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Aminoalcohol Synthesis through Nonprecious Metal Catalysis: Enantioselective Cu-Catalyzed Reductive Coupling of Aldehydes and Allenamides

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Cite This: *Org. Lett.* 2023, 25, 4730–4734 Read Online

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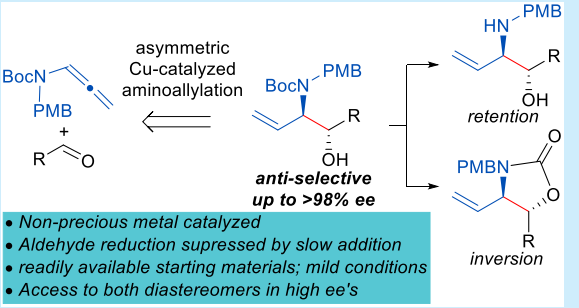
ABSTRACT: Herein, we report the development of a Cu-catalyzed aminoallylation of aldehyde electrophiles through reductive coupling by circumventing the problematic competitive reduction of the aldehyde electrophile by a CuH catalyst. This leads to a highly diastereo- and enantioselective process for the synthesis of chiral 1,2-aminoalcohols containing secondary alcohol substitution. Cleavage of the N substituents on the reaction products was performed, allowing access to the other diastereomer of the aminoalcohol, which was investigated in the context of a synthesis of eligulstat.



Catalysis is an enabling technology for complex molecule organic synthesis due to the ability to access previously unknown reactivity via the catalytic process and to control important reaction parameter outcomes (e.g., stereoselectivity, regioselectivity, and chemoselectivity) by modulation of the catalyst.[1] These features enable access to new synthetic pathways that were previously unattainable to allow for improvements in synthetic efficiency and atom economy to promote environmental sustainability of the chemical enterprise.[2] Important late transition metal-catalyzed reactions (e.g., cross-coupling,[1e] hydrogenation,[3] hydroformylation,[4] metathesis[1c]) were largely pioneered utilizing catalysts derived from the second and third row of the d block (e.g., Pd, Pt, Rh, Ir).[1] However, due to the low natural abundance of these precious elements (1 ppb in the earth's crust[5]), there are obvious benefits (e.g., cost, sustainability) to developing these same powerful transformations utilizing nonprecious metal catalysts derived from the first row of the transition series (e.g., Fe, Ni, Co, Cu) instead since these metals have ≥4 orders of magnitude higher natural abundance in the earth's crust[5] (Fe, 56300 ppm; Ni, 90 ppm; Co, 30 ppm; Cu, 68 ppm). As a result, development of nonprecious metal-catalyzed organic transformations has garnered considerable interest from research groups over the years.[6]

Arguably, one of the most powerful methods in organic synthesis is the reductive allylation of carbonyl electrophiles using unsaturated hydrocarbons (Scheme 1).[7] This area has largely been pioneered by the Krische group[7] utilizing allenes (**1**) (Scheme 1A),[8] enynes,[9] or 1,3-dienes[10] as the allyl nucleophile precursors with H_2 or a H_2 surrogate as the terminal reductant. While these processes are transformative, they require the use of precious metal catalysts derived from Ir, Rh, or Ru. More recently, the Buchwald group[11] has developed Cu-catalyzed versions of these processes utilizing silane as the terminal reductant (Scheme 1B) that are attractive due to the low cost, low toxicity,[12] and high availability of Cu. Notably, the techniques of Krische (Scheme 1A) and Buchwald (Scheme 1B) are orthogonal, whereby precious metal-catalyzed reductive allylation primarily works well with aldehydes, with numerous published examples,[7−9] whereas ketones are more problematic, with only four known examples[13,14] (Scheme 1A). In contrast, the Cu-catalyzed processes work well with ketone electrophiles,[11a−d] yet aldehydes are problematic (two reported examples)[11e,15] due to competitive reduction of the aldehyde by the CuH catalyst (Scheme 1B).

