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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Enantioselective CuH-Catalyzed Reductive Coupling of Aryl Alkenes and Activated Carboxylic Acids

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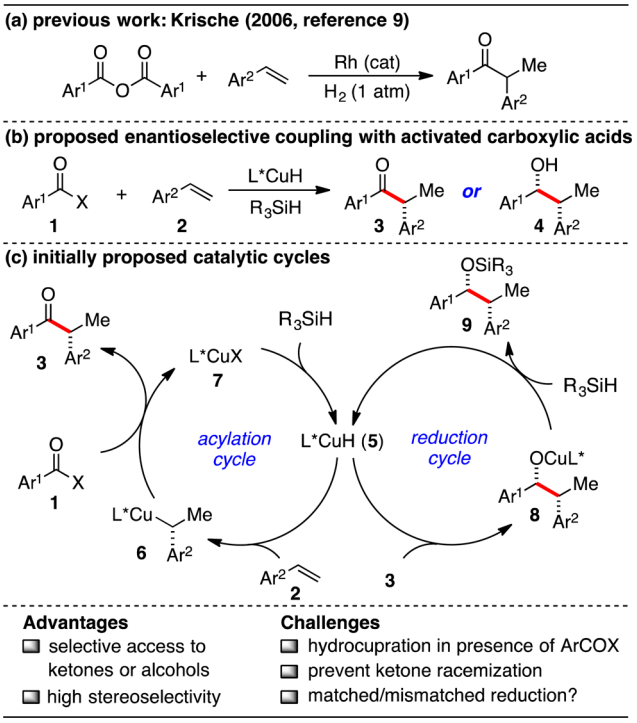
Supporting Information

ABSTRACT: A new method for the enantioselective reductive coupling of aryl alkenes with activated carboxylic acid derivatives via copper hydride catalysis is described. Dual catalytic cycles are proposed, with a relatively fast enantioselective hydroacylation cycle followed by a slower diastereoselective ketone reduction cycle. Symmetrical aryl carboxylic anhydrides provide access to enantioenriched α-substituted ketones or alcohols with excellent stereoselectivity and functional group tolerance.

The asymmetric construction of chiral ketones and alcohols remains an important area of research in organic synthesis due to the high utility of these functional groups.[1] The reaction of an alkene with an aldehyde, via catalytic hydroacylation or reductive coupling, represents an attractive route to α-chiral ketones and alcohols, respectively.[2,3] These processes construct a carbon−carbon bond (and corresponding stereogenic center) while obviating the need for stoichiometric preformed organometallic reagents. Impressive developments toward generalizing these transformations have been reported although significant limitations and challenges remain. For example, numerous methods for highly enantioselective intermolecular alkene hydroacylation have been reported; however, a metal-coordinating substituent on either the alkene or aldehyde component is typically required.[4] Pioneering work by Krische has led to numerous methods for the asymmetric reductive coupling of alkenes to carbonyls for relatively activated C−C π-systems, such as electron-deficient alkenes, enynes, dienes, and allenes.[3,5−7] In contrast, stereoselective catalytic intermolecular reductive coupling of aryl alkenes to carbonyls remains largely undeveloped, likely a consequence of the lower reactivity of these alkenes.[8,9] Building upon an initial report by Miura,[10] Krische developed a highly efficient Rh-catalyzed coupling of aryl alkenes and anhydride reagents to selectively access branched ketones in a racemic manner (Scheme 1a).[9,11] We reasoned that using a similar approach, namely, using a carboxylic acid derivative as an aldehyde surrogate, the limitations described above for hydroacylation and reductive coupling could be addressed via copper(I) hydride (CuH) catalysis. We herein report a CuH-catalyzed protocol for the reductive coupling of aryl alkenes to activated carboxylic acids that, depending on the reaction conditions, selectively yields enantioenriched ketones or alcohols (Scheme 1b).

We, as well as Hirano and Miura, have developed enantioselective CuH-catalyzed hydroamination reactions that proceed through catalytically generated chiral organocopper intermediates that are formed from hydrocupration of an alkene substrate.[12,13] As an expansion of this work, we recently reported methods for the synthesis of enantioenriched carbo- and heterocycles via intramolecular trapping of a putative organocopper intermediate with alkyl bromides and imines.[14] We reasoned that this strategy could be applied to the intermolecular coupling of an alkene to an appropriately activated carboxylic acid derivative to initially yield an α-chiral ketone, constituting a formal hydroacylation process.[15,16] Subsequent reduction of the ketone would additionally yield an alcohol containing two stereocenters. The proposed catalytic cycle (Scheme 1c) proceeds via asymmetric Markovnikov hydrocupration of aryl alkene **2** followed by electrophilic interception with an acyl electrophile (**1**) to deliver enantioenriched ketone (**3**) and L*CuX (**7**).[17] σ-Bond metathesis of L*CuX (**7**) with a hydrosilane is required to regenerate L*CuH (**5**). Under

