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Mild and Regioselective Benzylic C−H Functionalization: Ni-Catalyzed Reductive Arylation of Remote and Proximal Olefins

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Supporting Information

ABSTRACT: The synergistic combination of NiH-catalyzed alkene isomerization with nickel-catalyzed cross-coupling has yielded a general protocol for the synthesis of a wide range of structurally diverse 1,1-diarylalkanes in excellent yields and high regioselectivities from readily accessible olefin starting materials. Furthermore, the practicality and synthetic flexibility of this approach is highlighted by the successful employment of isomeric mixtures of olefins for regioconvergent arylation.

The development of protocols for the activation of ubiquitous C−H bonds present in organic molecules has resulted in fundamental changes in the strategy of organic synthesis.[1] These changes have resulted in synthetic routes that are more concise or utilize starting materials that are more widely available.[2] Despite the encouraging progress in the development of C−H functionalization reactions, the selective functionalization of sp^3 C−H bonds remains a synthetic challenge.[3] Most reported processes require polar directing groups to be present nearby to ensure good reactivity and regioselectivity. The requirement for these directing groups limits the applicability of these methods. The mild and selective benzylic functionalization of sp^3 C−H bonds, applicable to simple hydrocarbons, as well as more functionalized starting materials, would serve as a useful addition to the collection of currently available C−H functionalization methods.

Alkenes are easily accessed and abundant feedstock starting materials. Compared to inert sp^3 C−H bonds, the C=C double bond is more reactive and readily undergoes hydro- and difunctionalization (Figure 1a). In particular, over the past two decades, hydrofunctionalization mediated by metal-hydride chemistry has attracted significant attention.[4] The application of alkenes and metal-hydride chemistry in remote functionalization, however, is reported in only a few contexts.[5] In particular, their use in the arylation of remote benzylic C−H bonds is rare,[6a,b] although Hartwig has reported a terminal-selective C−H arylation of internal alkenes.[6c] Such a transformation would lead to the synthesis of 1,1-diarylalkanes, a privileged scaffold in medicinal chemistry and materials science, present as a key structural element in a variety of pharmaceutical agents, natural products, agrochemicals and functional materials (Figure 1b).[7]

Over the past decade, abundant nickel catalysis has emerged as a powerful coupling protocol for carbon−carbon bond formation.[8] Although nickel-catalyzed reactions often suffer from isomerization mediated by β-hydride elimination, we felt

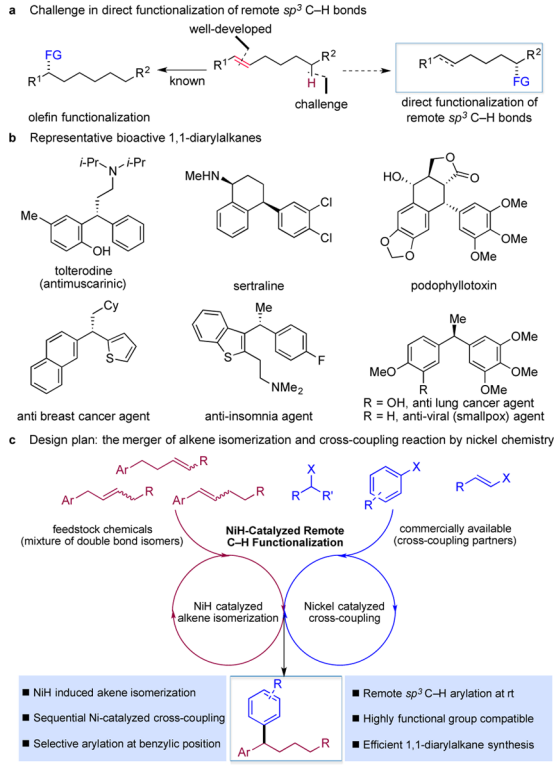

Figure 1. Design plan: remote C−H arylation enabled by alkene isomerization and sequential cross-coupling.

