Enantioselective Generation of Adjacent Stereocenters in a Copper-Catalyzed Three-Component Coupling of Imines, Allenes, and Diboranes

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Abstract: A highly enantio- and diastereoselective copper-catalyzed three-component coupling affords the first general synthesis of homoallylic amines bearing adjacent stereocenters from achiral starting materials. The method utilizes a commercially available NHC ligand and copper source, operates at ambient temperature, couples readily available simple imines, allenes, and diboranes, and yields high-value homoallylic amines that exhibit versatile amino, alkenyl, and boryl units.

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Scheme 1. Important homoallylic amines from the enantioselective allylation of imines.

Scheme 1.

A) Traditional asymmetric allylation of imines & adjacent stereocenters: rare

B) Asymmetric multicomponent reaction of imines, allenes, and diboranes by Morken

C) This work:

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struction of homoallylic amines bearing adjacent stereocenters from simple imines and allyl copper species is unprecedented.[3] This is also the first example of an enantioselective process that combines borocupration with the allyl cupration of imines.[22]

We began by surveying various commercially available phosphine ligands to selectively induce asymmetry in the three-component coupling of imine 1a, cyclohexyllallene (2a), and Bpin; mediated by catalytic CuI. However, the reaction proceeded with poor conversion (≤30%) and enantioselectivity (≤60-40 e.r.).[22] We then turned our attention to chiral NHCs, which were formed in situ from the corresponding commercially available imidazolium salts (Scheme 2). The NHC ligand derived from 4 failed to provide any of the desired product, whereas Kündig’s NHC ligand (derived from 5, Ar = o-tolyl),[24] afforded high diastereo- and enantioselectivity (>95:5 d.r., >98.4% yield, and 93.7 e.r.). Gratifyingly, upon replacing the o-tolyl substituent with 1-naphthyl (6),[22] another one of Kündig’s imidazolium salts, the enantioselectivity (98.2 e.r., >95.5 d.r.) was further improved. Interestingly, copper-based asymmetric transformations with NHCs derived from 5 and 6 have not been previously reported. Furthermore, the addition reaction of the intermediary Cu–Bpin species to the imine, which might be expected based on prior literature, was not observed.[26]

With the reaction conditions established, we set about assessing the scope of the asymmetric three-component coupling (Scheme 3–5). Generally, the reaction proceeded with a variety of imines and allenes in high yield and enantioselectivity with low catalyst loading (5 mol%). We first explored the scope of the imine carbon substituent, and observed excellent tolerance with regard to steric and electronic variation (Scheme 3). Pleasingly, the use of more hindered ortho-substituted imines 3a–3d gave high yields (>70%) and excellent enantioselectivities (98.2-97.3 e.r.) with the exception of ortho-SMe (3e), which was obtained in 84.16 e.r. Electron-neutral (3f), electron-rich (3b, 3c, 3g, and 3h), and electron-deficient arenes (3i), including those bearing functionalizable bromo substituents (3j), all gave the corresponding products in high yield and exceptional enantioselectivity (≥96:4 e.r.). Heterocyclic imines, including 2- and 3-furyl (3k and 3l) and 2-thienyl (3l and 3m; Scheme 4), were also tolerated, but gave the corresponding products with lower yield (34-60%) and diastereoselectivity, albeit with high enantioselectivity (≥90:10 e.r.).

We next examined the allene component of the reaction (Scheme 4). 1-Substituted allenes bearing primary and more hindered secondary alkyl groups gave the expected coupling products in universally high enantioselectivity (≥93.7 e.r.). Alkyl substituents bearing no substitution (3n), a silyl ether (3n), a free alcohol (3o), or a phenyl group (3p), were tolerated.

The use of 1-phenylallene under the standard conditions gave the coupled product 3q in low yield (40%) and in virtually racemic form (53.47 e.r., 68.52 d.r.). Use of the o-tolyl ligand precursor 5, however, gave 3q in 81.19 e.r. When 1,1-disubstituted allenes were employed, poor conversions were observed under the standard conditions. Increasing the loading of Cu salt and ligand (10 and 11 mol %, respectively) restored synthetically useful yields, and highly enantioenriched homoolylic amines bearing quaternary carbon atoms in the β-position were obtained across a range of imines (3r–3w, 97.3–90:10 e.r.).

We also explored various nitrogen substituents on the imine by incorporating medicinally relevant and functionalizable motifs (Scheme 5). Methyl ester (3x), 5-quinoiynil (3y), morpholinolo (3z), and (pinacolato)boryl (3au) moieties were successfully incorporated into the coupling products. To further probe the utility of the asymmetric three-component coupling, we employed Procaine, a classic local anesthetic,[27] in imine formation. Procaine was condensed with o-tolualde-
enantioselective three-component coupling. The complex homoallylic amine 3ab was obtained in 30% yield (2 steps) in 94:6 d.r. and 96:4 e.r. It is interesting to note that basic nitrogen atoms, moieties that are often avoided in synthetic methodology, are well tolerated by the copper-catalyzed process (3y, 3z, and 3ab).

Single-crystal X-ray crystallography of 3w revealed its R configuration.[23] Analysis of the X-ray crystal structures of complexes of Kündig’s C2-symmetric ligands[24,25,29] with other metals has allowed us to propose a model for the stereochemical outcome of the enantioselective three-component coupling reaction where the flanking naphthyl rings allow approach of the imine towards the allyl copper species from one face (Scheme 6). The anti selectivity arises from a six-membered-ring chair transition state.[17i]

Finally, the scalability of the process was assessed. Using just 1.0 mol% of CuI and 1.1 mol% of ligand precursor 6, 1 g of imine 1a was converted into 2 g of product 3a, with high levels of efficiency and selectivity (98%, > 95:5 d.r., 99:1 e.r.; Scheme 7).

To demonstrate the synthetic utility of products 3, we oxidized 3a under standard H2O2/NaOH conditions and obtained β-amino ketone 7, which bears α- and β-stereocenters, in high yield (82%) and importantly without erosion of the stereochemical integrity (> 95:5 d.r., 98:2 e.r.; Scheme 7). The B–N interaction present in the products of the copper-catalyzed three-component coupling make them particularly amenable to highly stereoselective manipulation. For example, by simply using Pd/C, 3a underwent a substrate-controlled highly stereoselective hydrogenation, and gave secondary boronic ester 8, which exhibits three contiguous stereocenters (54%, > 95:5 d.r., > 99:1 e.r.).[30]
In conclusion, we have developed the first general method for the enantioselective and diastereoselective synthesis of homoallyl amines containing adjacent stereocenters from achiral starting materials, utilizing an unprecedented sequence of allene borocupration followed by allyl cupration at ambient temperature. The reaction utilized allyl metal derivatives are not required, and simple achiral starting materials, utilizing an unprecedented homoallylic amines containing adjacent stereocenters from a) Chiral Amine Synthesis: Methods, Developments and Applications (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, 2010; b) G. K. Friestad, A. K. Mathies, Tetrahedron 2007, 63, 2541; c) M. Shibasaki, M. Kanai, Chem. Rev. 2008, 108, 2853; d) C. O. Puente, V. Kouznetsov, J. Heterocycl. Chem. 2009, 39, 595. [2] For reviews on the asymmetric allenylation of imines, see: a) H. Ding, G. K. Friestad, Synthesis 2005, 2815; b) H.-X. Huo, J. R. Duvall, M.-Y. Huang, R. Hong, Org. Chem. 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