

Enantioselective Cross-Coupling of *meso*-Epoxides with Aryl Halides

Yang Zhao and Daniel J. Weix*

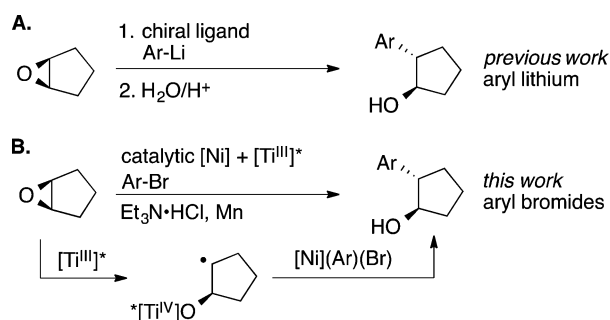
Department of Chemistry, University of Rochester, Rochester, New York 14627-0216, United States

S Supporting Information

ABSTRACT: The first enantioselective cross-electrophile coupling of aryl bromides with *meso*-epoxides to form *trans*- β -arylcycloalkanols is presented. The reaction is catalyzed by a combination of (bpy)NiCl₂ and a chiral titanocene under reducing conditions. Yields range from 57 to 99% with 78–95% enantiomeric excess. The 30 examples include a variety of functional groups (ether, ester, ketone, nitrile, ketal, trifluoromethyl, sulfonamide, sulfonate ester), both aryl and vinyl halides, and five- to seven-membered rings. The intermediacy of a carbon radical is strongly suggested by the conversion of cyclooctene monoxide to an aryl [3.3.0]bicyclooctanol.

The opening of epoxides with carbon nucleophiles is a useful transformation in organic synthesis because of the availability of epoxides and the versatility of the alcohol products.¹ The enantioselective opening of *meso*-epoxides forms two new, adjacent stereocenters, and highly selective catalysts have been reported for a variety of heteroatom nucleophiles,^{1,2} carbon monoxide,³ and cyanide.^{1,4} In contrast, the enantioselective coupling of aryl and vinyl nucleophiles with *meso*-epoxides has proven to be more challenging.^{5,6} The best results to date are with aryllithium reagents and stoichiometric⁷ or catalytic⁸ amounts of chiral ligands (Scheme 1A).⁹ In general, a more functional-group-tolerant procedure would be a useful advance, suggesting a cross-electrophile approach.¹⁰

Scheme 1. Enantioselective Arylation of *meso*-Epoxides

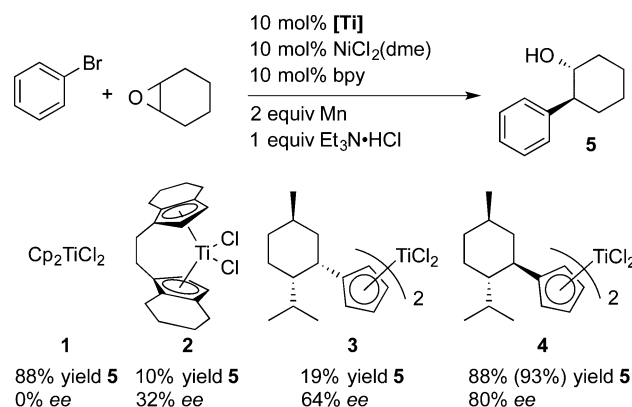


We report here that the combination of an *achiral* nickel catalyst with a *chiral* titanium catalyst can enantioselectively couple aryl halides with *meso*-epoxides in high yield (Scheme 1B). While we had previously demonstrated that the radical generated from titanium(III)-mediated epoxide opening¹¹ could be intercepted by aryl nickel intermediates (Scheme 1B),^{12,13} it was not clear that an enantioselective version of the catalysis

would be possible because more sterically hindered catalysts were poorly reactive.

