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Catalytic, Transition-Metal-Free Semireduction of Propiolamide Derivatives: Scope and Mechanistic Investigation

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02567 Read Online

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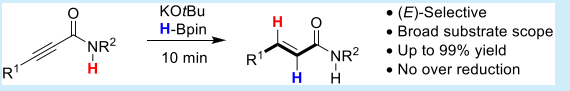
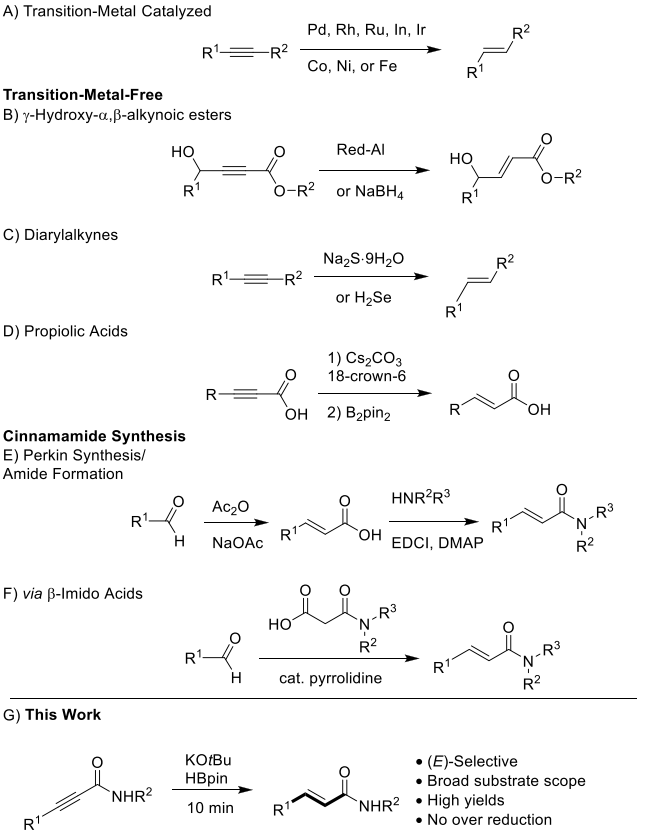
ABSTRACT: We report a transition-metal-free *trans*-selective semireduction of alkynes with pinacolborane and catalytic potassium *tert*-butoxide. A variety of 3-substituted primary and secondary propiolamides, including an analog of FK866, a potent nicotinamide mononucleotide adenyltransferase (NMNAT) inhibitor, are reduced to the corresponding (*E*)-3-substituted acrylamide derivatives in up to 99% yield with >99:1 *E*/*Z* selectivity. Mechanistic studies suggest that an activated Lewis acid−base complex transfers a hydride to the α-carbon followed by rapid protonation in a *trans* fashion.



The semireduction of an alkyne to a (*Z*)- or (*E*)-alkene is fundamental in organic synthesis. Methods toward the (*Z*)-selective semireduction of alkynes are well established,[1] with the most popular being semihydrogenation mediated by Lindlar's catalyst ($Pd/CaCO_3/Pb$/quinoline).[2] The complementary reduction methods affording (*E*)-alkenes are limited. Early work involved treating alkynes with dissolved metals,[3] low-valent chromium salts,[4] or metal hydrides;[5] however, these methods are harsh and highly substrate-dependent. Trost and coworkers later developed a general method for the (*E*)-selective semireduction of alkynes via a ruthenium-mediated hydrosilylation, which is subsequently protodesilylated with TBAF, affording (*E*)-alkenes in high yield with excellent stereoselectivity.[6] Similarly, Fürstner developed a one-step, stereoselective semireduction of alkynes using a similar ruthenium catalyst.[7] Beyond these two examples, various transition-metal-catalyzed methods toward the (E)-selective semireduction of alkynes have been developed, such as Pd,[1i,n,8] Rh,[9] Ru,[1q,10] In,[11] Ir,[1ab,12] Co,[1ac,13] Ni,[1ad,14] and Fe[15] (Scheme 1A).

