Enantioselective Synthesis of Carbo- and Heterocycles through a CuH-Catalyzed Hydroalkylation Approach

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Supporting Information

ABSTRACT: The enantioselective, intramolecular hydroalkylation of halide-tethered styrenes has been achieved through a copper hydride-catalyzed process. This approach allowed for the synthesis of enanitoeenriched cyclobutanes, cyclopentanes, indanes, and six-membered N- and O-heterocycles. This protocol was applied to the synthesis of the commercial serotonin reuptake inhibitor (−)-paroxetine.

The formation of carbon–carbon bonds has long been recognized as a central process in organic synthesis and remains a fundamental objective in the field. In particular, the construction of C–C bonds between sp^3 centers represents a strategically important approach for the introduction of stereochemical information. A diverse array of catalytic and stoichiometric approaches have been developed for the construction of C(sp^3)–C(sp^3) bonds with high stereoselectivity. However, the majority of these methods rely on the presence of nearby reactive functional groups in the target compound. The formation of stereochemically well-defined sp^3–sp^3 C–C bonds in the absence of such functional groups remains a formidable synthetic challenge.

The Corey–Posner–Whitesides–House reaction between an organocuprate and alkyl halide serves as a prototypical method for the generation of bonds between unfunctionalized saturated carbon atoms. Subsequent work has shown that organocopper species generated under catalytic conditions similarly react with alkyl halides to form C–C bonds. Our group’s recent work on copper hydride (CuH)-catalyzed enantioselective alkene hydroamination suggested that hydrocupration of an olefin could provide a general approach for the formation of an enantioenriched organocopper species under catalytic conditions. In this context, we posited that an olefin bearing an alkyl (pseudo)halide tether (II, Figure 2) would undergo a formal intramolecular hydroalkylation in the presence of a catalytically generated L*CuH species (I) to furnish enantioenriched, cyclized products. Although the analogous borocupration/ring closure sequence has previously been disclosed, competitive reduction of alkyl (pseudo)-halides by CuH complexes renders the proposed hydrocupration/ring closure process nontrivial to execute. Nevertheless, we felt that if suitable conditions could be identified, this strategy would constitute a flexible approach for the synthesis of a variety of 4-, 5-, and 6-membered rings, which are featured prominently in biologically active natural products and pharmaceuticals (Figure 2).

We began our study by examining the reactivity of a homoallylic methanesulfonate in the presence of a DTBM-SEGPHOS-based copper catalyst with diethoxymethylsilane as the hydride source (Table 1). At the outset, we anticipated that an olefin bearing an alkyl (pseudo)halide tether (II, Figure 2) would undergo a formal intramolecular hydroalkylation in the presence of a catalytically generated L*CuH species (I) to furnish enantioenriched, cyclized products. Although the analogous borocupration/ring closure sequence has previously been disclosed, competitive reduction of alkyl (pseudo)-halides by CuH complexes renders the proposed hydrocupration/ring closure process nontrivial to execute. Nevertheless, we felt that if suitable conditions could be identified, this strategy would constitute a flexible approach for the synthesis of a variety of 4-, 5-, and 6-membered rings, which are featured prominently in biologically active natural products and pharmaceuticals (Figure 2). Herein, we report the implementation of this strategy for the enantioselective synthesis of several classes of compounds, including substituted cyclobutanes, cyclopentanes, indanes, and saturated heterocycles.

We began our study by examining the reactivity of a homoallylic methanesulfonate in the presence of a DTBM-SEGPHOS-based copper catalyst with diethoxymethylsilane as the hydride source (Table 1). At the outset, we anticipated that the copper (pseudo)halide species (IV, Figure 2) generated upon C–C bond formation would be reluctant to undergo transmetalation with the hydrosilane. We envisioned that the use of an alkoxy base would result in the formation of an intermediate copper alkoxy species (V), which would more...
readily transmetalate with hydrosilane to regenerate copper hydride I. Thus, during preliminary investigations, a range of alkoxide bases were evaluated. Among them, lithium methoxide was found to be uniquely effective in promoting the desired transformation, providing the cyclobutane product in excellent enantioselectivity, albeit in low yield (entry 3). No desired cyclization product was observed in the absence of base, or when other common alkoxide bases were employed (entries 1, 2, and 4).10

The effect of the leaving group was then probed in this hydroalkylation protocol. In the presence of additional LiOMe (4.0 equiv), bromide was found to be superior to methanesulfonate as the leaving group, affording the desired cyclobutane product in moderate yield and still excellent enantioselectivity (entry 7 vs entries 3 and 8). Our initial choice of ligand, DTBM-SEGPHOS, was found to be superior to other chiral bisphosphine ligands explored in terms of reactivity (entries 9–11). Finally, the use of dimethoxymethylsilane as the stoichiometric hydride source, as well as further optimization of concentration and temperature, allowed the desired cyclobutane product to be obtained in high yield and excellent enantioselectivity (entry 12).