Our group[16] has been interested in developing reductive allylation reactions utilizing allenamides (**4**) as a tool to access important chiral 1,2-aminoalcohol motifs through aminoallylation[17,18] (Scheme 1C). We have strategically focused on Cu-catalyzed processes due to the improved sustainability of Cu over catalysts derived from precious metals.[5,6,12] Ketone electrophiles can be employed to provide 1,2-aminoalcohols **5** bearing a tertiary alcohol motif under either chiral catalyst control[16a,b] or through auxiliary control.[16c−f]

Received: May 24, 2023
Published: June 22, 2023

https://doi.org/10.1021/acs.orglett.3c01698
Org. Lett. 2023, 25, 4730−4734

Scheme 1. Enantioselective Reductive Allylation

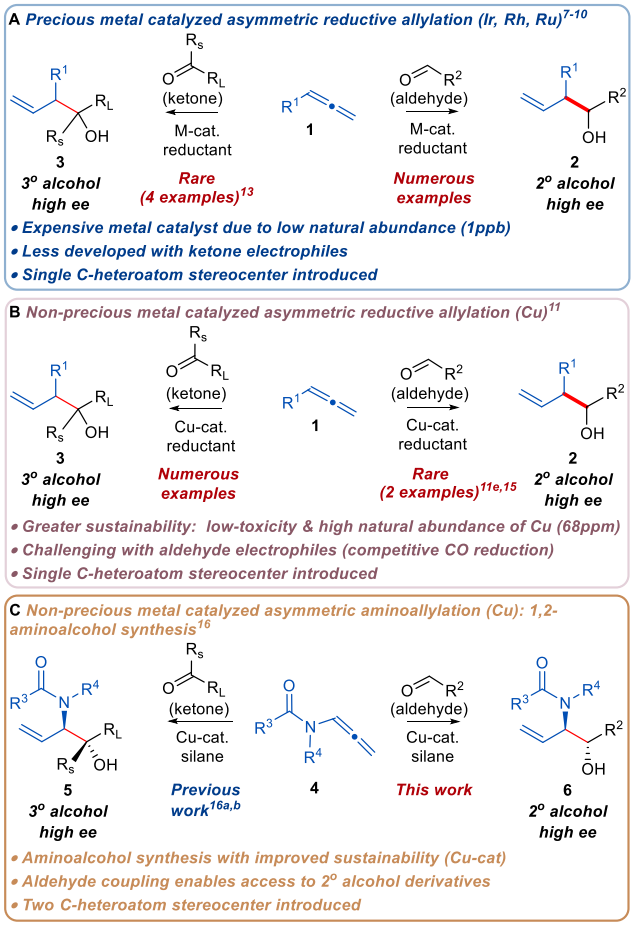
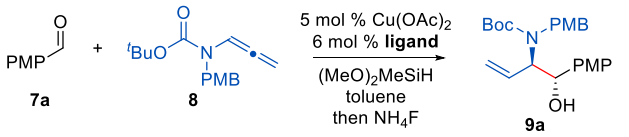
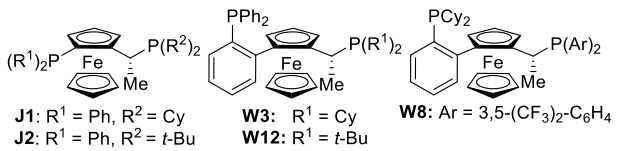


Table 1. Cu-Catalyzed Aminoallylation of Aldehydes[a]



entry	ligand[d]	T (°C)	yield (%)[b]	ee (%)[c]
1	**W3**	22	74	68
2	**W8**	22	47	6
3	**W12**	22	79	80
4	**J1**	22	69	14
5	**J2**	22	78	39
6	**W3**	0	81	76
7	**W12**	0	92	84
8	**W3**	−40	92	92
9	**W12**	−40	40	88
10	**W3**	−78	65	94