On the basis of the work of Gansäuer,¹⁴ we initially examined several different chiral titanocene catalysts (**2**,¹⁵ **3**, and **4**; Scheme 2) and found that menthol-derived catalyst **4**, first reported by

Scheme 2. Enantioselective Arylation of Cyclohexene Oxide^a



^aReactions were run with 1.0:2.0:0.1:0.1:0.1 Et₃N·HCl/Mn⁰/titanocene/NiCl₂(dme)/bipyridine in DMPU with stirring for 12 h at rt. Assay yields (GC area %) are shown, with an isolated yield in parentheses. Enantiomeric excesses were determined by chiral-phase GC or SFC analysis.

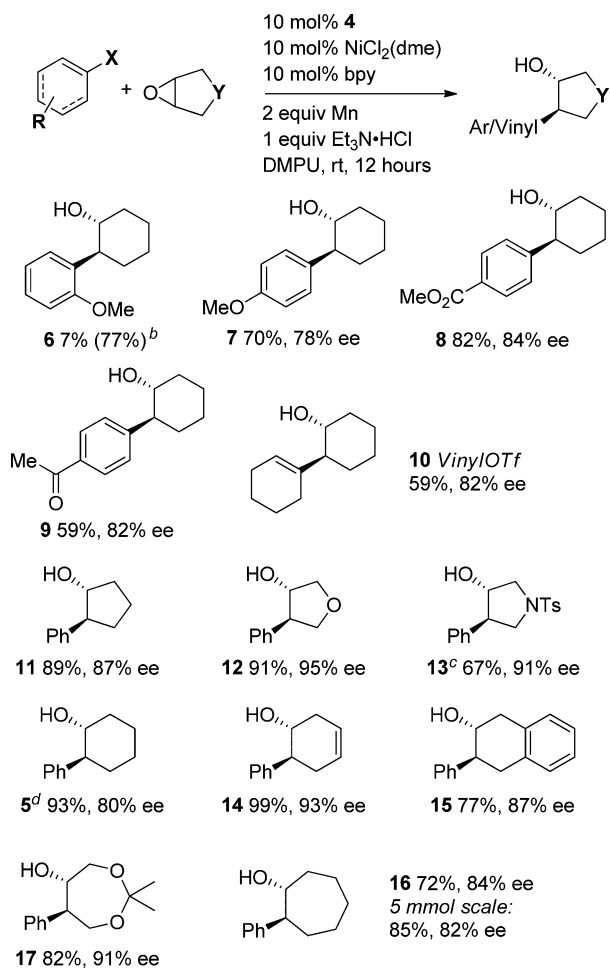
Kagan,¹⁶ provided the highest yield and enantioselectivity. These conditions proved general for a variety of *meso*-epoxides and aryl halides (Scheme 3). As expected, the enantioselectivity of the product was primarily determined by the epoxide and not by the electronics of the aryl halide. For example, products **5**, **7**, **8**, **9**, and **10** were all obtained with enantioselectivities of $\pm 5\%$ ee. While ortho-substituted aryl halides did not couple well with cyclohexene oxide under catalysis by titanocene **4**, the use of a smaller titanocene catalyst (**1**) or a less hindered epoxide (cyclopentene oxide; Scheme 4) provided yields of up to 85% (products **6**, **18**, **19**).

Better enantioselectivities were obtained from more planar epoxides. For example, a reaction with cyclohexadiene monoxide (**14**) was more selective than the same reaction with cyclohexene oxide (**5**). Only the *trans* diastereomer of the product was observed regardless of the epoxide. Finally, *cis*-stilbene oxide was found to be unreactive under these conditions.

Although most of these reactions were set up on a 0.5 mmol scale in a nitrogen-filled glovebox for convenience, the chemistry

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Scheme 3. Epoxide and Aryl Halide Scope^a