The transition-metal-free semireduction of alkynes to (*E*)-alkenes is limited to a few examples. Koide treated γ-hydroxy-α,β-alkynoic esters with Red-Al or $NaBH_4$ and obtained alkenoic esters in good yield with good stereoselectivity, although the substrate scope is limited by the necessity of the directing ability of the γ-hydroxyl moiety (Scheme 1B).[16] Chen and Liu employed sodium sulfide nonahydrate as a reducing reagent to facilitate the stereoselective semihydrogenation of diarylalkynes to (*E*)-alkenes (Scheme 1C). This method successfully reduced a broad scope of diarylalkynes in good to excellent yield with high stereoselectivity (98:2 *E*/*Z*).[17] Similarly, Zhou and Liu demonstrated the semireduction of diarylalkynes utilizing H_2Se, which was generated *in situ* from $Se/DMF/H_2O$ (Scheme 1C), to obtain alkenes in good yield with high stereoselectivity (>95:5 *E*/*Z*).[18] However, both aforementioned methods were limited to diarylalkynes, and the reaction conditions were fairly harsh. Recently, our group

Scheme 1. Methods toward E-Selective Semireduction of Alkynes and Cinnamamide Synthesis



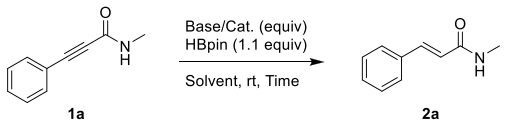
Received: July 31, 2020

reported the α-boronation−protodeboronation of propiolic acids (Scheme 1D). After boryl transfer to the α-carbon, the α-boryl cinnamic acid is readily protodeboronated upon workup, furnishing (*E*)-cinnamic acids in good yield with good stereoselectivity.[19] (*E*)-Cinnamic acids are commonly used as precursors to (*E*)-cinnamamides, which are omnipresent pharmacophores in synthetic pharmaceuticals and natural products.[20]

Only one method has been disclosed for the (*E*)-selective semireduction of propiolamides, which requires a Pd catalyst and superstoichiometric Mn to reduce 3-phenylpropiolamide as well as tertiary propiolamides to the corresponding (*E*)-cinnamamides. Typically, the (*E*)-configuration of cinnamamides is derived from *E*-cinnamic acid, a precursor commonly synthesized by the condensation of aryl aldehydes with acetic anhydride (Perkin reaction)[21] or malonic acid (Knoevenagel−Doebner condensation).[22] The corresponding (*E*)-cinnamamides are synthesized by coupling (*E*)-cinnamic acid using activating agents and the desired amine (Scheme 1E), the synthesis of which remains widely used today but is nonideal. More recently, Zacuto designed a direct synthesis of (*E*)-acrylamides via the Knoevenagel−Doebner condensation of β-imido acids with aldehydes (Scheme 1F).[23] The paucity of methods and the shortcomings of the current protocols (including over-reduction) motivated us to develop an E-selective method toward the semireduction of propiolamides.[24]

We initiated our investigation by treating *N*-methyl-3-phenylpropiolamide (**1a**) with stoichiometric pinacolborane and LiO*t*Bu. To our delight, this afforded methyl (*E*)-cinnamamide **2a** with excellent stereoselectivity (>99:1 *E*/*Z*) in 82% yield (Table 1, entry 1). A stoichiometric base was unnecessary, as catalytic amounts of base efficiently produced **2a** in good yield (entry 2). Upon increasing the size of the *tert*-butoxide counterion from Li to K (entries 2−4), a remarkable increase in the reaction efficiency was observed with KOtBu, delivering a near-quantitative yield and >99% (*E*)-stereoselectivity, even at higher concentrations (0.5 M, entry 5).

Table 1. Optimization of Reaction Conditions[a]