[a]Conditions: **8** (0.375 mmol), $Me(MeO)_2SiH$ (0.500 mmol), $Cu(OAc)_2$ (5 mol %), and ligand (6 mol %) in toluene (0.25 mL) followed by addition of **7a** (0.250 mmol/0.5 mL of toluene) by syringe pump over 9 h (0.05 mL/h) followed by an additional 15 h; see the Supporting Information for details. In all cases, a single diastereomer of **9a** was obtained (^{1}H NMR spectroscopic analysis). [b]Determined by ^{1}H NMR spectroscopy on the unpurified reaction mixture using dimethyl fumarate as a standard. [c]The value for the *anti* diastereomer was determined by HPLC. [d]Ligand structures:



However, there are cases where the aminoalcohol product having secondary alcohol substitution (i.e., **6**) may be desired that would require the use of an aldehyde electrophile, which may not be straightforward with CuH catalysis due to competitive aldehyde reduction (*vide supra*). While there is a single known example of an asymmetric aminoallylation of aldehydes,[17] the protocol utilizes an *N*-phthaloylallenimide under Ir catalysis through the hydrogen autotransfer technique; low catalyst loadings of Ir were not reported (5 mol % Ir loading employed), and a high reaction temperature was required (100 °C). The ability to conduct an asymmetric aminoallylation process with the nonprecious metal Cu as the catalyst has significant advantages from a sustainability perspective and warrants investigation. Herein we disclose the development of a Cu-catalyzed enantioselective aminoallylation of aldehydes that occurs under mild conditions (−40 to 40 °C) with high stereoselectivities.[19]

To realize a CuH-catalyzed aminoallylation of aldehydes, competitive reduction of the aldehyde over hydrocupration of the allene must be circumvented. One solution may be to utilize the allene in large excess to increase the rate of hydrocupration over aldehyde reduction through a concentration effect. While use of large excesses of allene is not practical from an atom economy perspective, the same effect can be achieved through slow addition of the aldehyde.[11e] Accordingly, as the test reaction, a solution of anisaldehyde (**7a**) in toluene was added to the reaction mixture containing allenamide **8** using a syringe pump (Table 1).[20] Gratifyingly, the desired aminoallylation product **9a** was obtained by this approach. Survey of a variety of chiral bis(phosphine) ligands (entries 1−5)[20] led to relatively modest enantioselectivities, with the Walphos family of ligands being optimal, with **W3** and **W12** affording 68 and 80% ee, respectively (entries 1 and 3). Interestingly, use of **J2** that proved optimal in previous reactions using ketone electrophiles afforded only modest enantioselection (39% ee; entry 5).[16a] Additional optimization identified that reaction temperature had the most significant impact on enantioselectivity (entries 6−10). While **W12** generally afforded higher levels of enantioselection compared to **W3** when the reactions were conducted at ≥0 °C (entries 3 and 7 vs 1 and 6), similar enantioselectivities were obtained at ≤ −40 °C (entry 8 vs 9). However, at temperatures ≤ −40 °C, **W3** afforded a better reaction yield. While reducing the reaction temperature to −78 °C led to the highest observed enantioselectivity (94% ee), the yield was reduced compared to the reaction performed at −40 °C (entry 10 vs 8). As a result, the conditions in entry 8 were identified as optimal.

The aldehyde scope in the Cu-catalyzed aminoallylation reaction was next investigated (Scheme 2). Electron-rich aldehydes (**9a**, **9e**−**h**) performed well in the reaction, generating products in good yields and enantioselectivities. In contrast, electron-deficient aldehydes (**9b**−**d**) generally afforded products in lower yield due to increased amounts of aldehyde reduction byproducts. Notably, sterically hindered *ortho*-substituted aldehydes (**9f**, **9g**) and heteroaryl aldehydes (**9i**−**o**) performed well in the reaction. Finally, aliphatic aldehydes (**9p**−**u**) could also be employed, but these noticeably performed better with the use of **W12** as the ligand and required higher reaction temperatures (22−40 °C).