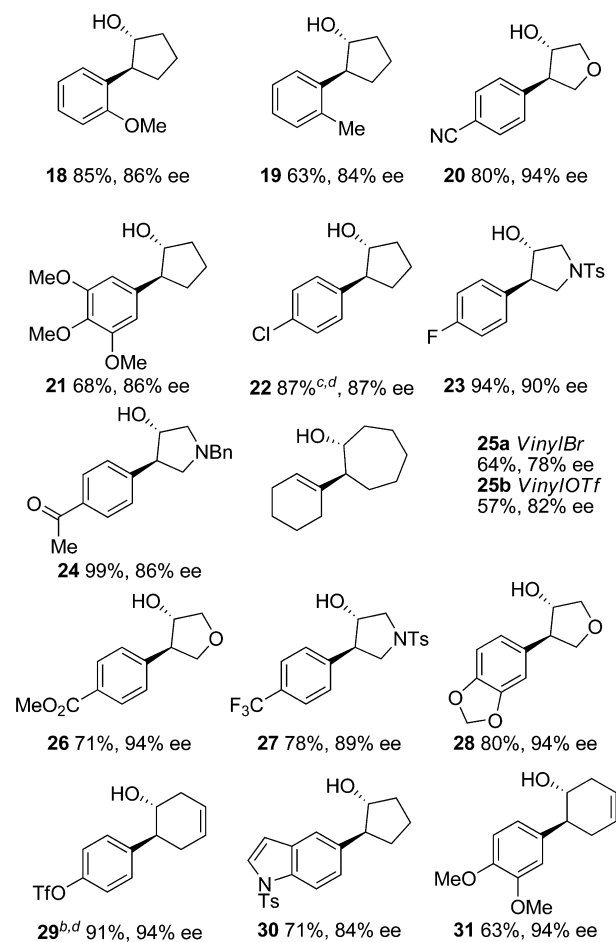
^aAs in Scheme 2 footnote a. ^bThe yield in parentheses is for a racemate obtained with catalyst 1. ^cThe absolute configuration of **13** was determined by X-ray analysis (see the Supporting Information). Other products were assigned by analogy. ^dThe same reaction conducted with 3 equiv of Mn was finished in 4 h vs 8 h (see Table S1 in the Supporting Information).

can be run on the benchtop in a Schlenk flask under argon at a preparative scale (5 mmol) without any loss of yield or selectivity (**16**).

Functional groups such as tosyl, nitrile, ketal, triflate, trifluoromethyl, and chloride were all well-tolerated (Scheme 4). Although titanium(III) is known to catalyze the pinacol coupling of ketones,¹⁷ 4-bromoacetophenone coupled without observable pinacol side product (**9**, **24**). On the other hand, a reaction with 4-bromobenzaldehyde favored pinacol coupling over epoxide ring opening (data not shown).

Chemoselective coupling at the C–Br bond was achieved for 1-bromo-4-chlorobenzene (**22**), 1-bromo-4-fluorobenzene (**23**), and 4-bromophenyl triflate (**29**), so long as the reactions were not permitted to run past full conversion to the desired product. At longer reaction times, lower yields were obtained. Functionalized amines, such as benzyl- and tosyl-protected pyrroline oxide, were also well-tolerated by our reaction conditions (**23**, **24**, **27**, **30**).

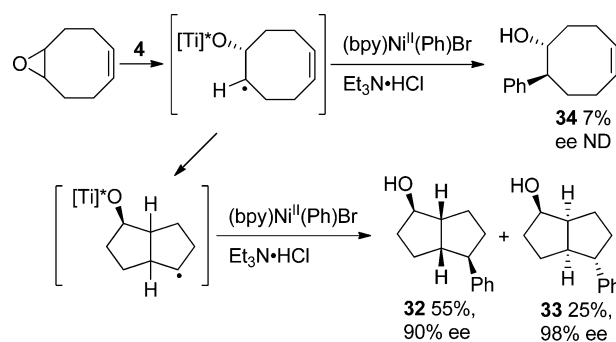
Although relatively few of these functionalized 2-arylcycloalkanol have been reported in the literature previously, even in racemic form, they are useful synthetic intermediates. Product **5**,

Scheme 4. Aryl Halide Scope^a

^aAs in Scheme 2, footnote a. ^bExtended reaction time resulted in hydrodehalogenation of the product. ^cProduct was isolated after 7 h. ^dProduct was isolated after 7.5 h.

the Whitesell auxiliary,¹⁸ has been synthesized by a variety of methods. Our process compares favorably with these previous syntheses.^{19–21}