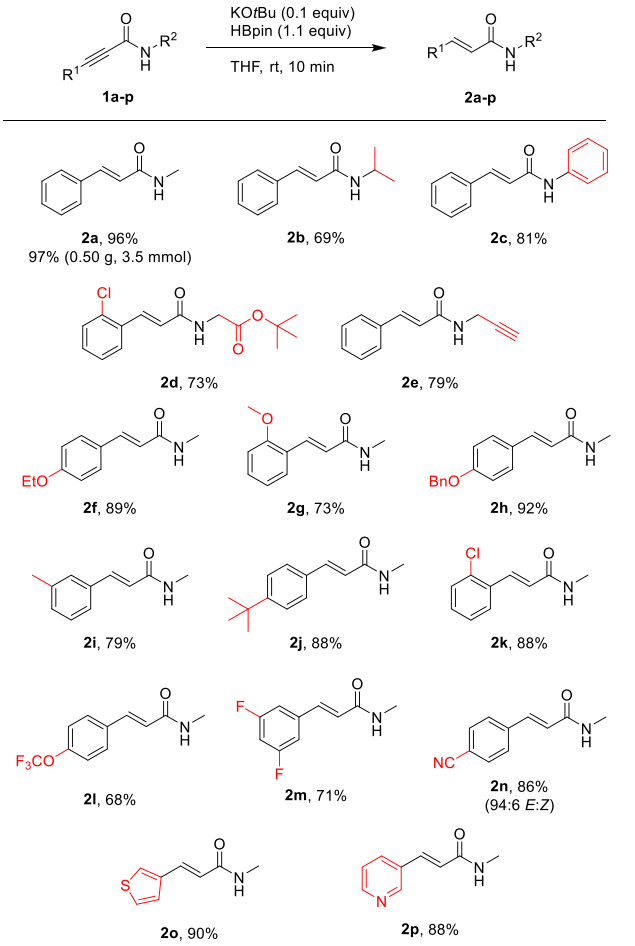
entry	base (equiv)	solvent	time	yield[b]
1[c,d]	LiO*t*Bu (1.1)	THF	4 h	82
2[e,f]	LiO*t*Bu (0.1)	THF	7 h	62
3[f]	NaO*t*Bu (0.1)	THF	10 min	75
4[f]	KO*t*Bu (0.1)	THF	10 min	95
5	KO*t*Bu (0.1)	THF	10 min	96
6	KOH (0.1)	THF	10 min	39
7	NaOMe (0.1)	THF	10 min	58
8	K_2CO_3 (0.1)	THF	10 min	0
9	KO*t*Bu (0.1)	1,4-dioxane	10 min	47
10	KO*t*Bu (0.1)	MeCN	10 min	85
11	KO*t*Bu (0.1)	CH_2Cl_2	10 min	78
12	KO*t*Bu (0.1)	DMF	2 h	52

[a]General procedure: **1a** (0.2 mmol), THF (0.5 M), base (0.02 mmol), and HBpin (0.22 mmol). [b]Isolated yield (>99:1 E/Z). [c]Base and HBpin added at −78 °C, then heated to 40 °C for 4 h. [d]Propiolamide diluted to 0.1 M. [e]Base and HBpin added at 25 °C, then heated to 60 °C for 7 h. [f]0.2 M.

These studies also demonstrated that the reaction is finished within 10 min. KOH (entry 6) and NaOMe (entry 7) mediated the semireduction to **2a**, albeit in reduced yields. However, the use of a weaker carbonate base such as K_2CO_3 was nonproductive (entry 8). With the optimal base conditions in hand (entry 5), we screened a variety of different solvents. Switching to 1,4-dioxane (entry 9) afforded **2a** in modest yield. Acetonitrile (entry 10) and dichloromethane (entry 11) were sufficient solvents, although the yield was lower. DMF was also a useful solvent for the semireduction of **1a** (entry 12), but the reaction time was considerably longer.

With the optimal conditions in hand (Table 1, entry 5), we investigated the substrate scope against a wide variety of secondary propiolamides (Scheme 2). Sterically encumbered

Scheme 2. Secondary Propiolamide Scope[a]



[a]General procedure: Same as in Table 1, entry 5. >99:1 *E*/*Z* unless otherwise specified. Isolated yields reported.

N-substitutions such as *N*-isopropyl (**1b**) and *N*-phenyl (**1c**) were well-tolerated under these conditions, as cinnamamides **2b** and **2c** were produced in good yield. The Boc-protected glycine derivative **1d** was chemoselectively reduced to cinnamamide **2d**, with no ester reduction products observed. Substrate **1e** bearing a propargyl group was chemoselectively reduced to cinnamamide **2e** in excellent yield. Likewise, electron-donating substituents (**1f−h**) and alkyl substitutions such as *m*-methyl (**1i**) and *p*-*tert*-butyl (**1j**) afforded **2f−j** in good to excellent yields with near-exclusive E-selectivity. Substrates bearing halogens such as *o*-Cl (**1k**), *p*-trifluorome-

