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Nickel-Catalyzed Stereoselective Diarylation of Alkenylarenes

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Abstract

A three-component coupling of aryl bromides, arylboron reagents, and alkenylarenes is presented. The method tolerates a variety of substitution patterns on all of the components. In particular, 1,2-disubstituted alkenylarenes are suitable and undergo highly diastereoselective diarylation.

Alkenes represent an appealing class of molecules for chemical synthesis because of their wide availability and ease of preparation.¹ While alkene difunctionalization is known, reactions that incorporate two distinct carbon-based groups are more rare.² In particular, addition of two different aryl groups across an alkene represents an attractive goal for method development because of the prevalence of polyarylalkanes in natural products and pharmaceutical agents.

One strategy to achieve alkene diarylation is to interrupt a cross-coupling reaction with a migratory insertion event.² However, challenges with this strategy lie in competing direct cross-coupling and β -hydride elimination of alkylmetal intermediates (Mizoroki–Heck reaction). To mitigate these concerns, methods involving intramolecular variants,^{2,3} substrates with coordinating groups,⁴ and/or use of select classes of activated alkenes have been developed.⁵ Several examples of related intermolecular aryl/alkenylation of activated alkenes are known.⁶ In addition, intermolecular aryl/alkylation by metalloradical processes have been reported.⁷

As noted above, while several classes of activated alkenes are known to undergo diarylation, three examples of diarylation of vinylarenes have been reported. The first is a

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b05680.

Crystallographic data for **21** (CIF)

Crystallographic data for **22** (CIF)

Crystallographic data for **37** (CIF)

Experimental procedures and analytical data for all compounds (PDF)

The authors declare no competing financial interest.

homodiarlylation of vinylarenes with aryltin reagents.^{5d} The other two examples involve heterodiarlylation; while one requires the use of a coordinating group,^{4a} the second necessitates substrates with extended conjugation (Scheme 1A), thus limiting the reaction scope.^{5g} Furthermore, reactions of 1,2-alkenylarenes are not known yet particularly important, as the opportunity for stereocontrol becomes apparent. Only two examples of diarylation of 1,2-disubstituted alkenes are known and are limited to norbornene derivatives^{5a-c} and 1,3-cyclohexadiene (Scheme 1B).^{5e} It is evident that despite the significant advances outlined above, heterodiarlylation of simple styrene derivatives and reactions of 1,2-disubstituted alkenylarenes are lacking. Herein we disclose a stereoselective Ni-catalyzed diarylation of mono-, 1,1-di-, and 1,2-disubstituted alkenylarenes with aryl bromides and arylboron reagents (Scheme 1C).⁸ The method is notable in that it is stereoselective, a range of substitution patterns are tolerated, and gram-scale synthesis can be achieved.

In the context of recent efforts from our lab on Ni-catalyzed carboboration of unactivated alkenes⁹ and Cu-catalyzed alkene diarylation reactions,¹⁰ we discovered a novel diarylation of styrene (**1**) with *p*-tolB(neop)¹¹ (**2**) and 3,5-dimethylbromo-benzene (**3**). The optimized reaction conditions (Table 1, entry 1) utilize inexpensive NiCl₂ at 80 °C in toluene. Under these conditions, triarylethane **4** was formed in 77% yield, accompanied by the direct cross-coupling product in ~25% yield (<2% yield of products derived from β -hydride elimination was observed).¹² Key to the development of this reaction was the identification of 0.1 equiv of (Bpin)₂ in the presence of KOEt as a suitable reductant for NiCl₂, presumably to generate a Ni(0) complex.¹³ Use of the common reductants Zn and Mn (Table 1, entry 4) was ineffective. In addition, use of Ni(COD)₂ (with or without (Bpin)₂) allowed for product formation, albeit in reduced yield, thus confirming that Ni(0) is a competent catalyst (Table 1, entries, 5 and 6). Phosphine and amine-based ligands suppressed the alkene functionalization and allowed only direct cross-coupling to occur (Table 1, entries 7 and 8). When lower amounts of ArBr or ArB(neop) were employed, slightly lower yields were observed (compare Table 1, entries 10 and 11 with entry 1). Finally, for reasons that are unclear at this time, the reaction is sensitive to the counterion of the base, as NaOEt was significantly less effective than KOEt (compare Table 1, entry 12 with entry 1).

