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Asymmetric Cu-Catalyzed 1,4-Dearomatization of Pyridines and Pyridazines without Preactivation of the Heterocycle or Nucleophile

Michael W. Gribble, Jr.,[†] Sheng Guo,[†] and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Supporting Information

ABSTRACT: We show that a chiral copper hydride (CuH) complex catalyzes C−C bond-forming dearomatization of pyridines and pyridazines at room temperature. The catalytic reaction operates directly on free heterocycles and generates the nucleophiles *in situ*, eliminating the need for stoichiometric preactivation of either reaction partner; further, it is one of very few methods available for the enantioselective 1,4-dearomatization of heteroarenes. Combining the dearomatization with facile derivatization steps enables one-pot syntheses of enantioenriched pyridines and piperidines.

Dearomatization of electron-deficient heteroarenes with carbon nucleophiles is an essential transformation for the synthesis of pyridines and piperidines, which are the two most common azaheterocycles in FDA-approved small-molecule drugs.[1,2a−e] However, direct dearomative addition to pyridine generally requires harsh conditions[2c,3b] and has limited compatibility with complex, functionalized molecules. Most C−C bond-forming pyridine dearomatizations employ activated substrates generated through stoichiometric functionalization of the heterocyclic nitrogen with strong electrophiles.[2−7] Though useful, this approach has a number of limitations. For instance, many methods require presynthesis of the activated heterocycle[2c] or prior formation of the nucleophile, and separate deprotection steps are commonly required to cleave the activating group from the dihydropyridine (DHP) product. Further, whereas numerous methods exist for asymmetric 1,2-dearomatization,[4a−e] achieving stereocontrol in 1,4-selective variants has proven much more challenging. The latter transformation is seldom possible without auxiliaries or preformed chiral nucleophiles (Figure 1A,B);[5,6a−c] asymmetric catalysis of pyridine 1,4-dearomatization[7a−d] was unknown until very recently,[2c] and highly enantioselective catalytic reactions (Figure 1C)[7b−d] are currently only possible with a narrow set of multiply activated cationic substrates. A number of catalyzed additions of hydride or silyl nucleophiles have been reported that operate directly on pyridine rather than on stoichiometrically activated derivatives,[8a−j] but there are no reactions of this type that achieve either C−C bond-formation or asymmetric induction. In this Communication, we show that a chiral copper complex catalyzes C−C bond-forming dearomatization under mild conditions without requiring activation of the heterocycle, preformation of the nucleophile, or protecting group manipulations (Figure 1D). Moreover, the reaction is a very rare example of highly enantioselective catalytic 1,4-dearomatization, it succeeds with a broad selection of substituted pyridines and pyridazines, and it generates DHPs that can be converted to enantioenriched pyridines or piperidines in the same pot.

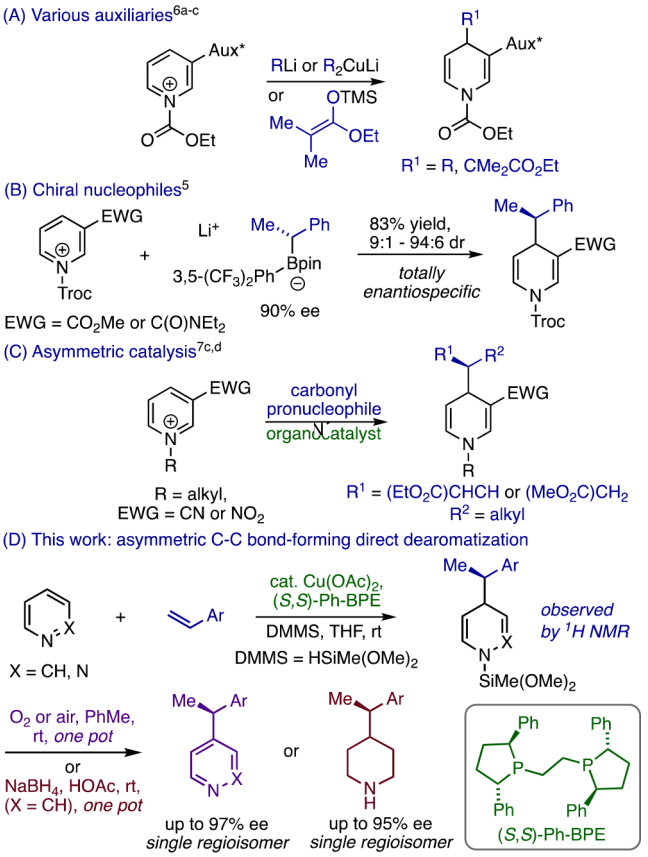

Figure 1. Methods for stereocontrolled 1,4-dearomatization; (A) with chiral auxiliaries; (B) with chiral nucleophiles; (C) using asymmetric catalysis; (D) this work: asymmetric direct catalytic dearomatization.

