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Nickel Catalyzed Cross-Coupling of Vinyl-Dioxanones to Form Enantiomerically Enriched Cyclopropanes

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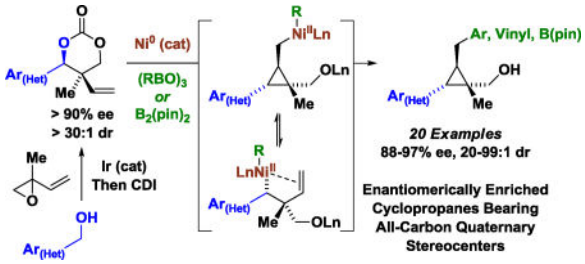
Abstract

Under the conditions of nickel(0) catalysis, enantiomerically enriched vinyl-dioxanones engage boroxines or $B_2(pin)_2$ in stereospecific cross-coupling to form diverse tetrasubstituted cyclopropanes bearing all-carbon quaternary stereocenters. The collective data corroborate a mechanism involving nickel(0)-mediated benzylic oxidative addition with inversion of stereochemistry followed by reversible olefin insertion to form a (cyclopropylcarbinyl)nickel complex, which upon reductive elimination releases the cyclopropane.

Graphical abstract



Cyclopropanes appear as substructures across diverse secondary metabolites[1] and are frequently found in commercial medicines, agrochemicals and fragrances.[2] Hence, the development of methods for cyclopropane formation represents a persistent challenge in chemical research.[3] Among the most effective methods for the preparation of enantiomerically enriched cyclopropanes is the reaction of olefins with metal carbenoids.[3] Here, we report a strategy for the asymmetric synthesis of cyclopropanes under the conditions of metal catalyzed cross-coupling. Specifically, nickel(0) catalysts[4,5] react with enantiomerically enriched 4-aryl-5-vinyl-1,3-dioxanones to form (cyclopropylcarbinyl)nickel(II) species, which, in the presence of organoboron reagents or $B_2(pin)_2$deliver cyclopropanes in a stereospecific manner. Thus, the enantioselective synthesis of tetra-substituted cyclopropanes bearing all-carbon quaternary stereocenters is achieved (Scheme 1).

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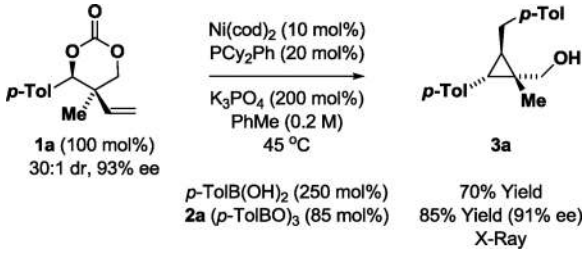
Supporting Information **Available:** Experimental procedures and spectral data. HPLC traces corresponding to racemic and enantiomerically enriched samples. Single crystal X-ray diffraction data for **3a**. This material is available free of charge *via* the internet at http://pubs.acs.org.

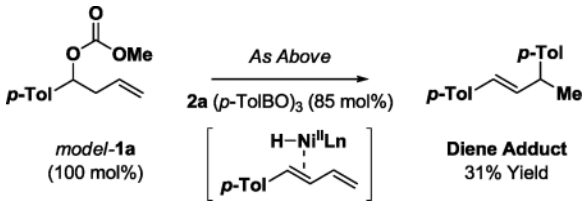
The authors declare no competing financial interest.

In connection with ongoing investigations into the formation of C-C bonds via hydrogenation and transfer hydrogenation,[6] we recently reported an iridium catalyzed coupling of primary alcohols with isoprene oxide to form products of *tert*-(hydroxy)-prenylation – a byproduct-free transformation that occurs with exceptional control of *anti*-diastereo- and enantioselectivity.[7] It was posited that cyclic carbonates derived from these reaction products should be predisposed toward cyclopropane formation under cross-coupling conditions, as geminal substitution of the neopentyl glycol precludes competing β-hydride elimination of the σ-benzylmetal intermediate and should conformationally bias the system toward olefin insertion[8] *via* Thorpe-Ingold effect.[9] However, the facility of conventional benzylic cross-coupling rendered the feasibility of the proposed cyclopropane formation uncertain.[10]