After the optimized conditions were established, the scope of the diarylation was evaluated. With respect to the alkene component, styrene derivatives bearing electron-donating (products **7** and **10**) and electron-withdrawing substituents (products **8** and **9**) worked well (Scheme 2). Sterically demanding 2-methylstyrene was tolerated; however, the yield was slightly diminished (product **11**). Substrates that have extended conjugation also allowed for product formation (products **12** and **13**).

One of the most notable aspects of this method is that 1,1- and 1,2-disubstituted alkenylarenes were also tolerated (Scheme 2). For example, reaction of α -methylstyrene allowed for formation of **14**, which bears a quaternary carbon (see also products **15** and **16**). Reaction of 1,2-disubstituted alkenylarenes occurred with control of the stereoselectivity; in all cases, syn addition of the aryl group was observed as the major product regardless of the alkene geometry (compare products **21** and **22**, from trans- and cis-stilbene, respectively). In the case of cis-stilbene, slightly lower levels of diastereoselectivity were observed relative to

trans-stilbene. Substitution at the β -position could be varied to a silyl-protected hydroxyalkyl group (product **19**), i-Pr (product **20**) or Ph (products **21** and **22**). With respect to known limitations, attempted diarylation of a trisubstituted alkene and an unactivated alkene did not lead to product formation.¹²

Reactions with a variety of aryl bromides were investigated and found to tolerate electron-donating (products **29**, **30**, and **34**), electron-withdrawing (products **27** and **32**), and sterically demanding (product **33**) substituents (Scheme 3A). The functional group tolerance was also evaluated and included esters (product **32**), amides (product **28**), and tertiary amines (products **29** and **35**). The moderate yield observed in the formation of **35** is likely due to the Lewis basic nitrogen, which partially inhibits catalysis. It should also be noted that heterocyclic aryl bromides, such as 3-bromopyridine, are not tolerated in the reaction, likely for similar reasons.¹² A similar scope with respect to the arylboron reagent compared to the aryl bromide was observed, with electron-donating, electron-withdrawing, and sterically demanding substituents being tolerated (Scheme 3B). In addition, an alkenylB(neop) could be used to access **47**, thus demonstrating an example of aryl/alkenylation. However, mono- or disubstituted alkenylboranes did not function well and resulted only in direct cross-coupling.¹²

The reaction was performed on a gram scale with similar yield and selectivity as in the smaller-scale reactions (Scheme 4A). It should be emphasized that the reaction conditions employ inexpensive and readily available reagents, making for a practical synthesis of polyaryllkanes.

To compare this method with existing strategies for polyaryllkane synthesis, *rac*-lasofoxifene (**48**) was chosen as a representative target (Scheme 4B). The established approach toward *rac*-lasofoxifene involves hydrogenation of a tetrasubstituted double bond, wherein the exocyclic aryl groups are installed at an earlier stage in the synthesis.^{14,15} The strategy outlined herein is orthogonal but has the advantage that the exocyclic aryl groups are installed at a late stage by the convergent assembly of simple components. This is significant when modular approaches to molecules are desired, such as in early-stage drug discovery chemistry. In practice, diarylation of 6-methoxy-3,4-dihydronaphthalene (**50**) with PhBr and ArB(neop) **49** allowed for the formation of a known precursor to *rac*-lasofoxifene with >20:1 dr in 36% yield. As noted previously with product **35**, the moderate yield observed for the formation of **52** is likely due to the presence of the Lewis basic nitrogen.

A reasonable catalytic cycle for the diarylation reaction is illustrated in Scheme 5.^{4a} It is proposed that NiCl₂ is reduced to Ni(0) with (Bpin)₂ and KOEt, perhaps via reductive elimination of EtOBpin from complex **54**.¹³ Oxidative addition of Ni(0) and Ar²Br generates Ni^{II}BrAr² (**56**), which upon migratory insertion provides π -benzyl-Ni complex **57** (this is likely why alkenyl arenes, as opposed to unactivated alkenes, are required). Transmetalation with Ar¹B(neop) assisted by KOEt generates **58**, which undergoes reductive elimination to form the diarylation product. The process likely does not involve radical intermediates, as reaction of (E)- and (Z)-alkene isomers gave rise to different major diastereomers resulting from syn diarylation (Scheme 2, products **21** and **22**). It should be

noted that this process might involve a heterogeneous/surface reaction, as strongly donating ligands are absent.

