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2-Azadienes as Reagents for Preparing Chiral Amines: Synthesis of 1,2-Amino Tertiary Alcohols by Cu-Catalyzed Enantioselective Reductive Couplings with Ketones

Kangnan Li,[‡] Xinxin Shao,[‡] Luke Tseng, and Steven J. Malcolmson*

Department of Chemistry, Duke University, Durham, North Carolina 27708, United States

Supporting Information

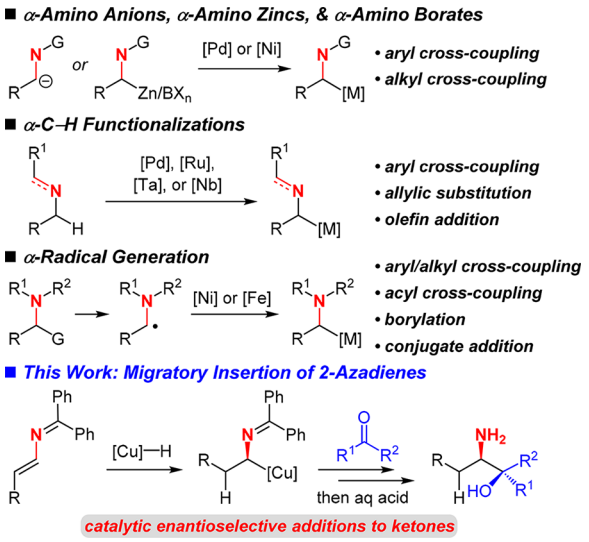
ABSTRACT: We introduce a new strategy for synthesis of chiral amines: couplings of α-aminoalkyl nucleophiles generated by enantioselective migratory insertion of 2-azadienes to a Cu−H. In this report, we demonstrate its application in catalytic reductive coupling of 2-azadienes and ketones to furnish 1,2-amino tertiary alcohols with vicinal stereogenic centers.

New methods for the stereoselective synthesis of chiral amines are highly valuable as these units are found within numerous natural products, pharmaceuticals, ligands for metals, and fine chemicals. Classic C−C bond-forming approaches to chiral amines rely on nucleophilic addition to imines.[1] Yet several classes of chiral amines, including 1,2-amino alcohols,[2] are challenging to prepare by this normal polarity paradigm. A traditional reverse polarity strategy that addresses this issue utilizes nitroalkanes as a means of accessing N-substituted carbanions;[3] however, this tactic requires subsequent nitro group reduction to form the amine, adversely affecting step/redox economy.[4] A streamlined approach would enantioselectively assemble the desired amine building block via C−C bond formation with all atoms in the correct oxidation state.

Direct enantioselective α-lithiation of alkylamines for addition to electrophiles provides one path, but these methods rely on strong alkyllithium bases and often stoichiometric quantities of sparteine or its analogues.[5] Catalytic formation of an α-aminoalkyl transition metal reagent (Scheme 1) is a powerful means of generating chiral amines with several established approaches. Deprotonation to form a 2-azaallyl anion and addition to a Pd catalyst[6] or alternatively transmetalation of an α-amino zinc[7] or α-amino borate[8] to Ni or Pd has enabled aryl and alkyl cross-coupling reactions. Metal-catalyzed C−H functionalization at the N-α-position has also permitted aryl cross-coupling,[9] allylic substitution reactions,[10] or addition to olefins.[11] Finally, catalytic formation of an α-amino radical, followed by recombination with a Ni or Fe catalyst, has allowed a variety of aryl, alkyl, or acyl cross-couplings,[12] borylations,[13] or conjugate additions to take place.[14] In each approach, enantioselective reactions are uncommon.[6b,7,10b,11b,c,12d]

In this work, we introduce a new strategy for catalytically forming an α-aminoalkyl transition metal for the enantioselective synthesis of amines. 2-Azadienes, which have rarely been used in synthesis,[15] undergo migratory insertion at their least-hindered π-bond with a Cu−H to generate a 2-azaallyl-Cu intermediate, which may participate in stereoselective addition to a carbon electrophile. This reaction modality thus constitutes umpolung reactivity of an enamine. We demonstrate the feasibility of this approach in reductive coupling[16−19] with ketones to furnish 1,2-amino tertiary alcohols in up to 87% yield, >20:1 dr, and >99:1 er.[20−23]