In an initial experiment, vinyl-dioxanone **1a** was exposed to the catalyst derived from $Ni(cod)_2$ (10 mol%) and PCy_3 (20 mol%) in the presence of tri(*p*-tolyl)boroxine **2a** and K_3PO_4 (200 mol%) in toluene (0.1 M) at 60 °C. To our delight, cyclopropane **3a** was formed in 36% yield as a single diastereomer. Conversion was found to be sensitive to concentration and temperature. At 45 °C under otherwise identical conditions, a 53% yield of cyclopropane **3a** was obtained. Using the nickel catalyst modified by PCy_2Ph (20 mol%), cyclopropane **3a** was obtained in 77% yield. Finally, at slightly higher concentration (toluene, 0.2 M), an 85% yield of cyclopropane **3a** was achieved (eq. 1). Stereospecificity was corroborated by chiral stationary phase HPLC analysis of cyclopropane **3a**. Relative stereochemistry of cyclopropane **3a** was confirmed by single crystal X-ray diffraction analysis. *p*-Tolylboronic acid also delivers cyclopropane **3a** (eq. 1), but in slightly lower yield. Application of these optimal conditions to unsubstituted methyl carbonate *model*-**1a** did not result in cyclopropane formation; rather, the indicated product obtained through β-hydride elimination of the σ-benzyl intermediate was formed (eq. 2). Cyclic carbonate **1a** reacted more efficiently than related acyclic carbonates, suggesting the internal alkoxide generated upon ionization-decarboxylation facilitates group transfer from boron to nickel through an internal boron ate-complex.

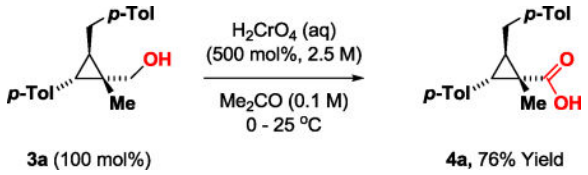


(eq. 1)

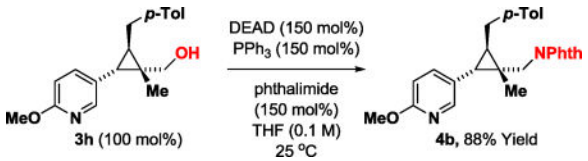


(eq. 2)

Optimal conditions utilizing tri(*p*-tolyl)boroxine **2a** were applied to a structurally diverse set of enantiomerically enriched vinyl-dioxanones **1a–1i** (Table 1). Vinyl dioxanones bearing a variety of substituted aromatic (**1a–1d**) and heteroaromatic (**1e–1i**) rings were converted to cyclopropanes **3a–3i** in good yield with complete levels of diastereoselectivity. Relative stereochemistry was assigned in analogy to that determined for **3a**. Although the preexisting non-epimerizable quaternary stereocenter serves as an "internal standard," stereospecificity was spot-checked for compounds **3a, 3b, 3d** and **3h**. Notably, unlike prior work involving nickel catalyzed benzylic substitution, extended aromatic systems are not required.[11] Standard conditions also were applied to the coupling of vinyl-dioxanones **1a** and **1h** with boroxines **2b–2d**, which incorporate *p*-CF_3-phenyl, *p*-methoxyphenyl and (*E*)-styryl moieties, respectively (Table 2). The resulting cyclopropanes **3j–3o** were formed in good yield in a completely stereoselective fashion. The coupling of vinyl-dioxanones **1a, 1b, 1d, 1h** and **1f** with $B_2(pin)_2$ under standard conditions delivers the cyclopropylcarbinyl boronates **3p–3t** in good yield with complete stereocontrol (Table 3).[12] To briefly illustrate the utility of coupling products, the neopentyl alcohol **3a** was subjected to Jones oxidation to provide the cyclopropyl carboxylic acid **4a** in good yield (eq. 3). Additionally, the cyclopropylcarbinyl alcohol **3h** was exposed to Mitsunobu conditions in the presence of phthalimide to furnish **4b** in excellent yield (eq. 4).



(eq. 3)



(eq. 4)

A general mechanism for stereospecific cyclopropane formation under the conditions of nickel catalyzed cross-coupling has been proposed (Scheme 2). Stereospecific oxidative addition of a nickel(0) species to the benzylic C-O bond occurs with inversion to furnish the indicated σ-benzylnickel(II) complex.[10] Decarboxylation and transmetalation delivers the indicated alkene complex, which upon reversible migratory insertion[8] provides a (cyclopropylcarbinyl)nickel(II) complex. Regardless of the kinetic diastereoselectivity of olefin insertion, reductive elimination occurs exclusively from a single stereoisomer of the (cyclopropylcarbinyl)nickel(II) species to release the cyclopropane and regenerate the zero-valent nickel catalyst.