The conditions outlined herein allow for diarylation in preference to direct cross-coupling or Mizoroki–Heck reaction, likely for several reasons. The first is the absence of strongly donating ligands (e.g., phosphines and amines), which allows for alkene coordination and subsequent migratory insertion. In the presence of strongly donating ligands, alkene coordination is likely to be inhibited, and thus, direct cross-coupling dominates. The second is the use of arylboronic esters, which reduces the rate of cross-coupling because of slower transmetalation relative to other nucleophiles. For example, if an arylzinc reagent is used in place of ArB(neop), the cross-coupling product is the major product observed.¹² In addition, the use of 1.7 equiv of ArBr and 2.0 equiv of ArB(neop) is required not because of competing direct cross-coupling, as the cross-coupling product is formed in <25% yield, but rather to ensure rapid capture of intermediates 55 and 57 prior to off-cycle reactions (e.g., Ni–C bond homolysis or Ni aggregation). Finally, use of Ni catalysts results in the formation of π -benzyl–Ni complexes, which are less prone to β -hydride elimination compared with π -benzyl–Pd complexes.¹⁶ In the latter case, β -hydride elimination is known to be rapid.^{5g}

In summary, a Ni-catalyzed diarylation of alkenylarenes has been developed. The method represents a substantial departure from known methods for reaction of vinylarenes in that specialized substrates are not required and the process is uniquely effective for diarylation of 1,2-disubstituted alkenylarenes. Such advances allow for the efficient and modular synthesis of a wide variety of polyaryllkanes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

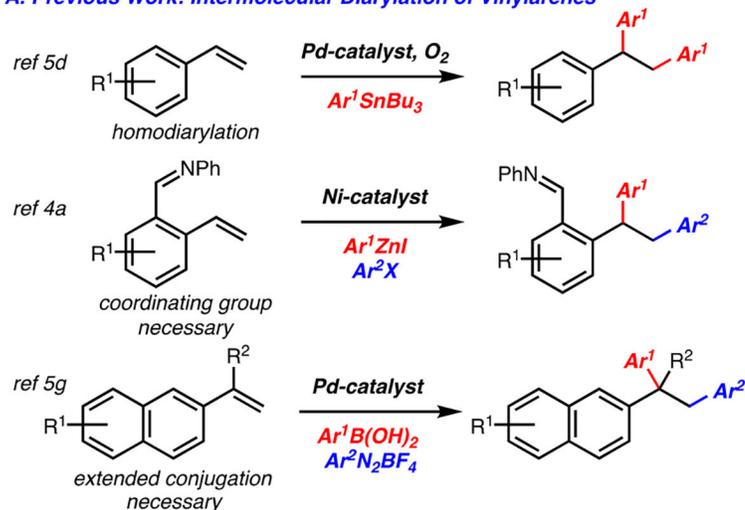
We thank Indiana University and the NIH (5R01GM114443) for financial support. P.G. thanks the China Scholarship Council and the National Natural Science Foundation of China (21602168) for generous financial support. This project was partially funded by the Vice Provost for Research through the Research Equipment Fund.

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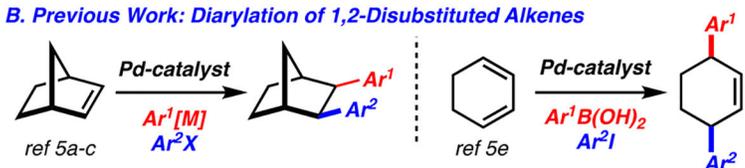
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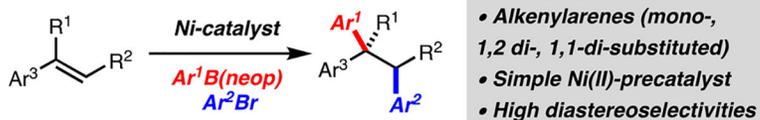
A. Previous Work: Intermolecular Diarylation of Vinylarenes



