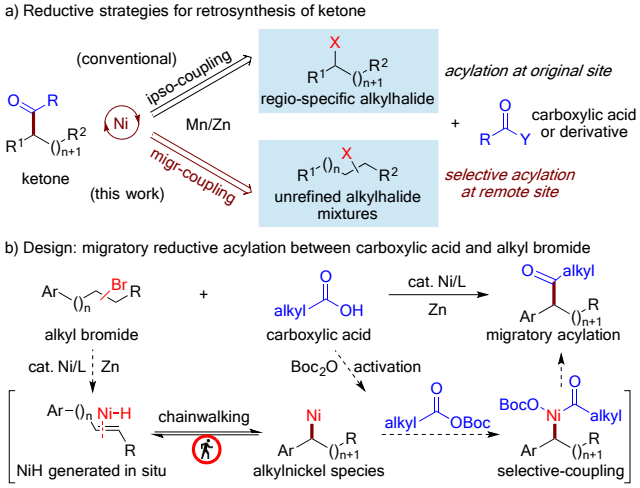
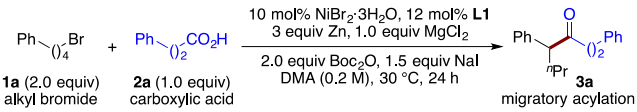


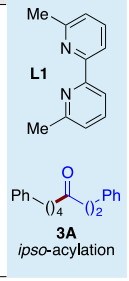
Figure 1. Design plan: Migratory reductive acyl cross-coupling for the synthesis of ketone.

Based on Gong's reductive *ipso*-acylation conditions,[3f] we began our investigation by studying the coupling of 1-bromo-4-phenylbutane (**1a**) with 3-phenylpropanoic acid (**2a**) (Table 1). After extensive examination of a range of nickel sources, ligands, reductants, additives, solvents, and a range of other parameters (for detailed optimization studies, see the Supporting Information, SI), we found that a combination of $NiBr_2{\cdot}3H_2O$/C6-methyl substituted bipyridine as the metal/ligand choice, Zn dust as the reductant, $MgCl_2$/NaI as the additive, and Boc_2O as the acid activation reagent (an acid anhydride is formed *in situ*) in DMA at 30 °C provides the desired migratory acylation product (**3a**) in 70% isolated yield as essentially a single regioisomer (entry 1). Use of other Ni(II) precatalysts, such as $NiBr_2$ or NiI_2 leads to diminished yields (entries 2, 3). It is particularly interesting that no migratory but only the *ipso*-coupling product (**3A**) is observed when $Ni(cod)_2$ is used (entry 4). Replacement of **L1**[14] by the parent bipyridine ligand also results in only the *ipso*-acylation product (entry 5),[3] demonstrating the critical role of C6-alkyl substituents in the ligand backbone. Changing the reductant to a manganese compound results in a lower yield (entry 6); and THF is not a suitable solvent (entry 7). The addition of sodium iodide dramatically improves the reactivity (entry 1 versus entry 8). In the absence of NaI, the alkyl bromide (**1a**) provides the desired product (**3a**) in lower yield while the corresponding alkyl iodide improves the reaction efficiency, indicating that the role of NaI is to generate the more reactive alkyl iodide *in situ* from the alkyl bromide (entries 8, 9). Notably, the alkyl chloride was unreactive under current reaction conditions regardless of the presence of NaI (entry 10). Control experiments show that the additive $MgCl_2$ and the activation reagent Boc_2O are essential for the reaction to occur (entries 11, 12).[15]

Table 1. Variation of Reaction Parameters.