In summary, we report a new method for the preparation of enantiomerically enriched cyclopropanes via stereospecific nickel catalyzed cross-coupling of vinyl-dioxanones with boroxines or $B_2(pin)_2$. The collective data are consistent with a catalytic mechanism involving nickel(0)-mediated benzylic oxidative addition with inversion of stereochemistry followed by reversible olefin insertion to form a (cyclopropyl-carbinyl)nickel complex, which upon reductive elimination delivers the cyclopropane. The novel reactivity embodied by this process should serve as the basis for the syntheses of diverse enantiomerically enriched cyclopropanes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. The requirement of naphthyl or furyl substituents in prior nickel catalyzed benzylic substitutions was rationalized on the basis of an S_N2' mechanism for leaving group ionization (refs. 5a, 10b–10d). We propose for less reactive leaving groups it is necessary to extend the lifetime of the η^2-nickel π-complex that precedes benzylic ionization and, for extended aromatic π-systems, lower LUMO energies strengthen π-backbonding. More reactive carbonate leaving groups compensate for a shorter lifetime of the η^2-nickel π-complex. Furyl substituted benzyl donors have weaker benzylic C-O bonds due to $\pi \rightarrow \sigma^*$ hyperconjugation. For discussion in the context of the ionization of allylic leaving groups, see: Hassan A, Townsend IA, Krische MJ. Chem. Comm. 2011:10028. [PubMed: 21829853]
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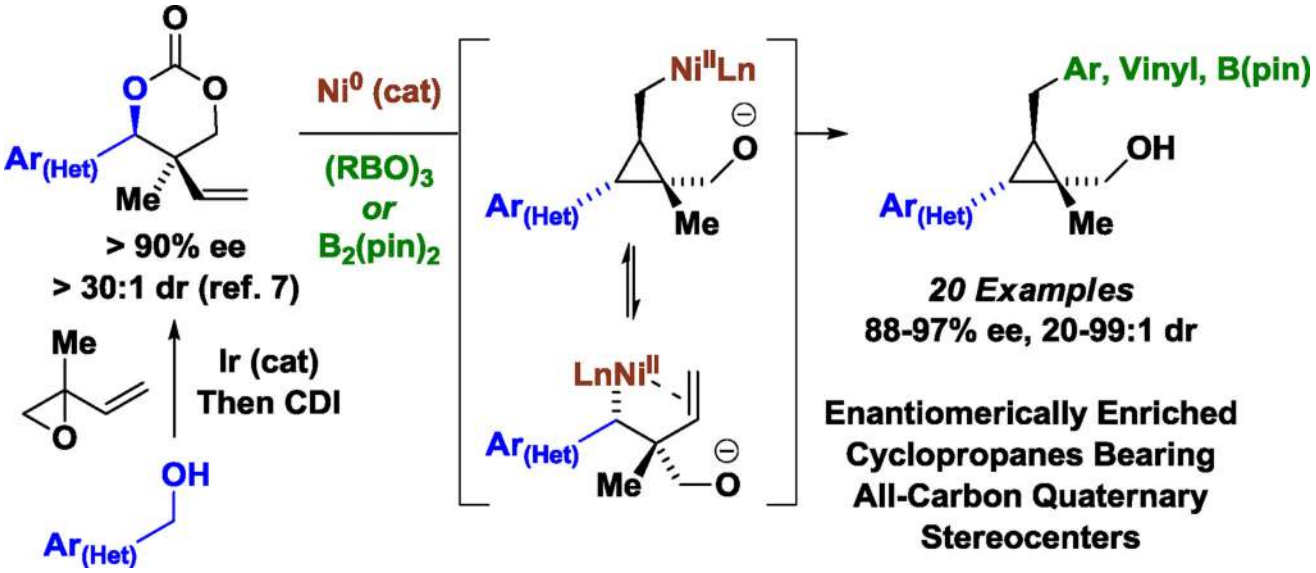
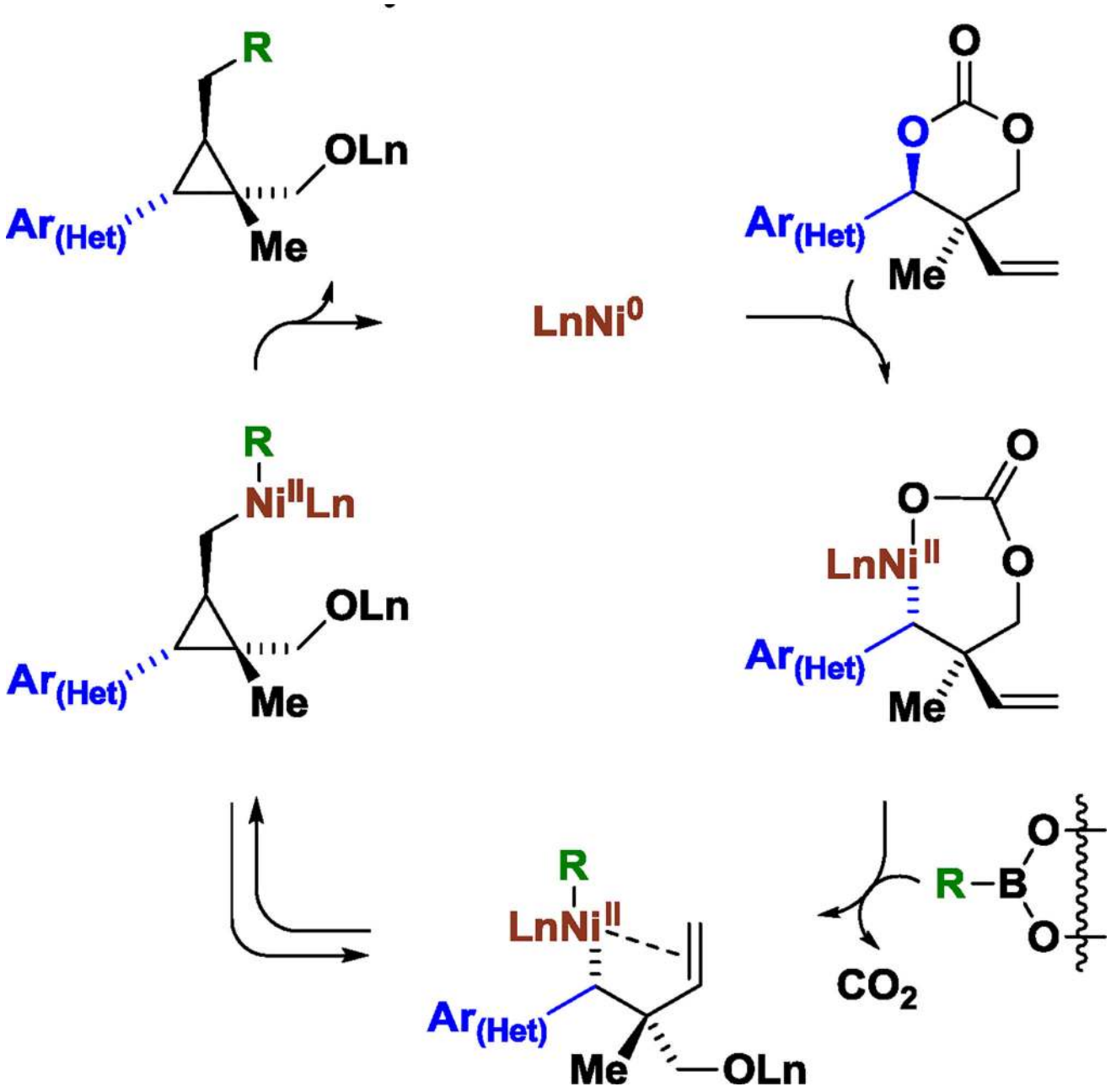