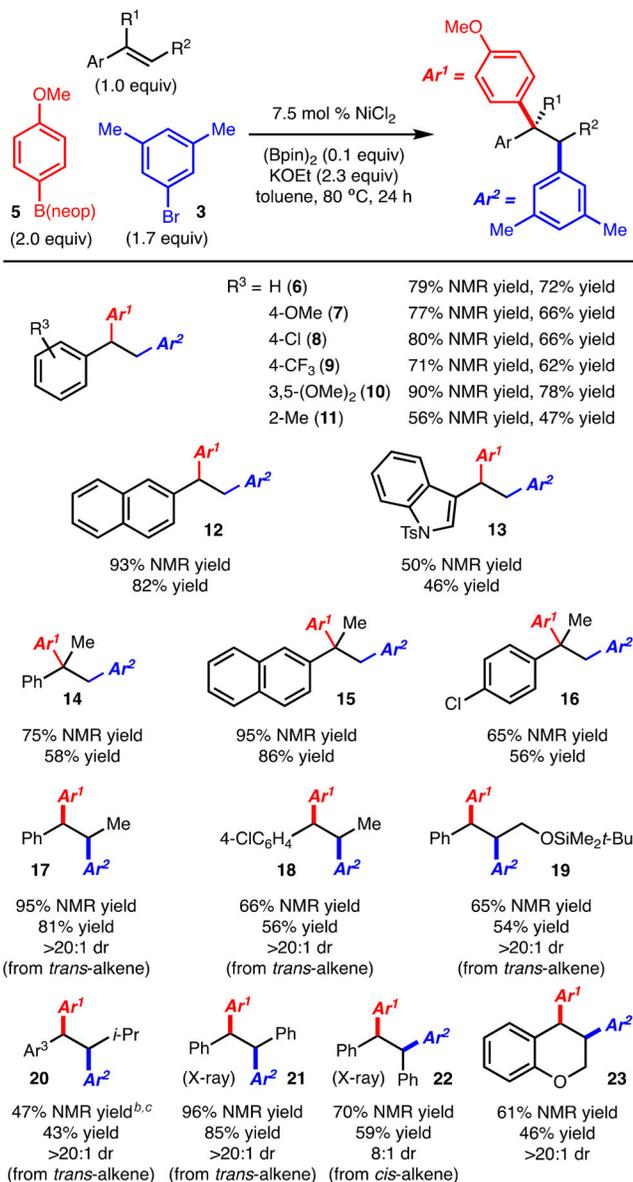
B. Previous Work: Diarylation of 1,2-Disubstituted Alkenes



C. This Work: Stereoselective Diarylation of Alkenylarenes



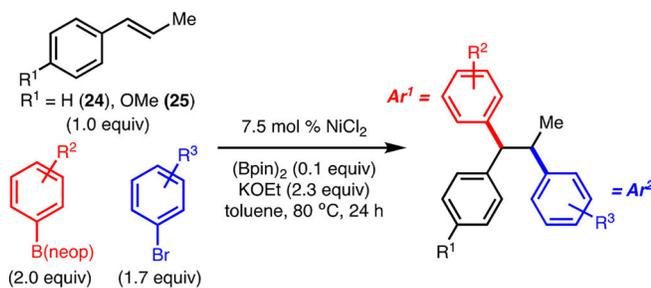
Scheme 1.
Intermolecular 1,2-Diarylation of Alkenes



Scheme 2.

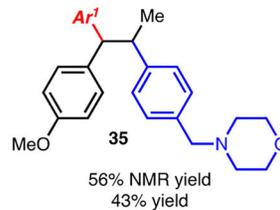
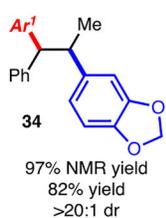
Evaluation of Various Alkenes^a

^aThe reactions were run on a 0.5 mmol scale. “NMR yield” refers to yields determined by ¹H NMR analysis of the unpurified reaction mixtures with an internal standard; “yield” refers to yields of isolated products after silica gel column chromatography. Diastereomeric ratios were determined by ¹H NMR analysis of the unpurified reaction mixtures. The conversion of styrene was >98%, except where noted. ^bAr¹ = 4-MeC₆H and Ar³ = 4-OMeC₆H₄. ^c27% of the alkene was recovered.



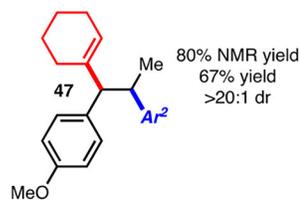
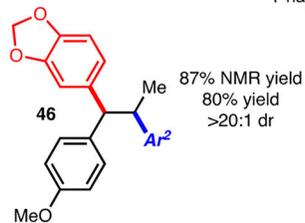
A) Variation of ArBr ($\text{Ar}^1 = 4\text{-OMeC}_6\text{H}_4$)