Scheme 1. Methods and Uses for Catalytically-Generated α-Aminoalkyl-Substituted Transition Metals



1,2-Amino tertiary alcohols are important building blocks for synthesis, but enantioselective construction of this functionality is all but unknown. Enantioselective Henry reactions with ketone electrophiles are few.[24] The direct catalytic enantioselective synthesis of amino tertiary alcohols is limited.[25,26] Furthermore, there are few examples where this functionality bears vicinal stereogenic centers. Typically this moiety is prepared by stepwise stereoselective addition of organometallics to α-amino acid derivatives.[27]

We envisioned that enantioselective Cu-catalyzed reductive coupling of 2-azadienes and ketones,[16a,d] followed by hydrolytic workup, would directly form a 1,2-amino tertiary alcohol (Scheme 1). We therefore began by examining the reaction of terminal azadiene **1a**, acetophenone **2a**, and a silane reducing agent (Table 1) and quickly identified Ph-BPE (**L1**) as uniquely effective at delivering desired product **3a** (entry 1).[16d] Other

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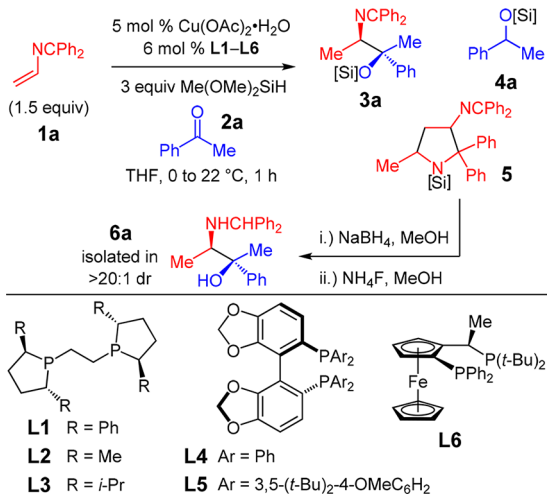
Table 1. Ligand Identification for Reductive Coupling of Acetophenone and 2-Azadiene 1a[a]



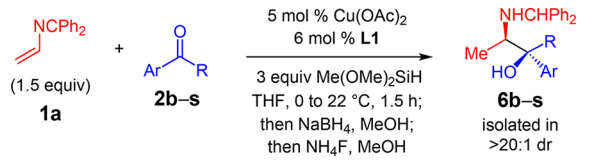
entry	ligand	conv of **2a** (%)[b]	**3a**:**4a**:**5**[c]	dr of **3a**[c]	er of **6a**[d]
1	**L1**	82 (60)[e]	9:1:0	5:1	99:1
2	**L2**	<2	–	–	–
3	**L3**	<2	–	–	–
4	**L4**	60	0:6:1	–	–
5	**L5**	>98	0:1:0	–	–
6	**L6**	>96	0:1:0	–	–
7[f]	**L1**	>98 (73)[e]	11:1:0	4:1	99:1

[a]Reaction under N_2 with 0.1 mmol ketone **2a** for 1 h. [b]Determined by 400 MHz ^{1}H NMR spectroscopy according to remaining **2a** in comparison to an internal standard. [c]Determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture. [d]Determined by HPLC analysis of purified **6a**. [e]Isolated yield of amino alcohol **6a** (>20:1 dr). [f]Reaction with 0.2 mmol ketone **2a** for 1.5 h. [Si] = $Si(OMe)_2Me$.