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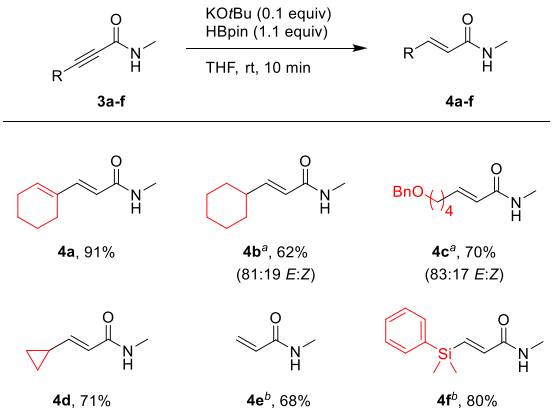
thoxy (**1l**), and 3,5-difluoro (**1m**) were reduced to the corresponding cinnamamides (**2k−m**) in high yield. Propiolamides with strong electron-withdrawing groups on the aryl ring such as *p*-cyano (**1n**) were also suitable substrates, although with a slight reduction in stereoselectivity. Heteroaromatics such as thiophene (**1o**) or pyridyl (**1p**) substitutions were also efficient substrates. We were pleased to find that the reaction was amenable to scale-up, as 3.5 mmol of **1a** was readily converted to **2a** without a loss in yield or stereoselectivity (Scheme 2).

To further explore the substrate scope, we investigated nonaromatic systems (Scheme 3). For example, enyne **3a** was

Scheme 3. Enyne and Aliphatic Secondary Propiolamide Scope[c]

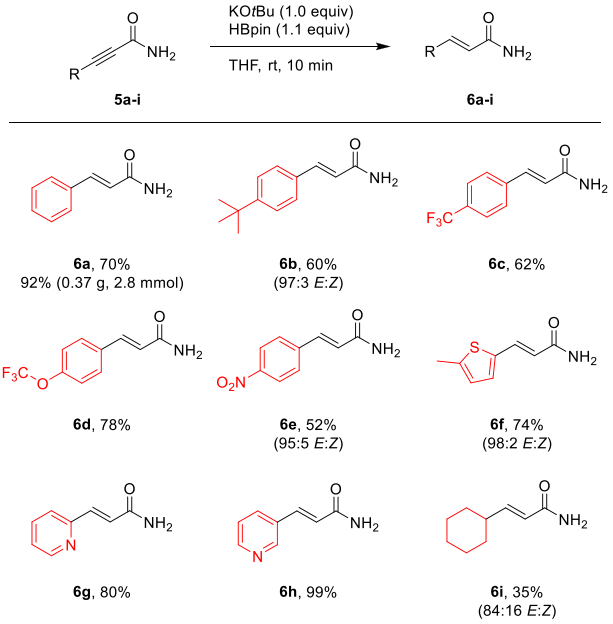


[a]THF (0.2 M), KO*t*Bu (1.0 equiv). [b]Order of addition: HBpin followed by KO*t*Bu. Isolated yields reported. [c]General procedure: Same as in Table 1, entry 5. Stereochemistry is >99:1 *E*/*Z* unless otherwise specified.

reduced to **4a** in high yield with high *E*-stereoselectivity and chemoselectivity for the alkyne. However, alkyl-substituted propiolamides required a stoichiometric base and diluted reaction conditions to afford satisfactory yields. Under these conditions, substrates **3b,c** were reduced to **4b,c** in good yield with good stereoselectivity. Fortunately, the 3-cyclopropyl propiolamide **3d** enhanced the reactivity and (*E*)-stereoselectivity compared with other aliphatic substrates, which we also observed in the hydroboration of propiolamides.[24c] Additionally, we found that the unsubstituted substrate *N*-methyl propiolamide (**3e**) and dimethyl(phenyl)silyl derivative **3f** could be converted to cinnamamides **4e** and **4f**, respectively, in good yield when first treated with pinacolborane then base, as treatment with base alone results in rapid degradation of the starting material.