 $>20:1$ dr	$R^3 = \text{H}$ (26)	92% NMR yield, 79% yield
	4-F (27)	76% NMR yield, 65% yield
	4-NMeBoc (28)	47% NMR yield, 42% yield
	4-pyrrolidine (29)	78% NMR yield, 65% yield
	3-OMe (30)	79% NMR yield, 75% yield
	3,5-(<i>t</i> -Bu) ₂ (31)	86% NMR yield, 76% yield
	3-CO ₂ Et (32)	42% NMR yield, 38% yield
	2-Me (33)	88% NMR yield, 81% yield



B) Variation of ArB(neop) ($\text{Ar}^2 = 3,5\text{-(Me)}_2\text{C}_6\text{H}_3$)

 $>20:1$ dr	$R^2 = \text{H}$ (36)	94% NMR yield, 86% yield
	4-CF ₃ (37) (X-ray)	63% NMR yield, 56% yield ^b
	4-Cl (38)	71% NMR yield, 61% yield
	4-Me (39)	92% NMR yield, 84% yield
	4-OBn (40)	91% NMR yield, 80% yield
	3-OMe (41)	91% NMR yield, 77% yield
	3-CO ₂ Et (42)	88% NMR yield, 79% yield
	3,5-(OMe) ₂ (43)	91% NMR yield, 77% yield
	2-Me (44)	82% NMR yield, 69% yield
	1-naphthyl (45)	81% NMR yield, 68% yield

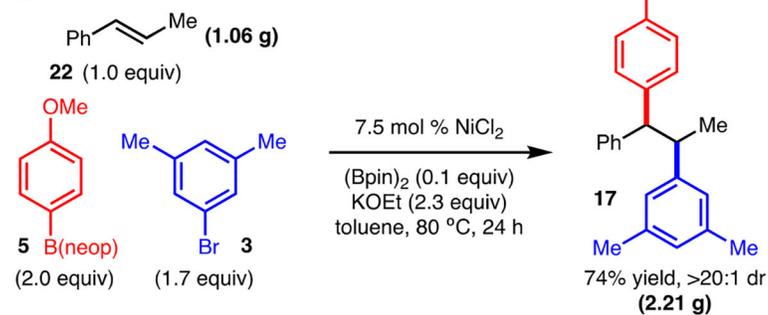
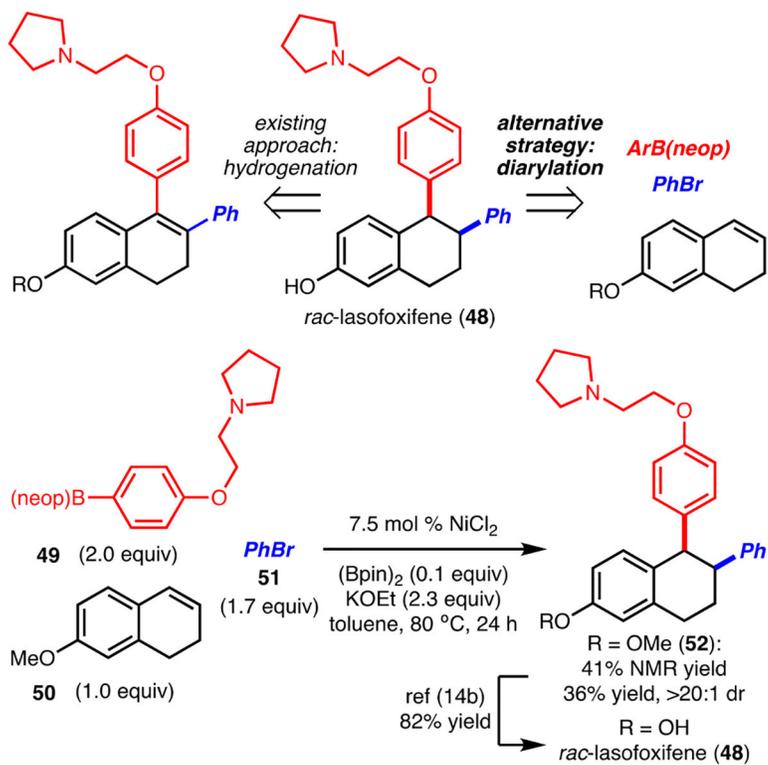


^aSee footnote a of Scheme 2. ^b**24** was used instead of **25**.