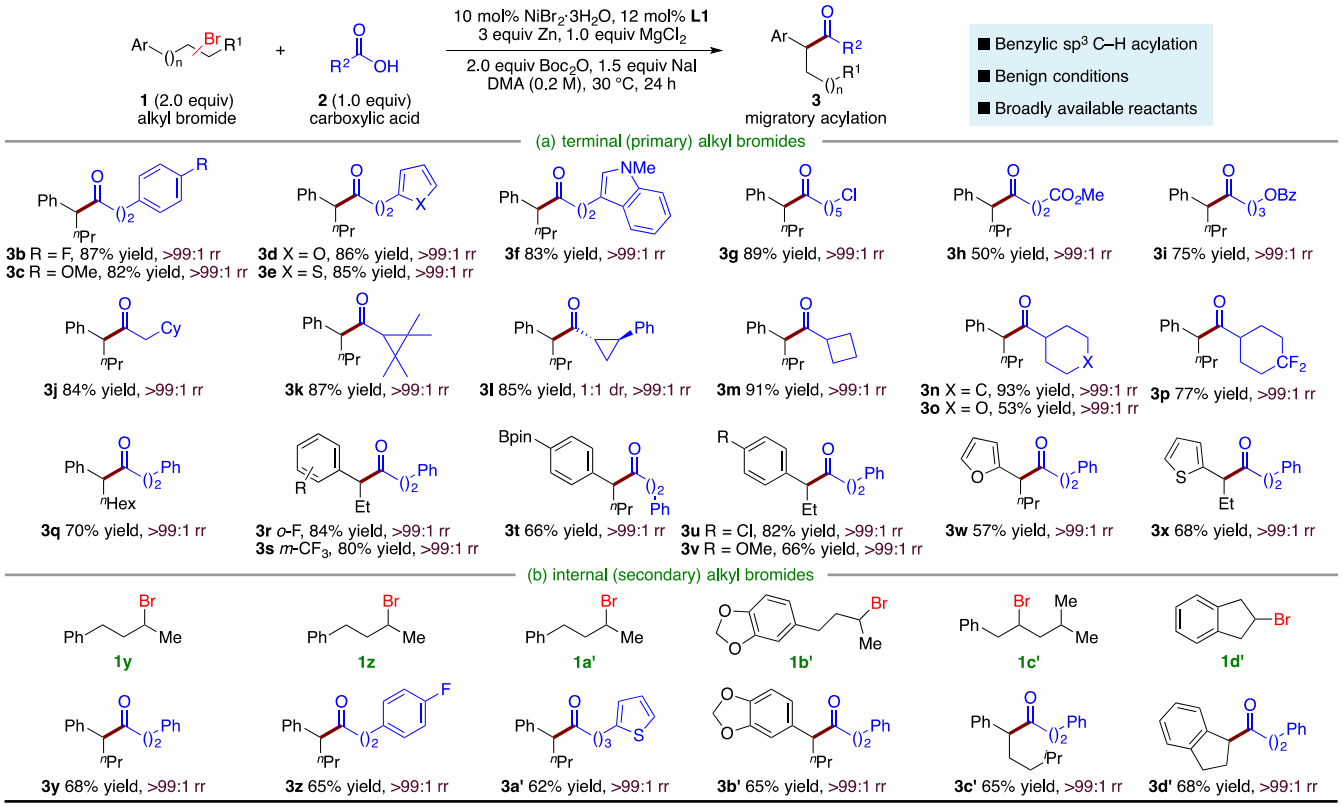
Entry	Deviation from standard conditions	Yield of **3a** (%)[a]	rr[b]
1	none	84 (70)	>99:1
2	$NiBr_2$, instead of $NiBr_2{\cdot}3H_2O$	67	>99:1
3	NiI_2, instead of $NiBr_2{\cdot}3H_2O$	58	>99:1
4[c]	$Ni(cod)_2$, instead of $NiBr_2{\cdot}3H_2O$	**3A** 63 (53)	97:3
5[c]	bpy, instead of **L1**	**3A** 67	>99:1
6	Mn, instead of Zn	32	>99:1
7	THF, instead of DMA	14	>99:1
8	w/o NaI	34	>99:1
9[d]	alkyl iodide, instead of **1a**	61	>99:1
10[e]	alkyl chloride, instead of **1a**	none	–
11	w/o $MgCl_2$	3	ND
12	w/o Boc_2O	trace	ND



[a]Yields determined by GC using *n*-dodecane as the internal standard, the yield in parentheses is the isolated yield and is an average of two runs (0.20 mmol scale). [b]Regioselectivities (rr) were determined by GC and GCMS analysis. [c]The major product was **3A**. [d]Without NaI. [e]With or without NaI.

