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

We report here that the combination of an achiral nickel catalyst with a chiral titanocene 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 aryllithium 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 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 ±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

Scheme 1. Enantioselective Arylation of meso-Epoxides

Scheme 2. Enantioselective Arylation of Cyclohexene Oxide

Scheme 3. Enantioselective Arylation of 3,4-dihydrocyclopentene Oxide

Scheme 4. Enantioselective Arylation of Cyclopentene Oxide

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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).

Although relatively few of these functionalized 2-arylcycloalkanols have been reported in the literature previously, even in racemic form, they are useful synthetic intermediates. Product 5, 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% yield in parentheses is for a racemate obtained with catalyst 1.

**Scheme 3. Epoxide and Aryl Halide Scope**

| X \ R | Yield | ee |
|-------|-------|----|
| OMe | 7% (77%) | |
| OMe | 70%, 78% | ee |
| OMe | 82%, 84% | ee |
| OMe | 69% | ee |
| OMe | 79%, 82% | ee |
| OMe | 87%, 91% | ee |
| OMe | 93%, 80% | ee |
| OMe | 99%, 93% | ee |
| OMe | 77%, 87% | ee |
| OMe | 72%, 84% | ee |

**Scheme 4. Aryl Halide Scope**

| X \ R | Yield | ee |
|-------|-------|----|
| OMe | 85%, 86% | ee |
| OMe | 63%, 84% | ee |
| OMe | 80%, 94% | ee |
| OMe | 88%, 86% | ee |
| OMe | 87%, 87% | ee |
| OMe | 94%, 90% | ee |
| OMe | 99%, 86% | ee |
| OMe | 57%, 82% | ee |
| OMe | 99% | ee |

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

| 4 | 7% ee ND |
| 4 | 55%, 90% ee |
| 4 | 25%, 98% ee |

As 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.7,22

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-titanyloxy radical with an arynickel intermediate is slowed by steric interactions. A longer radical lifetime with bulkier catalyst intermediate is slowed by steric interactions. A longer radical proceeds to a greater extent or the steric environment provided by β-unrearranged product (36 and 37). These intriguing results are consistent with the β-intermediate to form a diorganonickel(III) species (center),13,27 β-addition of a carbon radical from the internal epoxides.26 We are currently examining catalysts to improve the enantioselectivity for internal product 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 Ganssürer 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).11 The key steps are the enantioselective formation of a β-titanyloxy carbon radical from the meso-epoxide (blue arrow), the oxidative addition of a β-titanyloxy carbon radical to an arynickel(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.

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Notes

The authors declare no competing financial interest.

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