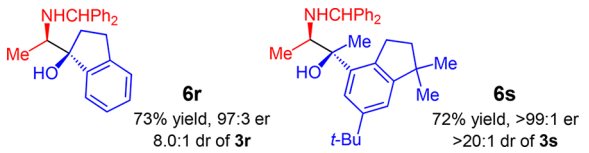
ligands (entries 2–6) afford <2% **3a** while generating significant amounts of ketone reduction product **4a** and/or iminopyrrolidine **5**, formed by reductive dimerization of **1a**.[28] In contrast, within 1.5 h **L1** gives >98% conv to **3a** (entry 7), which is formed in 4:1 dr as the major product (<10% ketone hydrosilylation). After imine reduction and ether desilylation (for ease of handling/assay purposes), the major diastereomer **6a** is solely isolated in 73% yield and 99:1 er.[29,30]

Several aryl/alkyl ketones undergo efficient reductive coupling with azadiene **1a** under the optimized conditions (Table 2); the major diastereomer may be selectively isolated after the reductive/desilylative workup and chromatographic purification.[29] A variety of substituents on the aromatic ring are tolerated (**6b–k**),[31] including N-heterocycles (**6d**) and free hydroxyl (**6g**) functionality (entries 1–10). For aromatic rings bearing *ortho* groups (**6h–i**), diastereoselectivity is significantly higher. For example, **6h** is formed as a single stereoisomer and **6i** is generated in 13:1 dr. Enantioselectivity is high in all cases (96.5:3.5 to >99:1 er) and the major product stereoisomer is isolated in 45–87% yield. Ketones containing aromatic heterocycles deliver amino alcohols **6l–n** in good diastereoselectivity and excellent enantioselectivity (5–9:1 dr and 95:5 to >99:1 er, entries 11–13). Longer alkyl chains within the ketone (**2o–p**) generate amino alcohols with improved diastereoselectivity (8–10:1 dr, entries 14–15) and with high enantioselectivity. Diaryl ketones undergo efficient azadiene coupling but with poor diastereoselectivity. For example, fenofibrate adduct **6q** is formed in only 1:1 dr. The isomers may be separately isolated; each is generated in

Table 2. Ketone Variation for Cu-Catalyzed Enantioselective Reductive Couplings with Azadiene 1a[a]



entry	product, Ar, R	dr of **3**[b]	yield (%)[c]	er of **6**[d]
1[e]	**6b**, 4-$MeOC_6H_4$, Me	3.5:1	60	96.5:3.5
2	**6c**, 4-$F_3CC_6H_4$, Me	4.0:1	50	>99:1
3	**6d**, 4-N-pyrazolylC_6H_4, Me	4.0:1	62	>99:1
4[e]	**6e**, 3-BrC_6H_4, Me	3.5:1	45	>99:1
5[e]	**6f**, 3-ClC_6H_4, Me	4.5:1	57	>99:1
6	**6g**, 3-HOC_6H_4, Me	7.5:1	62	>99:1
7[e]	**6h**, 2-BrC_6H_4, Me	>20:1	77	99:1
8	**6i**, 2-$MeOC_6H_4$, Me	13.0:1	87	97:3
9	**6j**, 2-napthyl, Me	3.5:1	65	99:1
10	**6k**, 3,4-dioxolatoC_6H_3, Me	5.5:1	61	98.5:1.5
11	**6l**, 2-furyl, Me	5.0:1	55	>99:1
12	**6m**, 3-thiophenyl, Me	9.0:1	83	99:1
13	**6n**, 3-pyrrolyl(NTs), Me	5.5:1	58	95:5
14	**6o**, Ph, Et	10.0:1	67	99:1
15	**6p**, Ph, CH_2CH_2Ph	8.0:1	63	98:2
16	**6q**, 4-ClC_6H_4, 4-(*i*-PrO_2CCMe_2O)C_6H_4	1.0:1	39, 37[f]	99:1, 99:1[g]



[a]Reaction with 0.2 mmol ketone **2**. [b]Diastereomeric ratio of **3** determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture prior to workup. [c]Isolated yield of purified **6** (>20:1 dr). [d]Enantiomeric ratio determined by HPLC analysis of **6**. [e]$Cu(OAc)_2 \cdot H_2O$ used. [f]Isolated yield of each diastereomer. [g]Enantiomeric ratio of each isomer.

99:1 er (entry 16). 2-Indanone undergoes reductive coupling to form **6r** in 73% yield, 8:1 dr, and 97:3 er. Azadiene addition to the fragrance celestolide delivers **6s** as a single stereoisomer in 72% yield.