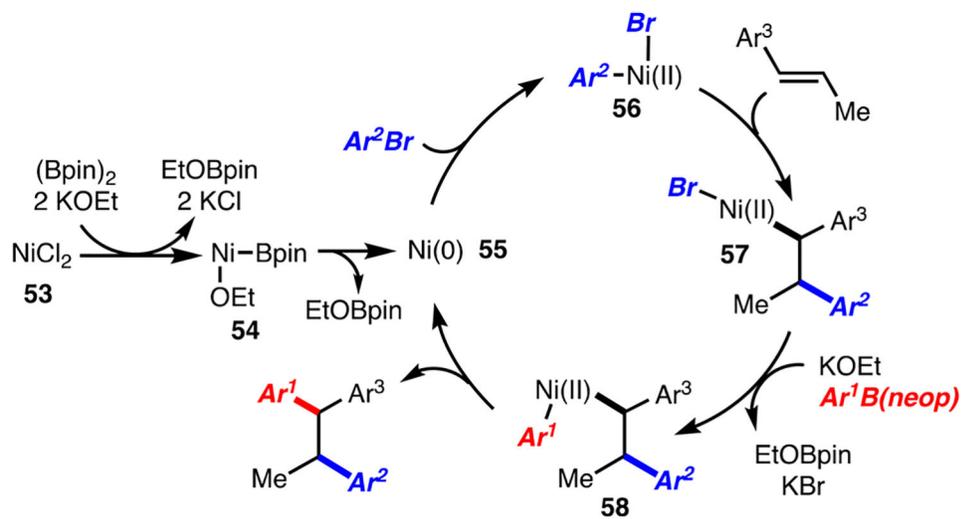
Scheme 3.

Evaluation of ArBr and ArB(neop) ^a

^aSee footnote a of Scheme 2. ^b**24** was used instead of **25**.

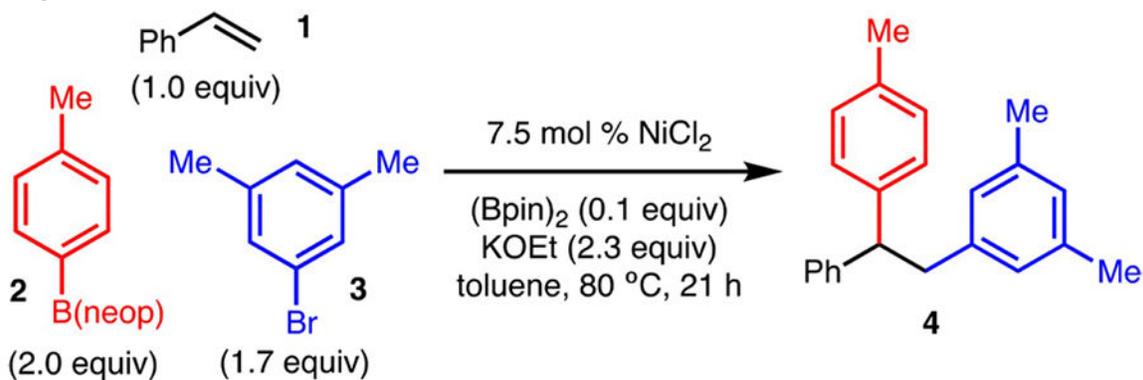
A) Gram Scale Reaction**B) Representative Application to Demonstrate Workflow**

Scheme 4.
Utility of the Method



Scheme 5.
Proposed Catalytic Cycle

Table 1.

Change from Standard Conditions ^a

entry	change from standard conditions	Yield (%) ^b
1	no change	77
2	no (Bpin) ₂	<2 ^d
3	0.1 equiv of (Bneop) ₂ instead of 0.1 equiv of (Bpin) ₂	70
4	1.0 equiv of Zn ⁰ or Mn ⁰ instead of 0.1 equiv of (Bpin) ₂	<2 ^c
5	Ni(COD) ₂ instead of NiCl ₂ and (Bpin) ₂	53
6	Ni(COD) ₂ instead of NiCl ₂	54
7	NiCl ₂ (PCy ₃) ₂ instead of NiCl ₂	<2 ^d
8	NiCl ₂ (bpy) instead of NiCl ₂	<2 ^d
9	NiCl ₂ (DME) instead of NiCl ₂	73
10	1.2 equiv of ArBr instead of 1.7 equiv of ArBr	68
11	1.8 equiv of ArB(neop) instead of 2.0 equiv of ArB(neop)	72
12	NaOEt instead of KOEt	16 ^d

^aThe reactions were run on a 0.2 mmol scale.^bYields were determined by GC analysis with a calibrated internal standard. The conversion of styrene was >98%, except where noted otherwise.^c>80% of the styrene was recovered.^d~50% of the styrene was recovered.