With the optimal conditions in hand, we proceeded to evaluate the substrate scope of both carboxylic acids and alkyl bromides. As shown in Table 2, the regioselectivity in general, is excellent and only one regioisomer (the benzylic isomer) is observed in all cases. For the carboxylic acid substrate (Table 2a), a myriad of primary (**2a**–**2j**) and secondary (**2k**–**2p**) aliphatic carboxylic acids all deliver the corresponding benzylic acylation products in good to excellent yields. Under these mild conditions, a wide range of functional groups, including an aryl fluoride (**2b**), ethers (**2c**, **2o**), an alkyl chloride (**2g**), and esters (**2h**, **2i**) are well tolerated. Gratifyingly, carboxylic acids bearing heterocyclic motifs, such as a furan (**2d**), a thiophene (**2e**), and an indole (**2f**) are also competent coupling partners. Moreover, a carboxylic acid with an α-stereocenter could participate in this reaction with full preservation of this adjacent stereocenter (**2l**). For the alkyl bromide substrate, both primary (Table 2a) and secondary (Table 2b) alkyl bromides underwent this transformation smoothly. Notably, when an isomeric mixture of alkyl bromides (e.g. equimolar amounts of **1a** and **1y**) was used, only one single regioconvergent benzylic acylation product (**3a**) was observed. Moreover, the efficacy of chainwalking was not hindered by the beginning position of the C–Br bond (**1a** versus **1q**). Substrates containing both electron-withdrawing (**1r**–**1u**) and electron-donating (**1v**) substituents on the remote aryl ring are suitable for this transformation. Additionally, heterocycle substrates, such as those containing a furan (**1w**) or a thiophene (**1x**) in place of the aryl group, are likewise suitable for this reaction.