that this usually undesired process might be leveraged for selective C−H benzylic arylation of (remote) olefin-containing substrates. Specifically, we recently questioned whether a nickel-hydride could be used to initiate a sequential elimination/reinsertion process to access the thermodynamically favored benzylnickel intermediate, allowing for the subsequent regioselective nickel-catalyzed cross-coupling reaction at the distal position to form a 1,1-diarylalkane product (Figure 1c). Such a process would entail a synergistic combination of two distinct platforms: alkene isomerization, mediated by nickel hydride and alkylnickel intermediates, and cross-coupling, mediated by organonickel intermediates in several oxidation states (I, II, and III).[8] Moreover, the development of a selective process hinged on sufficient kinetic and thermodynamic favorability for

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the formation and cross-coupling of the benzylnickel intermediate. Otherwise the formation of regioisomeric arylation products would occur. Despite the inherent complexity of such a system, the successful implementation of a reductive relay C−H arylation would provide a synthetically flexible arylation protocol for the synthesis of 1,1-diarylalkane from any isomer of an arylolefin starting material. Here we report a broad, functional group tolerant protocol for such a strategy, using a readily accessible bipyridyl−nickel complex as the catalyst.

A more complete depiction of the presumed mechanism for this remote reductive relay C−H arylation reaction is shown in Figure 2. Nickel hydride **I** inserts into alkene **1** to generate alkyl-

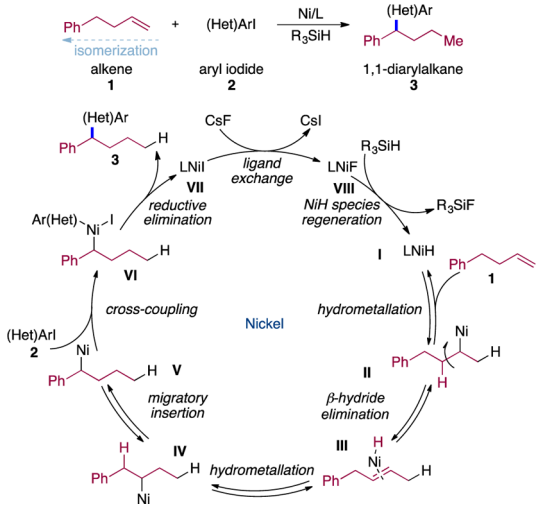
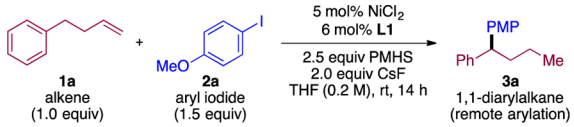


Figure 2. Proposed pathway of reductive relay hydroarylation.

nickel intermediate **II**, which readily undergoes β-hydride elimination to afford the isomeric complex **III**. After readdition of nickel hydride, a new alkyl−nickel species **IV** is formed.[9,10] Iteration of this process eventually gives rise to the thermodynamically favored benzylic alkylnickel intermediate (**V**). If formation of this species is sufficiently rapid and its reaction with aryl iodide **2** is favorable relative to other alkylnickel intermediates, selective cross-coupling via the reductive elimination of **VI** would then deliver arylation product **3** and nickel iodide **VII**. In the presence of stoichiometric fluoride salt and hydrosilane, the nickel hydride **I** is regenerated from **VII** via an intermediate nickel fluoride (**VIII**) to complete the catalytic cycle. A suitable catalyst must fulfill a number of requirements. First, the nickel-hydride catalyzed isomerization between the olefin-isomers must be rapid compared to oxidative addition. Second, the benzylnickel intermediate must readily undergo oxidative addition with the aryl iodide, overwhelmingly in preference to other alkylnickel intermediates. At the outset, it was unclear whether the requisite selectivity could be achieved.[11]