We hypothesized that pyridine could be activated toward nucleophilic dearomatization in an asymmetric hydrofunctionalization reaction,[9,10] thereby permitting direct dearomatization of the heterocycle while replacing preformed nucleophiles with abundant olefin precursors. Subjecting a mixture of pyridine and styrene to (Ph-BPE)CuH, prepared as before (eq 1),[11,12] gave 97% conversion (^{1}H NMR) to a mixture of dihydropyr-

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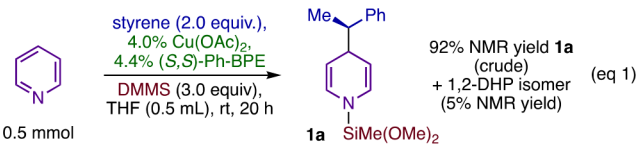
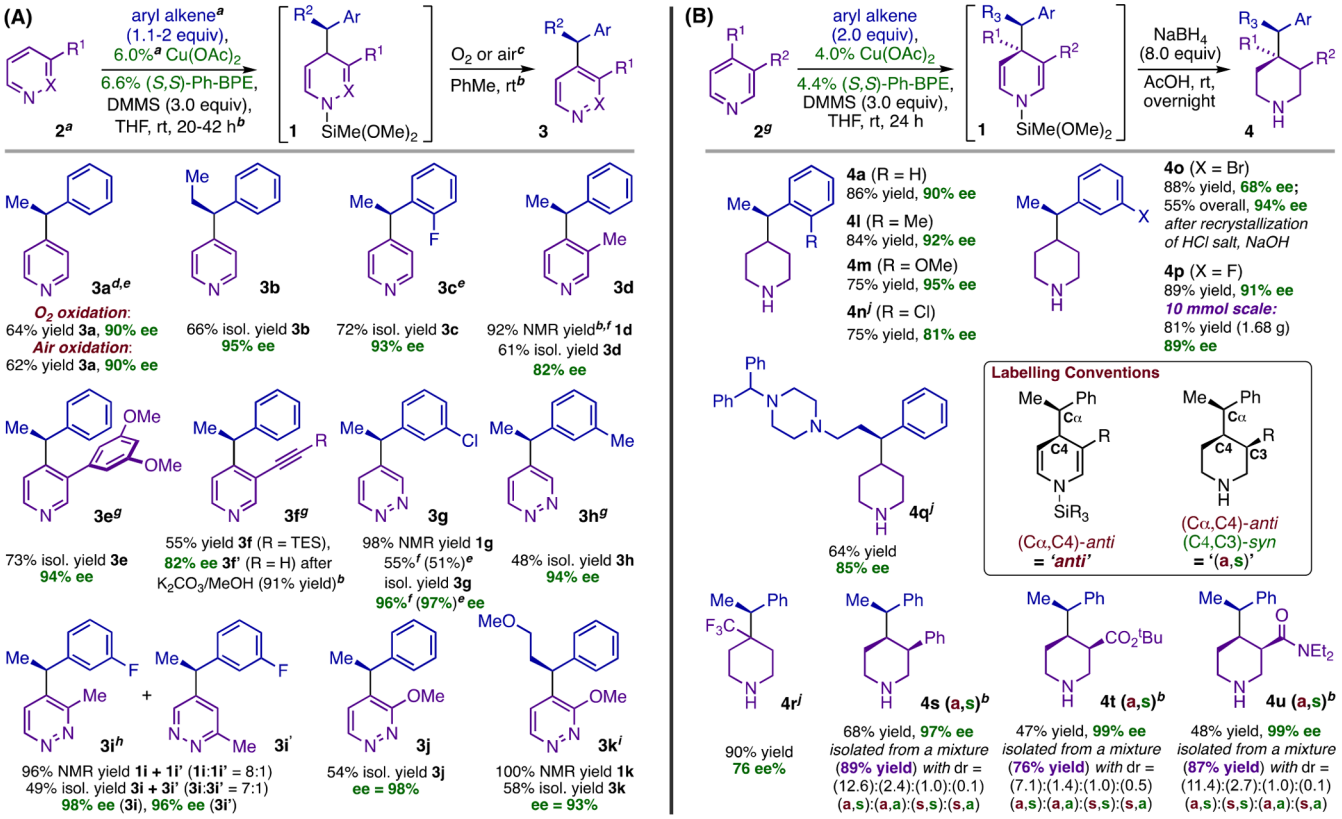