A number of 4-alkyl-substituted 2-azadienes efficiently react with ketone **2i** to afford α-alkyl chiral amines **7a–j** as a single diastereomer in 43–59% yield (Table 3). The added steric hindrance imposed by the alkyl group necessitates a 12 h reaction time and leads to competitive ketone reduction, a pathway which is exacerbated with less-hindered ketones (e.g., acetophenone leads to >90% ketone reduction). A variety of functional groups are tolerated, such as thioether (entry 4), ether (entries 6–8), ester (entry 9), and halogen (entry 10).

Carbamates **8–9** (Scheme 2) may be obtained by the sequential reductive coupling of azadiene **1a** and ketones **2h–i** with desilylative workup, imine hydrolysis under mildly acidic conditions,[27] and Boc protection of the resulting primary amine (40–60% overall yield for the three-step sequence). The stereochemistry of the major isomer of **9** has been assigned as (*R*) at the amino center and (*S*) at the hydroxyl center. The free amine (**10**) may also be utilized for C–N cross-coupling reactions such as the Ullman coupling to generate aniline **11**. The

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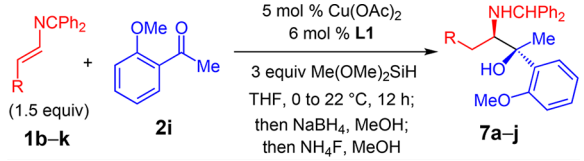
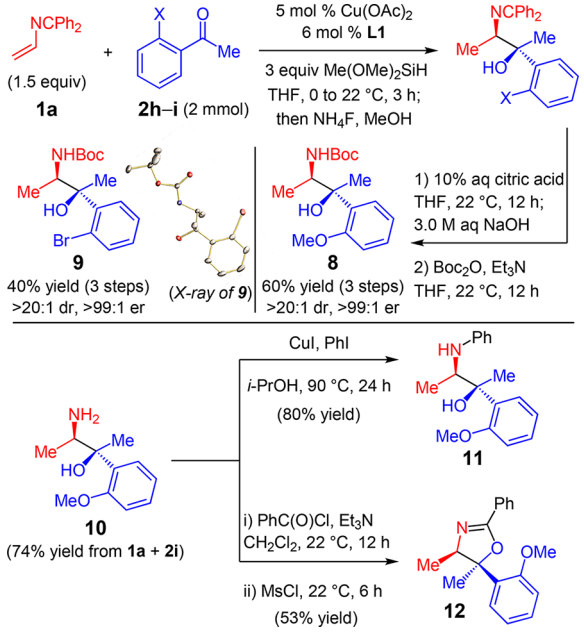
Table 3. Substituted 2-Azadienes for Enantioselective Additions to Ketones[a]



entry	product, R	dr of 3[b]	yield (%)[c]	er[d]
1	**7a**, *n*-Bu	>20:1	43	96.5:3.5
2[e]	**7b**, $(CH_2)_2Ph$	>20:1	54	98.5:1.5
3	**7c**, $(CH_2)_2$(3-thiophenyl)	>20:1	52	>99:1
4[f]	**7d**, $(CH_2)_2SMe$	>20:1	52	98.5:1.5
5	**7e**, $(CH_2)_3Ph$	>20:1	45	98:2
6	**7f**, $(CH_2)_3OBn$	>20:1	47	98:2
7	**7g**, $(CH_2)_3OPh$	>20:1	59	99:1
8	**7h**, $(CH_2)_3OTBS$	>20:1	45	98.5:1.5
9	**7i**, $(CH_2)_4OBz$	>20:1	46	99:1
10	**7j**, $(CH_2)_4C1$	>20:1	48	98.5:1.5

[a]Reaction of (*E*)-azadiene **1** unless otherwise noted. [b]Determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture prior to workup. [c]Isolated yield of purified **7**. [d]Enantiomeric ratio determined by HPLC analysis of **7**. [e](*E*)- and (*Z*)-azadienes **1c** deliver identical results. [f]From (*Z*)-**1e**.