Scheme 1.

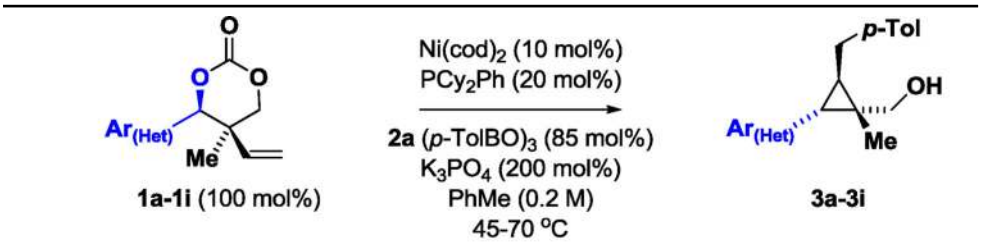
Synthesis of enantiomerically enriched cyclopropanes from vinyl-dioxanones by way of transient (cyclopropylcarbinyl)nickel species.



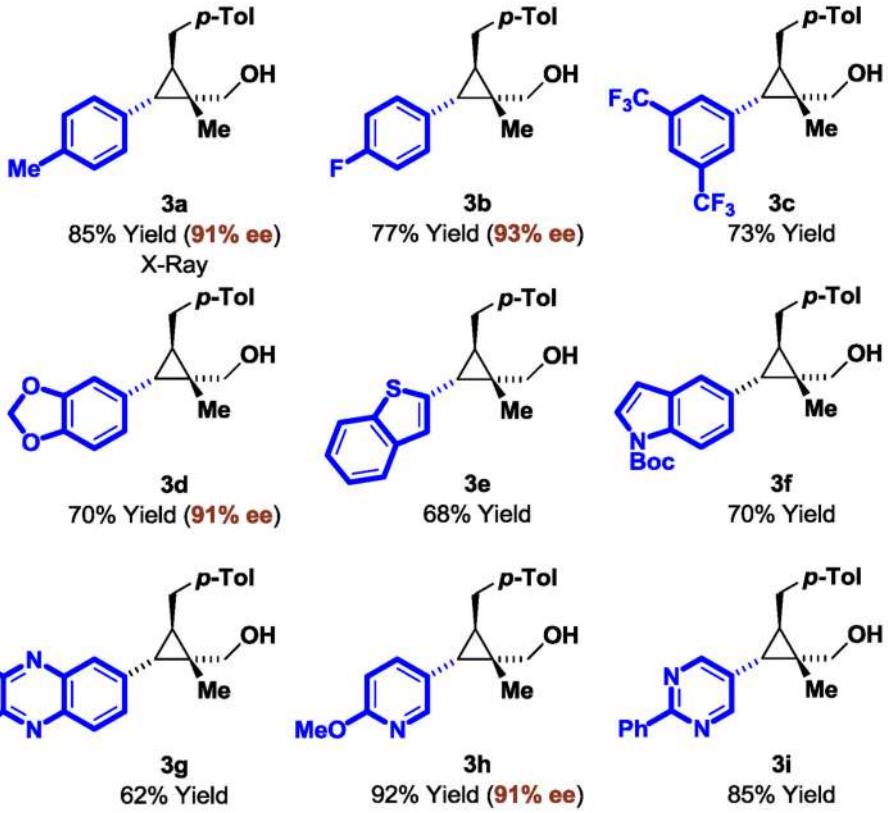
Scheme 2.
General catalytic mechanism. Haptomeric equilibria are excluded for clarity.

Table 1

Stereospecific nickel-catalyzed cross coupling of vinyl-dioxanones **1a–1i** with tri(*p*-tolyl)boroxine **2a** to form cyclopropanes **3a–3i**.[a]



1a, Ar = *p*-Tol (30:1 dr, **93% ee**)	**1b**, Ar = *p*-F-Ph (30:1 dr, **94% ee**)	**1c**, Ar = 3,5-$(CF_3)_2$-Ph (70:1 dr, **94% ee**)
1d, Ar = Benzodioxolyl (60:1 dr, **91% ee**)	**1e**, Ar = 2-Benzothienyl (20:1 dr, **97% ee**)	**1f**, Ar = 5-(*N*-Boc-Indolyl) (85:1 dr, **88% ee**)
1g, Ar = 6-(2,3-Me_2-Quinoxalyl) (30:1 dr, **90% ee**)	**1h**, Ar = 5-(2-MeOPyridyl) (99:1 dr, **90% ee**)	**1i**, Ar = 5-(2-Ph-Pyrimidyl) (99:1 dr, **96% ee**)



3a 85% Yield (**91% ee**) X-Ray

3b 77% Yield (**93% ee**)

3c 73% Yield

3d 70% Yield (**91% ee**)