Our initial study of the proposed remote C−H arylation commenced with the coupling of 4-phenyl-1-butene (**1a**) with 4-iodoanisole (**2a**). Investigation of a range of parameters showed that the desired remote arylation product could be obtained using a combination of $NiCl_2$ and C2-substituted bipyridine ligand **L1** in good isolated yield (84%) with excellent regioselectivity [rr (1,1-diarylalkane: all other isomers) = 98:2] (Table 1, entry 1). Using another nickel source ($NiBr_2$) lead to diminished yield (entry 2). Furthermore, it is worth pointing out that methyl groups of **L1** are critical.[12] Use of the parent bpy (**L2**) resulted in no desired arylation product (entry 3). Evaluation of

Table 1. Variation of Reaction Parameters



entry	deviation from standard conditions	yield of **3a** (%)[a]	rr[b]
1	**none**	**91 (84)**	**98:2**
2	$NiBr_2$ instead of $NiCl_2$	76	96:4
3	**L2** instead of **L1**	0	--
4	DMMS instead of PMHS	75	97:3
5	$(EtO)_3SiH$ instead of PMHS	91	97:3
6	KF instead of CsF	6	>100:1
7	40 °C	71	97:3
8	4-Bromoanisole instead of **2a**	24	>100:1
9	2.0 equiv **2a**	94	97:3

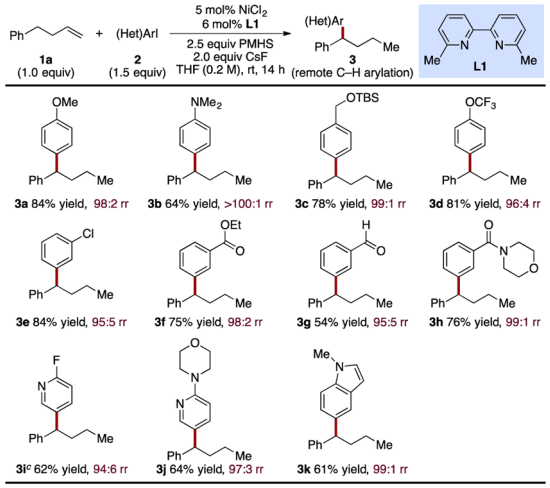
L1: R = Me
L2: R = H

[a]Yields determined by GC using dodecane as the internal standard; yield in parentheses was isolated yield of purified product and is an average of two runs (0.5 mmol scale). [b]rr is regioisomeric ratio, represents the ratio of the major (1,1-diarylalkane) product to the sum of all other isomers as determined by GC analysis (See Supporting Information for experimental details). PMP, 4-methoxyphenyl.

other silanes showed that dimethoxy(methyl)silane (DMMS) was less efficient whereas triethoxysilane was comparably effective (entries 4, 5). Because polymethylhydrosiloxane (PMHS) is an inexpensive, abundant and nontoxic byproduct of the silicone industry, it was chosen for subsequent investigations. Replacement of cesium fluoride with the potassium salt resulted in almost complete loss of reactivity (entry 6). Conducting the reaction at 40 °C instead of room temperature also led to somewhat lower yield (entry 7). Additionally, 4-bromoanisole was found be considerably less reactive than 4-iodoanisole (entry 8). Finally, marginally higher yield could be obtained at the expense of using 2 equiv of the aryl iodide, rather than 1.5 equiv (entry 9).

With the optimized conditions in hand, we next sought to examine the generality of this transformation by exploring the scope of aryl iodide coupling partner (Table 2). A variety of aryl- and heteroaryl iodides were tolerated. Both electron-rich (**2b**, **2c**) and electron-withdrawing aryl iodides (**2d**−**h**) were competent substrates. A variety of functional groups were also

Table 2. Scope of Aryl Iodide Coupling Partner[a,b]



[a]Isolated yields on 0.50 mmol scale (average of two runs). [b]rr is regioisomeric ratio, represents the ratio of the major (1,1-diarylalkane) product to the sum of all other isomers as determined by GC analysis. [c]2.0 equiv aryl iodide.