idines strongly biased in favor of the 1,4-adduct **1a** (22:1 average 1,4:1,2). Treating crude DHPs with O_2[3c] provided efficient rearomatization and enabled a one-pot synthesis of functionalized pyridines (generically, **3**; Table 1A). Chiral analysis of pyridine **3a** (90% ee) indicated that the dearomatization had occurred with high enantioselectivity and that the aerobic rearomatization was stereospecific.[13] Applying the dearomatization to the synthesis of enantioenriched piperidines also proved to be straightforward: adding NaHB(OAc)$_3$ to crude DHPs provided good yields of piperidines (generically, **4**; Table 1B) in a one-pot operation[14] that could be conducted on gram-scale without appreciable loss of yield or selectivity (**4p**; Table 1B).

The dearomatization/reoxidation protocol succeeded with pyridines, pyridazines, and a variety of C3-substituted derivatives thereof. The enantioselectivity obtained with pyridazines (**3g–k**; Table 1A) was consistently excellent and insensitive to the presence of electron-donor groups; in contrast, the ee's obtained with pyridines were moderately depressed by electron-releasing groups (e.g., **3d**; Table 1A) and enhanced by aryl and π-acceptor substituents (**3e**, **4s–u**; Table 1A,B). Substituted pyridines were also viable substrates for dearomatization/reduction, and stereochemical analysis of products **4s–u** (Table 1B) revealed that both transformations exert control over the endocyclic stereocenters they respectively generate, leading to mixtures of diastereomeric piperidines having a major bias for the **4** (**a**,**s**) diastereomers [see inset in Table 1B for explanation of nomenclature]. The major diastereomers were isolable in stereochemically pure form, and thus the dearomatization/reduction protocol enabled selective preparation of piperidines containing three contiguous stereocenters starting from prochiral substrates. Our work with this series provided key insights into the stereochemical properties of the asymmetric dearomatization. Single-crystal X-ray-diffraction analysis of **4s** (**a**,**s**)·HCl revealed its absolute configuration,[15,16] making it clear that dearomative addition is retentive with respect to the benzylic stereocenter set during hydrocupration and selective for (Cα,C4)-*anti* DHPs, whereas the reduction is selective for (C3,C4)-*syn* piperidines. The basis for *anti*-selective dearomative addition is unclear at present, but it appears to be general.[15,17] Notably, retention of the phenethylcopper stereocenter contrasts with the clean inversion Aggarwal observed in the addition of chiral phenethylboronates to acylpyridiniums (Figure 1B);[5] our result is mechanistically interesting given that the organocopper nucleophiles involved here do undergo invertive addition in other transformations.[12c]

Unlike C3 substituents, groups at C4 are only accommodated in special cases (as in **4r**; Table 1B), and substitution at C2 is not tolerated even for substituents that increase the intrinsic electrophilicity of the free heterocycle (e.g., CF_3, CO_2Me). Further, examples **3i–k** (Table 1A) show that organocopper nucleophiles preferentially add *para* to the less

Table 1. Asymmetric Dearomative Syntheses of Functionalized Pyridines (A) and Piperidines (B)



[a]Reactions used 1 mmol **2**, 2 equiv olefin except where noted. [b]see SI for details. [c]O_2 was used for **3b–k**.; [d]yields and ee's are averages for two runs except where noted; [e]reaction used 4.0% Cu(OAc)$_2$, 4.4% Ph-BPE; [f]one measurement; [g]used 0.5 mmol **2**; [h]used 1.5 equiv olefin; [i]used 1.1 equiv olefin; [j]ee determination used the *N*-BOC derivative.