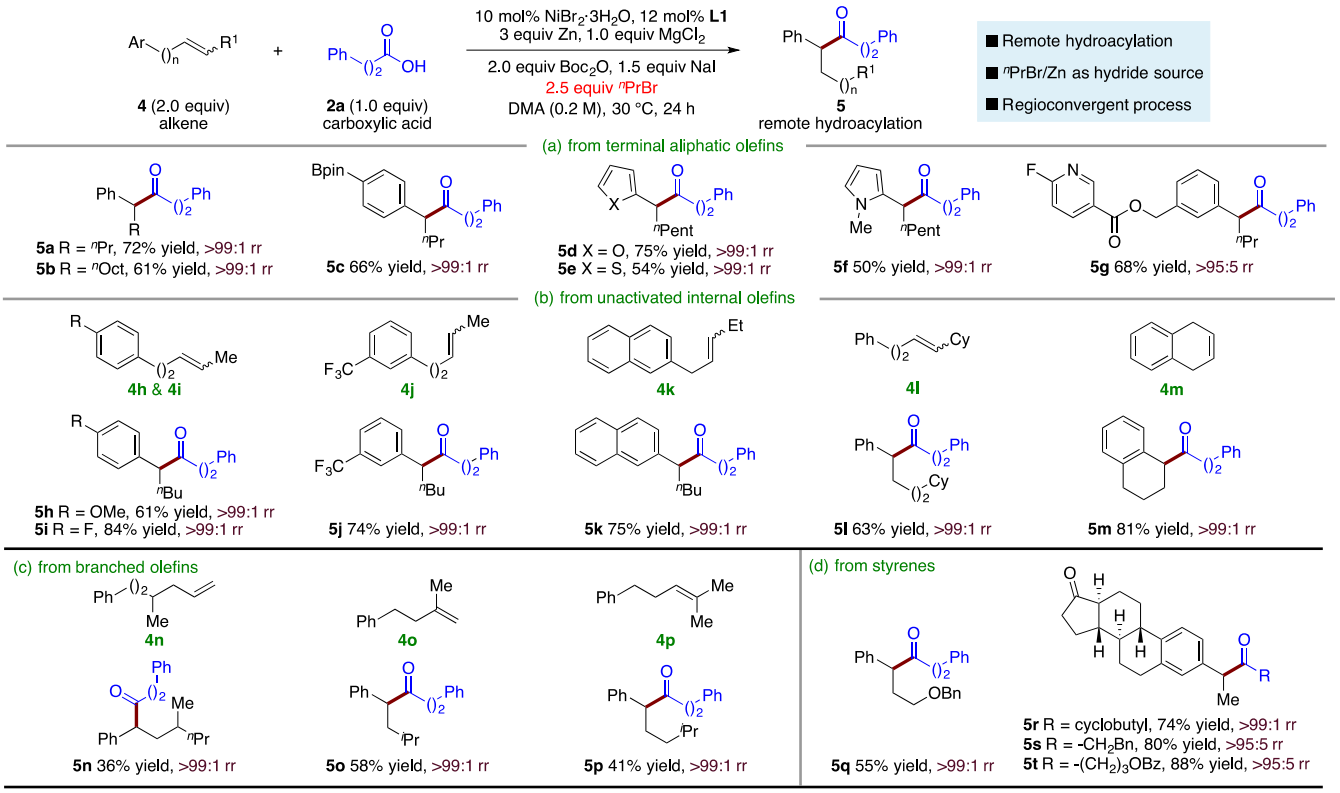
Table 2. Migratory Acyl Coupling: Scope of the Alkyl Bromide and Carboxylic Acid.[a]



[a]Under each product is the percentage of isolated yield and regioselectivity (rr) (0.20 mmol scale, average of two runs); regioselectivities were determined by GC and GCMS analysis.

The current migratory acyl coupling strategy could also be extended to readily accessible alkene substrates through the addition of a stoichiometric quantity of *n*-PrBr (*n*-PrBr is more cheap and stable compared with hydrosilane),[11h] which is used as an extra hydride source to generate, *via* β-H elimination, the NiH species required for the chainwalking process. Notably, migratory acylation of *n*-PrBr is not observed in this case. As depicted in Table 3, a wide range of alkenes are suitable substrates, providing the corresponding remote hydroacylation products in good to excellent yield as single regioisomers. Both terminal olefins (**4a**–**4g**) and unactivated internal olefins (**4h**–**4m**) are generally suitable, and a diverse range of electron deficient (**4c**, **4i**–**4j**) and electron-rich (**4h**) remote arenes are tolerated. Notably, heteroaromatic substrates, such as those containing a furan (**4d**), a thiophene (**4e**), a pyrole (**4f**), or a pyridine-linked aryl ring (**4g**) in place of the aryl group, are compatible with the reaction. As expected, E/Z mixtures of unactivated internal olefins (**4h**–**4m**) are also suitable partners, regardless of the starting position of the C=C bond. Moreover, olefins with a branched alkyl chain, including an internally branched alkene (**4n**), a 1,1-disubstituted alkene (**4o**), or a trisubstituted internal alkene (**4p**), could also afford the desired migratory products in moderate yields revealing that steric constraints can be overcome. Finally, an estrone-derived styrene (**4r**) is also a suitable partner to undergo hydroacylation under these conditions.[16]