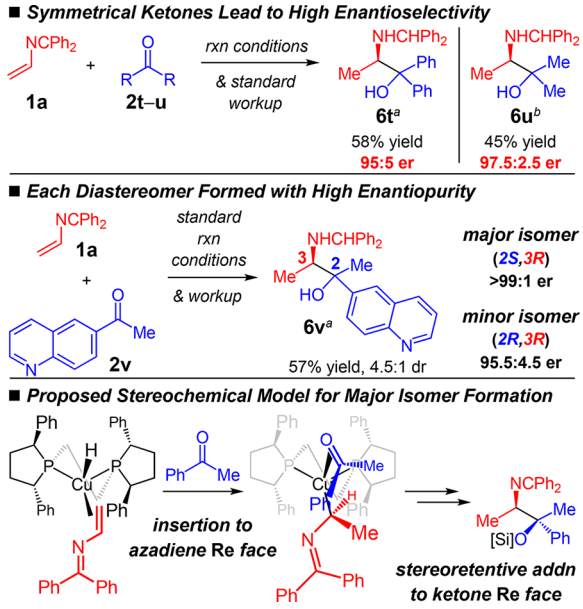
Scheme 2. Derivatization of Coupled Products



amine and hydroxyl group can instead both be engaged to form heterocycles such as oxazoline **12**.

Although we have been able in most cases to separate the two product diastereomers, we have not successfully isolated the minor stereoisomer of aryl/alkyl ketone addition in order to secure its stereochemical assignment. Experiments with symmetrical ketones (Scheme 3), however, suggest that the minor isomer differs in its stereochemistry at the hydroxyl-containing center. Both benzophenone and acetone[32] undergo coupling with **1a** with significantly higher enantioselectivity (**6t–u** formed in 95:5 to 97.5:2.5 er) than the diastereoselectivity observed in most other reactions (Tables 1–2). Additionally, unlike for **6q**, where each diastereomer is formed in equal enantiopurity, in the

Scheme 3. Implications for Stereochemistry of the Minor Diastereomer and Stereochemical Model



[a]Standard catalysis conditions; see Table 2. [b]3.0 equiv acetone, 5.0 equiv silane, 5 mol % $Cu(OAc)_2$, 6 mol % **L1**, THF, 22 °C, 1 h.

case of **6v** (Scheme 3), the major (2*S*,3*R*)-diastereomer is formed in >99:1 er but the minor, likely (2*R*,3*R*)-isomer, is furnished in only 95.5:4.5 er.

Based on the available data, a working model that accounts for the stereochemical outcome of the azadiene/ketone couplings is proposed in Scheme 3. Coordination of azadienes to [(*S*,*S*)-Ph-BPE]Cu–H occurs to place the benzophenone imine portion in the least hindered quadrant, leading to insertion into the *Re*-face, consistent with previous models.[16d,e] Stereorententive addition of the alkyl–Cu to the ketone's Re-face delivers the major stereoisomer. The minor isomer arises from addition to the ketone's *Si*-face, and all other stereoisomers are generated by stereoinvertive alkyl–Cu addition.

2-Azadienes are a promising class of reagents for preparation of chiral amines. Here, through reductive coupling with ketones, they have enabled catalytic enantioselective construction of 1,2-amino tertiary alcohols that have previously been inaccessible. Application of 2-azadienes for preparing other challenging amine scaffolds is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b12213.

Experimental procedures (PDF)
Analytical data for new compounds (PDF)
X-ray crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*steven.malcolmson@duke.edu

ORCID

Steven J. Malcolmson: 0000-0003-3229-0949

Author Contributions

‡These authors contributed equally.

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Notes

The authors declare no competing financial interest.

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(28) For additional ligand and other screening results, see the Supporting Information.

(29) The minor diastereomer is removed by chromatography and its fate is unclear at this time.

(30) *t*-BuOH addition increases the quantity of **4a** relative to **3a**.

(31) Ketones **2c** and **2e** undergo a more competitive reduction compared to C−C bond formation, which adversely affects yield.

(32) >90% ketone reduction is observed with other dialkyl ketones.

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