3e 68% Yield

3f 70% Yield

3g 62% Yield

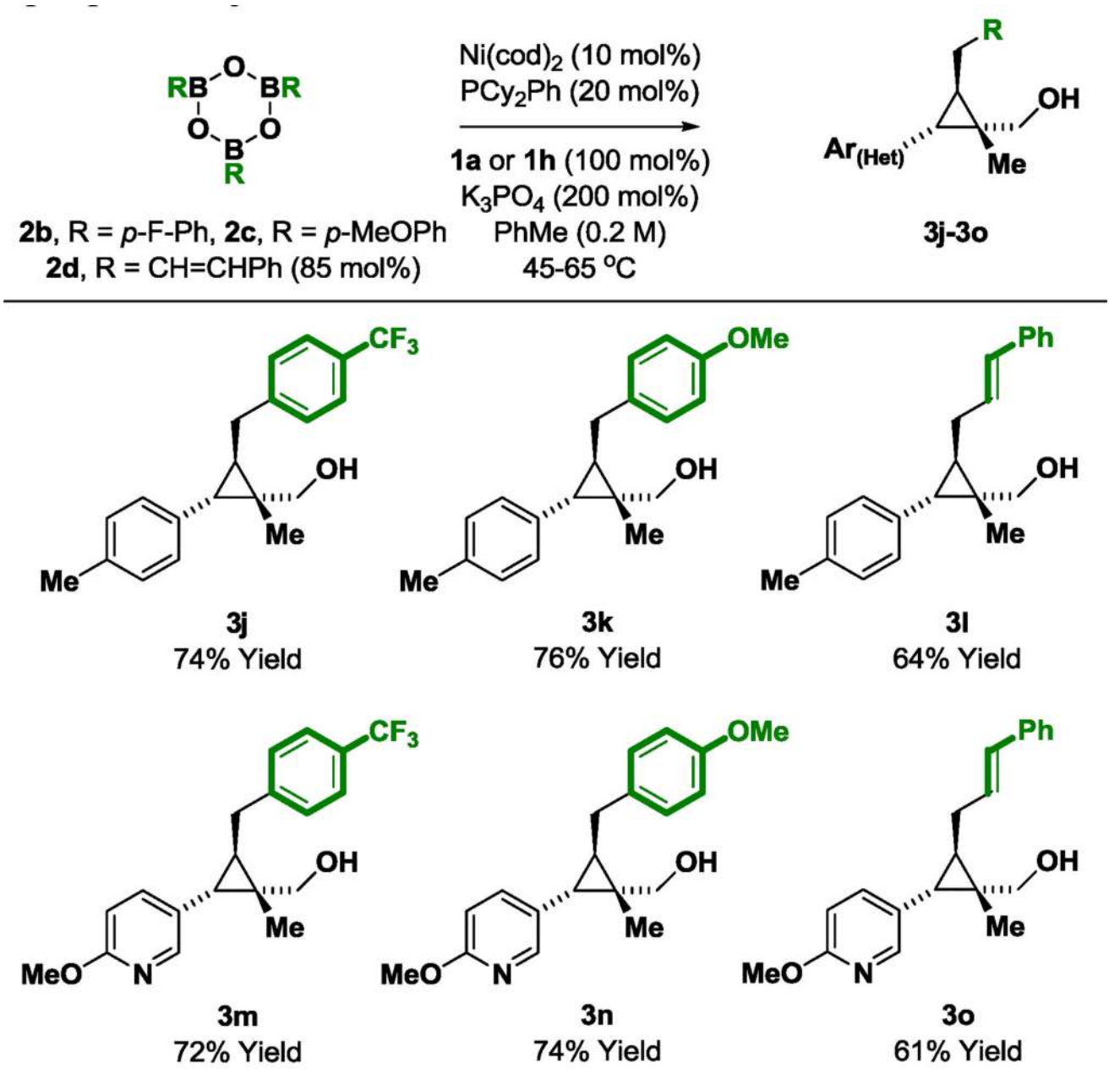
3h 92% Yield (**91% ee**)

3i 85% Yield

[a]Yields of material isolated by silica gel chromatography. All reactions were conducted using enantiomerically enriched starting materials. See Supporting Information for further experimental details.