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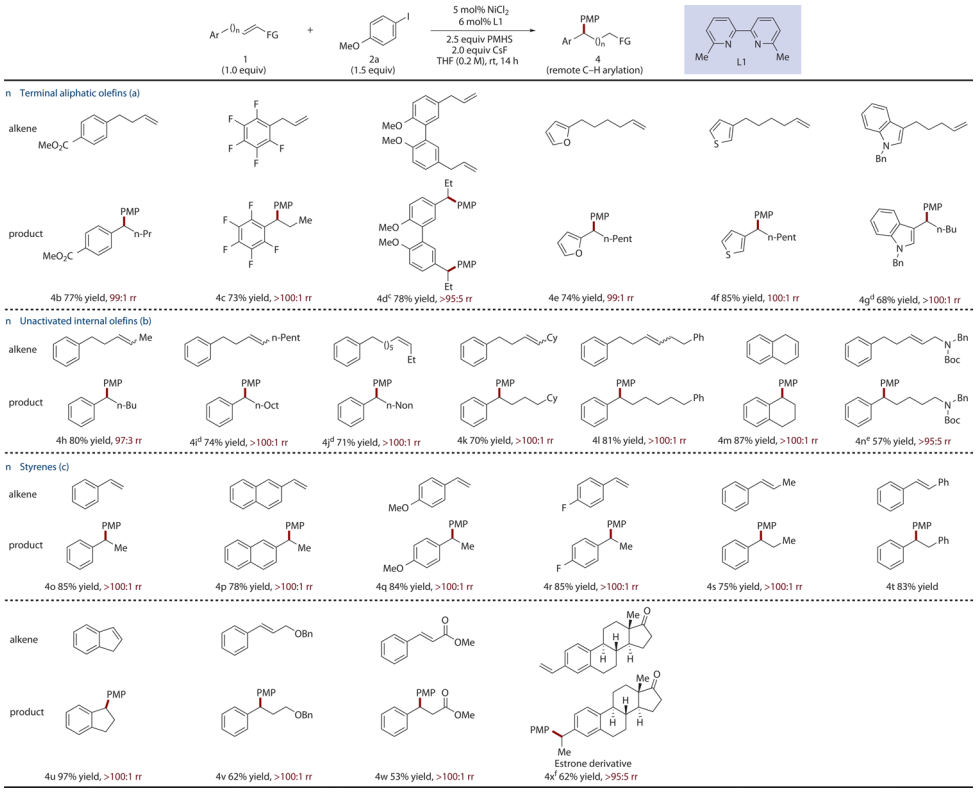
Table 3. Scope of Alkene Coupling Partner[a,b]



[a]Isolated yields on 0.50 mmol scale (average of two runs). [b]rr is regioisomeric ratio, represents the ratio of the major (1,1-diarylalkane) product to the sum of all other isomers as determined by GC analysis, ratios reported as >95:5 were determined by crude ^{1}H NMR analysis. [c]0.25 mmol **1d** used, see Supporting Information for experimental details. [d]2.0 equiv aryl iodide. [e]20 h. [f]dr = 1:1. PMP, 4-methoxyphenyl.

readily accommodated, including ethers (**2c**, **2d**, **2h**, and **2j**), amines (**2b**, **2j**), an aryl chloride (**2e**), an ester (**2f**), and an amide (**2h**). Notably, under these exceptionally mild reaction conditions, even a readily reduced aldehyde group was left intact (**2g**). Furthermore, a series of iodinated heterocycles, such as pyridines (**2i**, **2j**) and indole (**2k**) were also competent coupling partners. In addition, comparison of the two pyridyl iodides indicated that the less electron-deficient one afforded better regioselectivity (**2j** vs **2i**).

Further interrogation of the reaction scope demonstrated the broad scope of alkene partner. As illustrated in Table 3a, an array of terminal aliphatic alkenes could undergo alkene isomerization hydroarylation smoothly.[13] A wide variety of substituents on the remote aryl ring, bearing electron withdrawing (**1b**, **1c**) or electron donating substituents (**1d**) were all well-tolerated. Moreover, heteroaromatic substrates, such as those containing a furan (**1e**), a thiophene (**1f**), or an indole (**1g**) in place of the aryl group were likewise suitable for this reaction.