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hindered nitrogen even when this entails attack on the more encumbered and more electron-rich of the two activated sites. These observations concerning C2 substitution can be readily rationalized if one invokes coordination of the heterocycle to a sterically demanding Lewis acid (e.g., Cu) in the dearomative addition step.

The dearomatization is compatible with various aryl alkene substituents, but certain trends involving this reactant were very surprising. Dearomatization exhibits useful levels of selectivity for a variety of olefin β substituents (**3b**, **3k**, **4q**; Table 1A,B), and *ortho* substitution is broadly tolerated (**3c**, **4l**−**n**; Table 1A,B). But surprisingly, when groups such as F, Me and OMe are present at the *para* position of the styrene, they completely suppress dearomatization. This observation runs counter to all our previous experience with styrene hydrofunctionalization[12a−e] and leads us to propose that *para* substituents incur a destabilizing interaction unique to the dearomative addition transition state. Consistent with this, we observed some sensitivity to the steric demand of the *meta* substituent; thus, 3-methylstyrene is problematic for pyridine but not pyridazine (**3g**, **3h**; Table 1), whereas *meta*-halides are tolerated with both (**3g**, **3i**, **4o**−**p**; Table 1A,B).

Figure 2 illustrates one plausible mechanism for the Cu-catalyzed direct dearomatization. Activation of the heterocycle

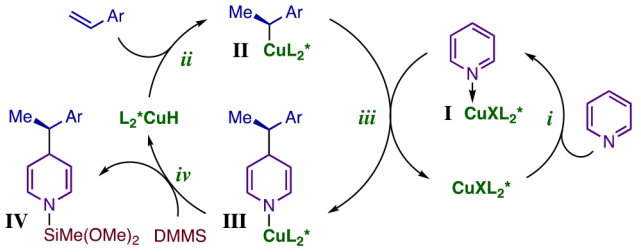

Figure 2. Plausible mechanism for the direct dearomatization.

occurs through formation of dative complex **I** (step *i*), which undergoes dearomatization with an organocopper nucleophile (**II**) (step *iii*).[12a,18] The resulting N-cuprated DHP intermediate (**III**) could then furnish product **IV** and the regenerated catalyst via σ-bond metathesis with the silane (step *iv*), similarly to transmetalation processes implicated in other catalytic hydrofunctionalizations.[12,18,19] We are currently undertaking a detailed mechanistic investigation directed at elucidating how activation and addition occur in this reaction.

In summary, we have demonstrated that pyridine and pyridazine undergo direct asymmetric dearomatization in the presence of a chiral CuH catalyst. This unique reaction eliminates the need for extraneous activation and nucleophile-formation steps, and it permits one-pot syntheses of highly enantioenriched C4-functionalized heterocycles. We expect that our ongoing mechanistic investigations will shed light on the unusual reactivity trends we observe and aid in the discovery of more general dearomative transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b02568.

Experimental procedures and characterization data for all compounds (PDF)

Data for $C_{19}H_{24}NCl$ (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*sbuchwal@mit.edu

ORCID

Michael W. Gribble Jr.: 0000-0003-2008-3264

Stephen L. Buchwald: 0000-0003-3875-4775

Author Contributions

†These authors contributed equally.

Notes

The authors declare no competing financial interest.

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(10) After our work was completed, a paper appeared by Yu, et al., showing that phenethylcopper species generated in asymmetric hydrocupration effect reductive *ortho* C−H-functionalization of quinoline N-oxides, probably via an initially dearomative mechanism Yu, S.; Sang, H. L.; Ge, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 15896−15900.

(11) For detailed information about the safe handling of dimethoxy(methyl)silane (DMMS), see the Supporting Information.

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(15) See Supporting Information for details.

(16) The (**a**,**s**) Relative stereochemistry of products **4t** and **4u** was confirmed through NMR-based structure-determination. See SI.

(17) For examples **s**−**u**, ^{1}H NMR assignments of **anti-1** and **syn-1** were possible using the known dr's for **4s**−**u**. Assignments made by analogy to these indicated that ***anti*-1** was also major for every other DHP we analyzed by ^{1}H NMR. (NMR estimates for the dr are 25:1 for **1d**, 13:1 for **1k**, 11:1 for **1s**, 7:1 for **1t**, 4.6:1 for **1u**; Table 1A,B.) See the Supporting Information for details.

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(19) See entry 19 on page S4 of the Supporting Information for reference 12c.

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