Table 2

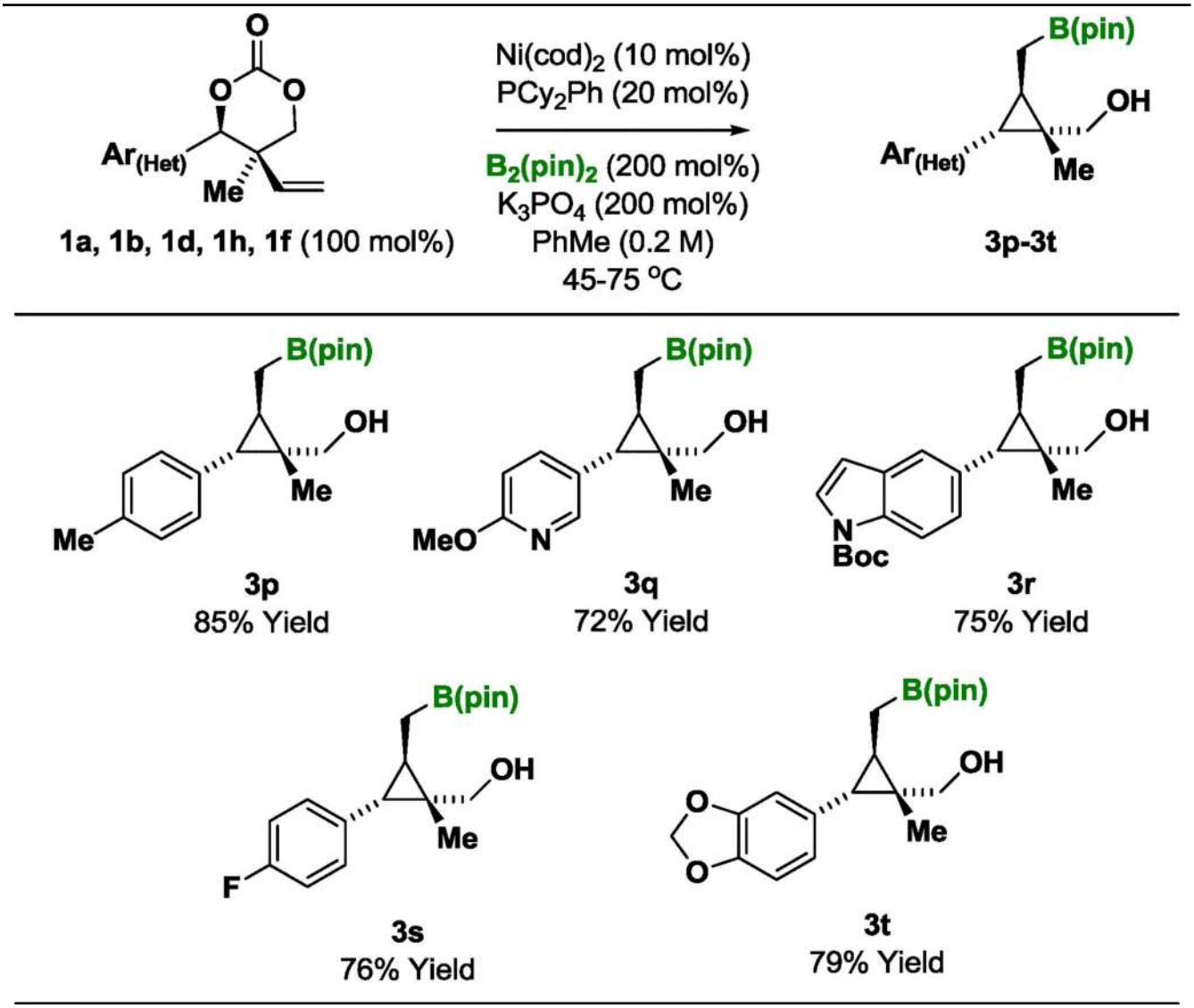
Stereospecific nickel-catalyzed cross coupling of vinyl-dioxanones **1a** or **1h** with boroxines **2b–2d** to form cyclopropanes **3j–3o**.[a]



[a]Yields of material isolated by silica gel chromatography. All reactions were conducted using enantiomerically enriched starting materials. See Supporting Information for further experimental details.

Table 3

Stereospecific nickel-catalyzed cross coupling of vinyl-dioxanones **1a, 1b, 1d, 1h** and **1f** with $B_2(pin)_2$ to form cyclopropanes **3p–3t**.[a]



[a]Yields of material isolated by silica gel chromatography. All reactions were conducted using enantiomerically enriched starting materials. See Supporting Information for further experimental details.