https://doi.org/10.1021/acs.orglett.3c01698
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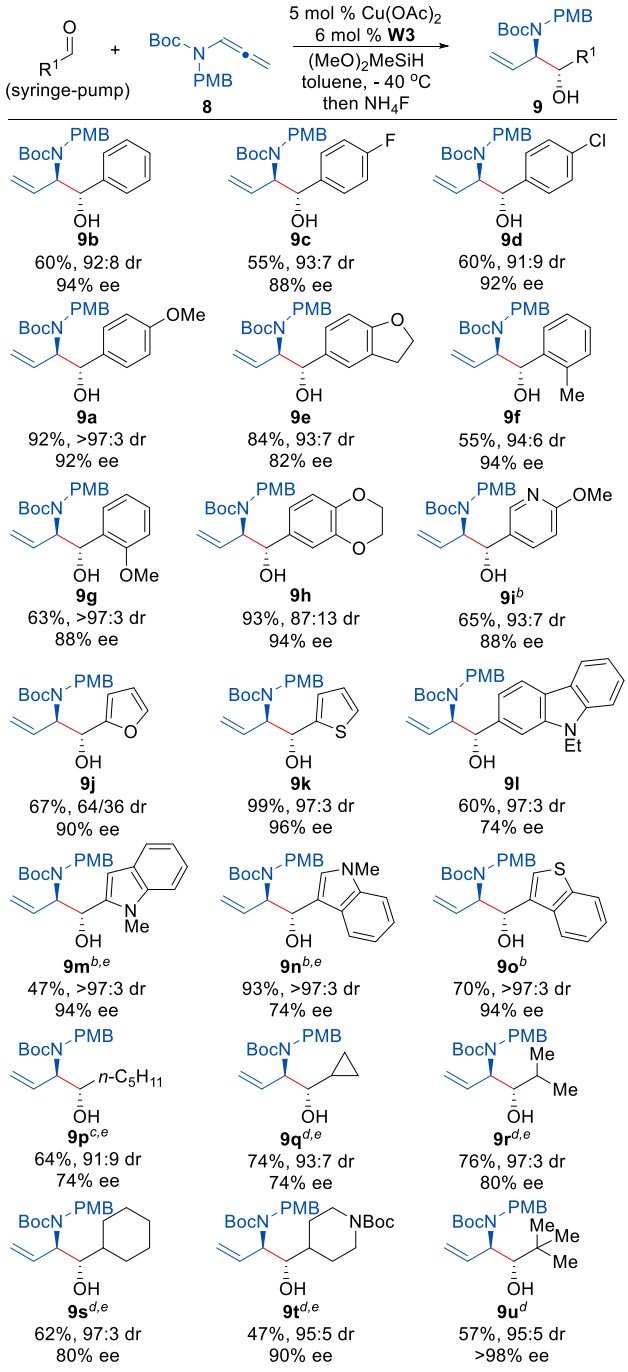
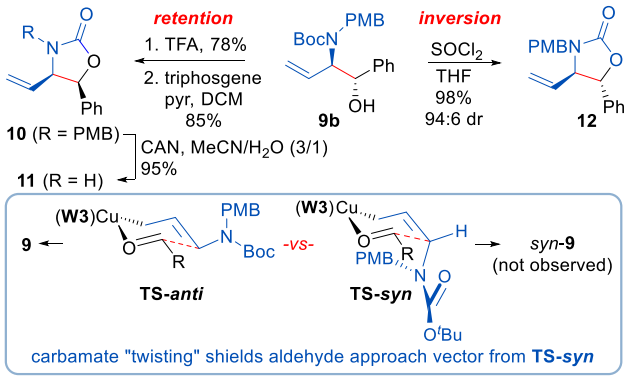
Scheme 2. Aldehyde Scope[a]



[a]The reaction utilizes 0.250 mmol of aldehyde in 0.5 mL of toluene added by syringe pump over 9 h (0.05 mL/h) followed by an additional 15 h; see the Supporting Information. Yields represent isolated material. [b]The reaction was performed at 0 °C. [c]The reaction was performed at 40 °C. [d]The reaction was performed at 22 °C. [e]The reaction was performed using **W12** as the ligand.