We next set out to apply this boron-mediated semireduction protocol to the more challenging primary propiolamides. Similar to most nonaryl secondary propiolamides in Scheme 3, we observed that the stoichiometric addition of KO*t*Bu and pinacolborane was optimal. Thus 3-phenylpropiolamide (**5a**) was reduced to **6a** in excellent yield with high stereoselectivity for the (*E*)-isomer, and this conversion was achieved in a near-quantitative yield upon scale-up (Scheme 4). *t*-Butyl (**5b**) and trifluoromethyl (**5c**) as well as trifluoromethoxy (**5d**) substitutions were effectively converted to (*E*)-cinnamamides **6b−d**. Strong electron-withdrawing *p*-nitro substitution (**5e**) caused a minor reduction in (*E*)-stereoselectivity (**6e**). Heterocyclic primary propiolamides were well-tolerated, as a

Scheme 4. Primary Propiolamide Scope[a]



[a]General procedure: **1a** (0.2 mmol), THF (0.2 M), base (0.2 mmol), and HBpin (0.22 mmol). >99:1 *E*/*Z* unless otherwise specified. Isolated yields reported.

5-thiophen-2-yl substrate **5f** was reduced in good yield. We were also pleased to find that 2- and 3-pyridyl substitutions in **5g** and **5h**, respectively, did not affect the reaction, as they were reduced in high to near-quantitative yield with excellent chemo- and stereoselectivity (**6g,h**). On the contrary, an aliphatic 3-cyclohexyl substitution (**5i**) resulted in a reduction in yield and stereoselectivity similar to the related *trans* diboration.

We then turned our attention toward the application of this protocol. Cinnamamides are important structural features in medicinal chemistry. For example, peptide **7** is an inhibitor of the main protease in coronaviruses, including picomolar activity against the Middle East Respiratory Syndrome (MERS) coronavirus.[25] FK866 is a potent inhibitor of the nicotinamide mononucleotide adenyltransferase (NMNAT) pathway[26] that completed clinical trials as a potential chemotherapeutic agent.[27] Furthermore, recent research suggests that FK886 is a promising treatment for various diseases.[28] Thus we decided that FK866 was a suitable substrate for late-stage modification. We augmented the initial portion of a previously described total synthesis of FK866[29] and eventually installed the propiolamide via amide formation by DCC/DMAP coupling to 3-phenylpropiolic acid (Scheme 5). Once installed, propiolamide **8** was stereoselectively reduced to **9** in 76% yield, resulting in a 20% overall yield of FK866 analog **9** in seven steps In comparison, previous syntheses have an overall 8−12% yield.[29,30] An advantage of the method is the potential for rapid structure−activity relationship studies and the control of olefin geometry, as commercially available cinnamic acid derivatives are sold as a mixture of *cis*/*trans* isomers.

To understand the origin of the *trans* selectivity of the semireduction, we performed a mechanistic investigation. Under the reaction conditions using deuterated **10**, compound **11** was isolated in 40% yield with the deuterium atom installed on the β carbon almost quantitatively (Scheme 6A). This result

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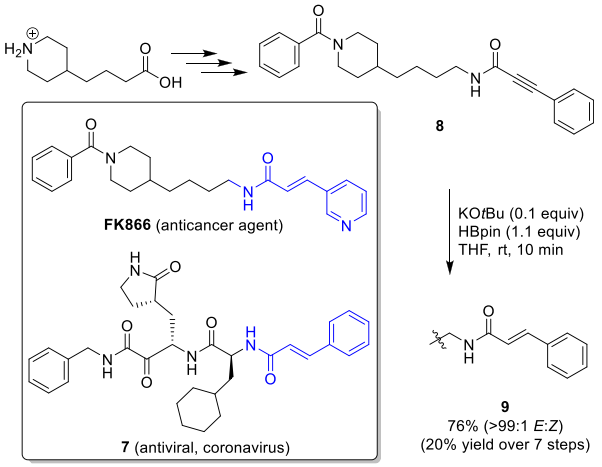
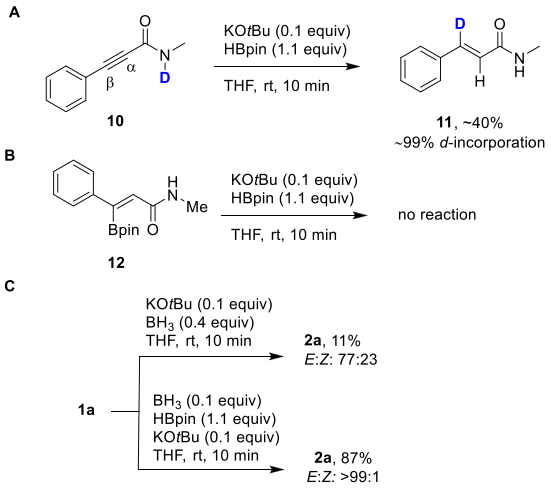
Scheme 5. Structures of Medicinally Relevant Cinnamamides and Synthesis of FK866 Analog