The intermediacy of an alkyl radical could be exploited to generate additional complexity (Scheme 5). For example, cyclooctadiene monoxide couples to form primarily [3.3.0]-bicyclooctanols **32** and **33** in 80% combined yield with 90–98%

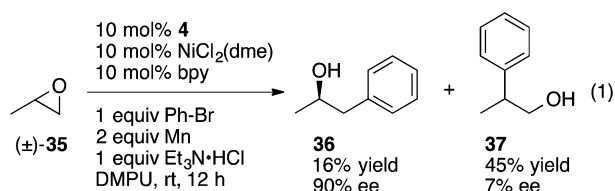
Scheme 5. Formation of [3.3.0]Bicyclooctanol Products from Cyclooctadiene Monoxide^a

^aAs in Scheme 2, footnote a. Absolute configurations were assigned by X-ray analysis of camphanic acid esters.

enantiomeric excess. Arylated [3.3.0]bicyclooctanols have not been previously reported, but the unsubstituted parent compound has been made with up to 84% ee by chiral-base-mediated rearrangement of cyclooctene oxide.^{7c,22}

Interestingly, a reaction conducted with the smaller titanocene dichloride **1** instead of chiral titanocene **4** formed only unrearranged product **34**. This is consistent with the idea that the coupling of the β -titanoxy radical with an arylnickel intermediate is slowed by steric interactions. A longer radical lifetime with bulkier catalyst **4** may allow for the cyclization to proceed to a greater extent or the steric environment provided by **4** may promote the cyclization.

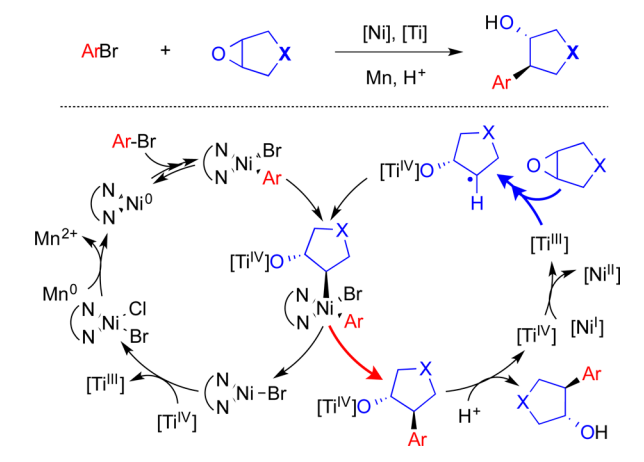
We also briefly examined the reaction of a primary epoxide, (\pm)-propylene oxide (**35**), with bromobenzene to form products **36** and **37** (eq 1). Although the internal alcohol **37** was formed



with poor stereocontrol, a parallel kinetic resolution²³ occurred, and the terminal product **36** was formed with high enantiopurity.²⁴ These intriguing results are consistent with the studies of Gansäuer on the mechanism of titanocene-mediated epoxide opening²⁵ and on the opening of nonsymmetrical internal epoxides.²⁶ We are currently examining catalysts to improve the enantioselectivity for internal product **37**.

We propose that the mechanism is analogous to the one we previously proposed for the achiral reaction (Scheme 6).¹² The

Scheme 6. Proposed Catalytic Cycle



key steps are the enantioselective formation of a β -titanoxy carbon radical from the *meso*-epoxide (blue arrow), the oxidative addition of a β -titanoxy carbon radical to an arylnickel(II) intermediate to form a diorganonickel(III) species (center),^{13,27} and the reductive elimination of the product (red arrow).²⁸ Finally, reduction of both catalysts would close the catalytic cycle.

In conclusion, we have developed the first enantioselective coupling of aryl halides with epoxides and demonstrated the first use of chiral titanium-catalyzed epoxide opening for enantioselective transition-metal-mediated C–C bond formation.²⁹ Both concepts appear to be general, and further results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Tables S1–S4; Schemes S1 and S2; detailed experimental procedures; characterization data; copies of ¹H, ¹⁹F, and ¹³C NMR spectra; and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*daniel.weix@rochester.edu

Notes

The authors declare no competing financial interest.

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