Furthermore, a range of unactivated internal olefins, a challenging class of substrates for transition metal catalysis, were suitable partner under these remote hydroarylation conditions (Table 3b). Both *E* (**1n**) and *Z* (**1j**, **1m**) alkenes, as well as *E*/*Z* mixtures (**1h**, **1i**, **1k**, **1l**) were well-tolerated, and high selectivity for arylation at the benzylic position was observed, regardless of the starting position of the C═C bond. Notably, even with a heteroatomic substituent at the other terminus of the alkyl chain (e.g., a Boc carbamate in **1n**), migration toward to aryl group and subsequent benzylic arylation was still preferred.

Additionally, styrenes themselves could also undergo hydroarylation to produce the desired 1,1-diarylalkanes exclusively (Table 3c).[14] This hydroarylation reaction tolerates a variety of substituents on the aryl ring of styrene (**1o**–**x**). For an estrone-derived styrene, the sensitive ketone group was again preserved under the mild reaction conditions (**1x**). Surprisingly, subjection of methyl cinnamate (**1w**) to hydroarylation conditions also provided exclusively the 1,1-diarylalkane product (**4w**). The observed regioselectivity for this substrate could be due to the preferential formation of the benzylnickel species during the hydronickelation step. Alternatively, the two hydronickelation products may equilibrate, with the selectivity determined by the relative rates of oxidative addition.[15]

Finally, because of isomeric mixtures of olefins are available on enormous scale as industrial feedstocks derived directly from the petrochemical sources, their use in regioconvergent reactions is of considerable interest. We wished to probe whether such mixtures could be utilized in the current isomerization–hydroarylation relay reaction. As a proof-of-concept, two sets of reactions were conducted with equimolar amounts of two or three olefin isomers. In both cases, arylation was highly selective for the benzylic position and produced only one regioconvergent arylation product (Scheme 1). To gain insight into the mechanism, we are currently performing computational studies to gain an accurate understanding of the origin of the high regioselectivity.

In conclusion, we developed a room temperature nickel-catalyzed selective remote sp^3 C–H bonds arylation reaction via alkene isomerization and sequential hydroarylation. This protocol provides an effective means to access an array of 1,1-diarylalkanes, a valuable structure in medicinal and materials chemistry. Excellent regio- and chemoselectivity were observed

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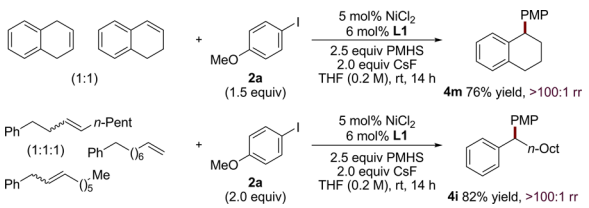
Scheme 1. Regioconvergent Isomerization−Hydroarylation Reaction by Using of a Mixture of Olefin-isomers[a,b]



[a]Isolated yields on 0.60 mmol olefin-isomers scale (average of two runs). [b]rr is regioisomeric ratio, represents the ratio of the major (1,1-diarylalkane) product to the sum of all other isomers as determined by GC analysis. PMP, 4-methoxyphenyl.

for a wide variety of both functionalized and unfunctionalized aryl iodides and alkenes partners. This versatile method provides a synthetically valuable addition to the current collection of remote sp^3 C−H functionalization reactions. Developing asymmetric version of the current transformation and engaging other electrophiles of significant synthetic utility in this process are topics of ongoing investigations in our laboratory. Progress in these areas 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/jacs.6b11962.

Experimental procedures, characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(10) Preliminary data (see the Supporting Information) supports olefin isomerization and C−C coupling as independent steps, with full dissociation of NiH from the olefin giving rise to olefin isomers when the reaction is run to partial conversion.

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(15) Experiments to distinguish between these possibilities are under way.

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