Subsequent reactions of the N substituents of **9** were next investigated (Scheme 3). An additional convenient feature of the methodology developed herein over existing asymmetric aminolallylation[17] is the presence of the more easily cleavable *N*-Boc group that could be removed using TFA. The resultant aminoalcohol was converted to carbamate **10** followed by PMB removal to afford **11**, which was compared with known[20] enantioenriched material to confirm the absolute and relative

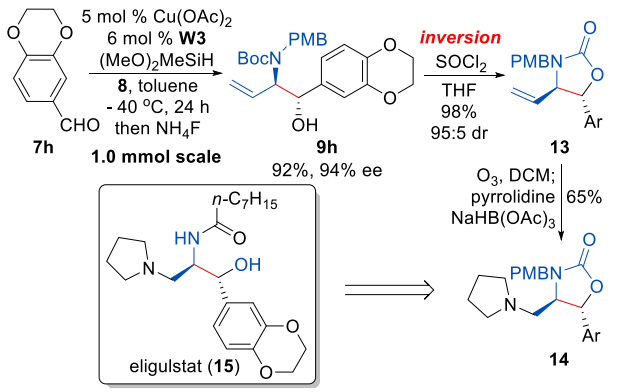
Scheme 3. Stereochemical Determination



stereochemistry of **9b**. Notably, the *anti* diastereomer (**9b**) could be transformed to an opposite diastereomeric arrangement through inversion[21] of the secondary alcohol stereocenter by neighboring group participation of the *N*-Boc group when activating with $SOCl_2$, affording carbamate **12**. The observed relative stereochemistry obtained in the Cu-catalyzed aminoallylation process conforms to our previously reported[16a] stereochemical model for ketone electrophiles with acyclic allenamides favoring the *anti* diastereomer through chairlike transition structures (**TS**-*anti* vs **TS**-*syn*). Formation of the minor *syn* diastereomer of the product through **TS**-*syn* is proposed to be inhibited through shielding of the aldehyde approach vector by the *N*-Boc group, which is twisted out of plane due to $A^{1,3}$ strain.[16a,22]

Taking the above stereochemical observations into consideration, the aldehyde aminoallylation reaction was demonstrated in the context of an asymmetric synthesis of the important Gaucher's disease treatment eligulstat[23] (**15**) (Scheme 4). The aminoallylation could be performed on a

Scheme 4. Application toward Eligulstat



1.0 mmol scale to provide **9h** with identical results. Subsequent inversion[21] of the hydroxyl stereocenter of **9h** using $SOCl_2$ afforded **13** in excellent yield and enabled access to the correct relative stereochemistry required for eliglustat. Finally, oxidative cleavage of the alkene of **13** using a reductive amination workup[24] with pyrrolidine afforded **14** as a potential protected precursor toward **15**.

In conclusion, we have reported the first enantioselective Cu-catalyzed aminoallylation of aldehydes by circumventing competitive aldehyde reduction by the CuH catalyst through the slow addition of the aldehyde. The *anti* selective process provides reaction products in good to excellent enantiose-

https://doi.org/10.1021/acs.orglett.3c01698
Org. Lett. 2023, 25, 4730−4734

lectivities, and the other diastereomer of the aminoalcohol can be obtained through an inversion process utilizing the *N*-Boc group.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01698.

Experimental procedures, characterization data for all compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding from the National Science Foundation (CHE-2143712) and startup support from Virginia Commonwealth University are gratefully acknowledged. We thank Solvias for the generous donation of ligand **W12** and Dr. Joseph Turner (VCU) for assistance collecting HRMS data.

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