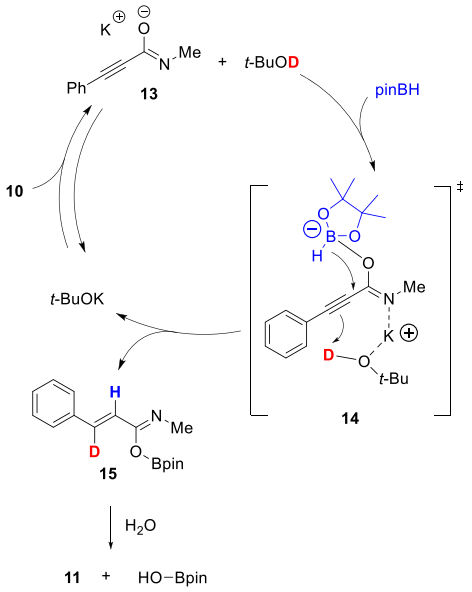


Scheme 6. Mechanistic Studies



suggests that (i) hydride is adding on the α-carbon, (ii) protonation occurs on the β-carbon, and (iii) a 1,4-conjugate addition pathway is unlikely via hydride addition to the β-carbon (i.e., from a Lewis base *t*-BuO−pinacolborane complex). Alternatively, β-borylation can occur followed by rapid protodeboration.[31] However, the reaction of **12** under the same conditions afforded only unreacted starting materials (Scheme 6B). Recently, Thomas[32] and Chang[33] reported that pinacolborane can decompose to BH_3 in the presence of catalysts such as *t*-BuOK. We thus treated **1a** with *t*-BuOK and BH_3 (Scheme 6C). When we used borane as the reducing agent, a significant loss in yield and a deterioration of stereoselectivity was observed (77:23 *E*/*Z*), suggesting that *in situ* formed BH_3 is unlikely mediating the transformation. Likewise, the addition of a catalytic amount of BH_3 under standard conditions afforded **2a** in excellent yield and with E selectivity. The BH_3-mediated reduction of alkynes affords the *Z*-alkene product, which is the opposite of what is observed here. Taken together, a proposed mechanism is shown in Scheme 7. The role of *t*-BuOK is to deprotonate propiolamide **10**, which is in equilibrium with *t*-BuOD and its conjugate base **13**. The Lewis-basic oxygen in **13** then complexes with pinacolborane, activating the B−H bond[24b,34] for an intramolecular pseudo-5-exo-dig[24c] hydride transfer to the α-carbon

Scheme 7. Proposed Mechanism



(i.e., transition state **14**). The deuteration occurs on the opposite side of the alkyne by coordination of *t*-BuOD with the potassium of *t*-butoxide, which establishes the *trans* alkene geometry in intermediate **15**; upon workup, **11** is generated.

In conclusion, we have developed a transition-metal-free semireduction reaction of primary and secondary propiolamides that selectively affords (*E*)-cinnamamides in good to excellent yields. The reaction is tolerant of a wide variety of substrates and is a facile process that uses inexpensive, commercially available reagents. The utility of the reaction is demonstrated in the late-stage alkyne reduction to achieve the cinnamamide-containing drug candidate FK866. Lastly, mechanistic studies suggest that the role of *t*-BuOK is to act as a Brønsted base to activate the propiolamide for Lewis acid−base complexation with pinacolborane, inducing an intramolecular hydride transfer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02567.

Experimental procedures and NMR data (PDF)

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https://dx.doi.org/10.1021/acs.orglett.0c02567
Org. Lett. XXXX, XXX, XXX−XXX

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support by the National Science Foundation (CHE-1414458) and the Virginia Tech Chemistry Department.

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