Under these optimized conditions, we explored the substrate scope of this copper hydride-catalyzed process (see Table 2). Substrates bearing electron-poor aryl substituents reacted efficiently to provide the desired cyclobutane product (2c, 2g, 2h). Replacement of the methyl substituent with a larger ethyl group was also well-tolerated (2b). Substrates containing several functional groups, including the tert-butyl (2g) and methyl (2h) esters, as well as a cis-dialkyl olefin (2e), were also suitable substrates for the transformation. Under these conditions, an alcohol substrate was rapidly transformed to the corresponding silyl ether, which underwent subsequent intramolecular hydroalkylation to furnish the desired cyclization product (2f).

| Effect of Base | entry | X | L* | base (equiv) | % yield | (% ee) |
|---------------|-------|---|----|-------------|--------|-------|
| 1             | OMs   | L1 | KOt-Bu (2.0) | 0      |        |
| 2             | OMs   | L1 | LiOt-Bu (2.0) | 0      |        |
| 3             | OMs   | L1 | LiOMe (2.0)  | 17 (96)|        |
| 4             | OMs   | L1 | NaOMe (2.0)  | 0      |        |

| Effect of Leaving Group | entry | X | L* | base (equiv) | % yield | (% ee) |
|-------------------------|-------|---|----|-------------|--------|-------|
| 5                       | OTs   | L1 | LiOMe (2.0)  | 9      |        |
| 6                       | Br    | L1 | LiOMe (2.0)  | 16     |        |
| 7                       | Br    | L1 | LiOMe (4.0)  | 70 (97)|        |
| 8                       | OMs   | L1 | LiOMe (4.0)  | 14     |        |

| Effect of Ligand | entry | X | L* | base (equiv) | % yield | (% ee) |
|------------------|-------|---|----|-------------|--------|-------|
| 9                | Br    | L2 | LiOMe (4.0)  | 16     |        |
| 10               | Br    | L3 | LiOMe (4.0)  | 8      |        |
| 11               | Br    | L4 | LiOMe (4.0)  | 5      |        |
| 12               | Br    | L1 | LiOMe (4.0)  | 92d (99)|       |

"NMR yield with 1,3,5-trimethoxybenzene as internal standard, 0.1 mmol scale. *% ee determined by chiral HPLC. **4.0 equiv (MeO)2MeSiH at 2.0 M in THF, 55 °C. ***83% isolated yield, 0.5 mmol scale.

Next, we sought to expand the hydroalkylation process to the synthesis of 1-alkylindanes through the use of mono- and disubstituted styrenes substrates bearing an alkyl bromide tethered at the ortho position. Indeed, substitution of 3a–3c to hydroalkylation conditions afforded 1-alkylindane products with high synthetic efficiency, though enantioselectivities were somewhat diminished compared to trisubstituted alkene substrates. We note that when a substrate containing both an alkyl chloride and bromide was used, complete selectivity for cyclization at the alkyl bromide was observed while the alkyl chloride remained inert under reaction conditions (4c).

To demonstrate the potential applicability of this process to the synthesis of biologically active molecules, we prepared the commercial selective serotonin reuptake inhibitor (−)-paroxetine in seven steps from known starting materials. The key hydroalkylation step on bromide 1r proceeded smoothly to afford the desired cyclization product in moderate yield and excellent enantioselectivity as one diastereomer. Subsequent deprotection of the sulfonyl group furnished the target compound (Scheme 1). Spectroscopic and optical rotation data matched literature values and further confirmed the stereochemical assignment based on X-ray diffraction (see the Supporting Information).

Table 1. Optimization of Reaction Conditions

| entry | X     | L*     | base (equiv) | % yield | (% ee) |
|-------|-------|--------|-------------|--------|-------|
| 1     | OMs   | L1     | KOt-Bu (2.0) | 0      |        |
| 2     | OMs   | L1     | LiOt-Bu (2.0) | 0      |        |
| 3     | OMs   | L1     | LiOMe (2.0)  | 17 (96)|        |
| 4     | OMs   | L1     | NaOMe (2.0)  | 0      |        |
| 5     | OTs   | L1     | LiOMe (2.0)  | 9      |        |
| 6     | Br    | L1     | LiOMe (2.0)  | 16     |        |
| 7     | Br    | L1     | LiOMe (4.0)  | 70 (97)|        |
| 8     | OMs   | L1     | LiOMe (4.0)  | 14     |        |
| 9     | Br    | L2     | LiOMe (4.0)  | 16     |        |
| 10    | Br    | L3     | LiOMe (4.0)  | 8      |        |
| 11    | Br    | L4     | LiOMe (4.0)  | 5      |        |
| 12    | Br    | L1     | LiOMe (4.0)  | 92d (99)|       |

"NMR yield with 1,3,5-trimethoxybenzene as internal standard, 0.1 mmol scale. *% ee determined by chiral HPLC. **4.0 equiv (MeO)2MeSiH at 2.0 M in THF, 55 °C. ***83% isolated yield, 0.5 mmol scale.
In summary, an intramolecular, enantioselective hydroalkylation of bromide-tethered styrenes was achieved through a copper-catalyzed process. Crucial to the success of this process was the use of lithium methoxide to facilitate regeneration of the proposed copper hydride species and the use of DTBM-SEGPHOS as the supporting ligand. The method presented here was amenable to gram-scale synthesis and could be applied to the synthesis of the pharmaceutical product paroxetine. Importantly, the hydroalkylation process proved general to the synthesis of several scaffolds, including cyclobutanes, cyclopentanes, indanes, and saturated 6-membered heterocycles, all with complete diastereoselectivity and good to excellent levels of enantioselectivity. Efforts toward the development of an intermolecular hydroalkylation reaction are currently under way.

**ASSOCIATED CONTENT**

**Supporting Information**
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07061.

Experimental procedures and characterization data for new compounds (PDF)
Crystallographic data for 2o (CIF)

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Notes
The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

Research reported in this publication was supported by the National Institutes of Health under award no. GM46059. Y.-M.W. thanks the National Institutes of Health for a postdoctoral fellowship (GM112218). Á.L.P. gratefully acknowledges the MIT Summer Research Program. We thank Dr. Peter Mueller for X-ray crystallographic data and Drs. Michael Pirnot and Aaron Sather for their advice on the preparation of this manuscript.
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