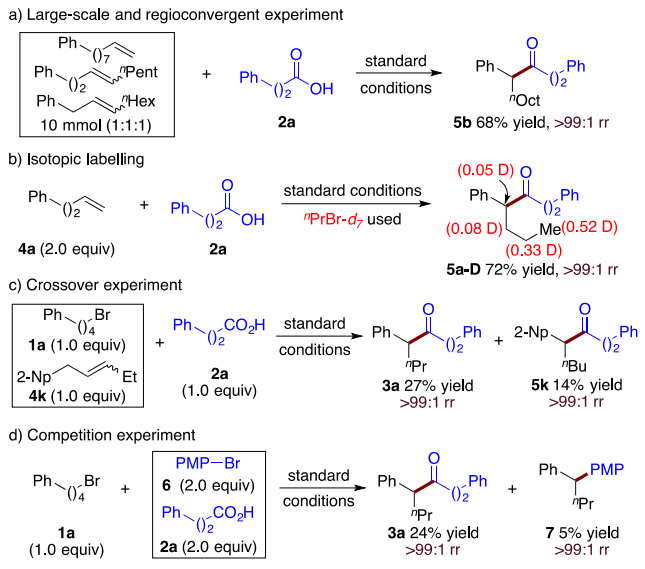
Table 3. Remote Hydroacylation: Scope of the Alkene and Carboxylic Acid.[a]



[a]Yield and rr are as defined in Table 2, regioselectivities (rr) reported as >95:5 were determined by ^{1}HNMR analysis of the crude reaction mixture.

This transformation is highly regioconvergent, and could be used for the conversion of isomeric mixtures of olefins, generally more widely available than the pure isomers, into value-added specialty chemicals. As shown in Scheme 1a, starting from equimolar amounts of three olefins - an isomeric mixture - on a 10 mmol scale, the benzylic acylation product **5b** can be obtained as a single regioisomer.

To shed light on the migratory acylation process, some preliminary experiments were carried out. Consistent with our previous reports,[11h] a significant amount of olefin isomers could be observed in the usual reaction conditions both in the presence and absence of the carboxylic acid, indicating chainwalking process is unrelated to acyl coupling (see SI for details). Furthermore, when deuterated ^{n}PrBr-d_7 is used (Scheme 1b), as its proposed role, transformation of deuterium from alkyl bromide (^{n}PrBr-d_7) to olefin **4a** and incorporation of deuterium at all positions along the hydrocarbon chain of the remote hydroacylation products (**5a-D**) were observed. Moreover, when a mixture of equimolar amounts of alkyl bromide **1a** and alkene **4k** were subjected to the coupling conditions, formation of both coupling products **3a** and **5k** was observed (Scheme 1c), providing additional evidence of fast dissociation and reassociation of the NiH/NiD species[17] from olefins during chainwalking process. Finally, to compare the reactivity of acylation with arylation,[11h] a competition experiment was carried out in the presence of both a carboxylic acid and an aryl bromide (Scheme 1d), and migratory acylation product (**3a**, 24% yield) was favorable relative to arylation product (**7**, 5% yield). This indicates that the cross-coupling rate of carboxylic acid (acylation) is faster than that of aryl bromide (arylation).



Scheme 1. Regioconvergent, Isotopic, Crossover, and Competition Experiments.

In summary, using a ubiquitous alkyl carboxylic acid directly as the acylation reagent, we have developed a mild nickel-catalyzed migratory acylation reaction from alkyl bromide or olefin substrates. This strategy provides an attractive approach to remote sp^3 C–H acylation under mild conditions with broad substrate scope and excellent regioselectivity. The asymmetric version of the current transformation is currently in progress and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.xxx.

Full experimental data, details on methods and starting materials, and copies of spectral data (PDF)

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Author Contributions

J.H, S.Z, and Y.W. designed the project. J.H. performed the experiments. P.S. and X.X. synthesized some of the substrates. All authors co-wrote the manuscript, analyzed the data, discussed the results and commented on the manuscript.

Notes

The authors declare no competing financial interest.

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