Scheme 1. (a) Prior Work in Aryl Alkene Reductive Coupling to Acyl Electrophiles; (b) Proposed Access to Chiral Ketones or Alcohols; (c) Proposed Catalytic Cycles



Received: March 24, 2016
Published: April 27, 2016

DOI: 10.1021/jacs.6b03086
J. Am. Chem. Soc. 2016, 138, 5821−5824

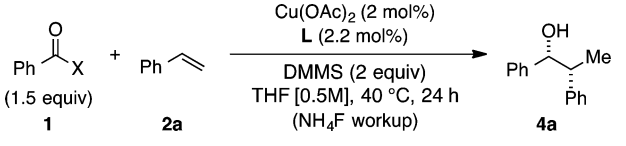
appropriate conditions, reformed L*CuH (**5**) could perform a highly diastereoselective 1,2-reduction of ketone **3** in the reduction cycle to produce silyl ether **9**. Ideally, these two catalytic processes could be performed in the same reaction vessel with a common electrophile, thus providing either enantioenriched ketone or alcohol products, depending upon the reaction conditions employed.

In the presence of a hydrosilane reductant, phosphine-ligated CuH species are typically very active catalysts for the 1,2-reduction of carbonyl functional groups, such as ketones and aldehydes.[18] This propensity for efficient carbonyl reduction presents a major challenge in the development of the proposed methodology (Scheme 1b), as hydrocupration of an alkene must occur in the presence of a carbonyl electrophile. Variation of the electronic, steric, and coordinating properties of the activating group provides an opportunity to achieve the desired chemoselectivity. A highly stereoselective process is further contingent on avoiding ketone racemization.

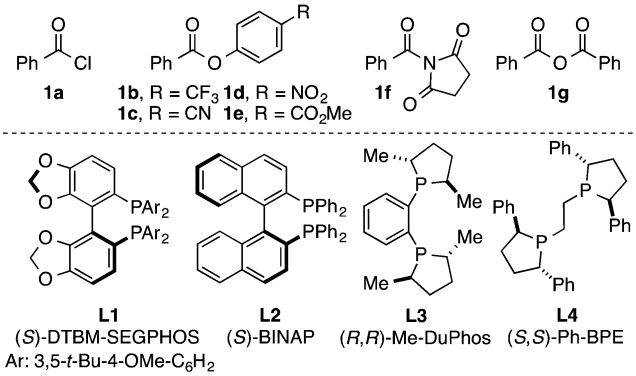
We began our studies with an examination of the reductive coupling of styrene (**2a**) to benzoyl electrophiles to yield chiral alcohol product (**4a**). Based on our catalyst system for enantioselective hydroamination, we initially employed a mixture of $Cu(OAc)_2$ (2 mol %), (*S*)-DTBM-SEGPHOS phosphine ligand (**L1**, 2.2 mol %), and dimethoxymethylsilane (DMMS) in THF.[12] Most of the electrophiles examined (**1a**–**f**) failed to react or underwent rapid reduction to form benzyl alcohol (Table 1, entries 1–6). When benzoic anhydride (**1g**) was used, 25% of the desired product was formed with high selectivity, but benzyl alcohol was still the major product (entry 7). Use of other biaryl-based diphosphine ligands, such as (*S*)-BINAP (**L2**), did not yield any product (entry 8), while monoaryl diphoshine (*R*,*R*)-Me-DuPhos (**L3**) increased the yield to 45% with drastically reduced stereoselectivity (entry 9). The trialkyl diphosphine (*S*,*S*)-Ph-BPE (**L4**) proved to be the optimal supporting ligand, increasing the yield to 77% with high selectivity (entry 10). The yield was further increased to 91% when (*S*,*S*)-Ph-BPE was used with added PPh_3 (2.2 mol %) as a secondary ligand, yielding the desired product in >20:1 dr and 94% ee (entry 11).[19]

The scope of the optimized coupling process was next explored using symmetrical aryl carboxylic anhydrides (Table 2). Many functional groups, such as esters (**4b**), nitriles (**4c**), phenols (**4d**), substituted alkenes (**4e**), carbamates (**4h**), and

Table 1. Optimization of Chiral Alcohol Synthesis via Styrene Reductive Coupling with Benzoyl Electrophiles[a]

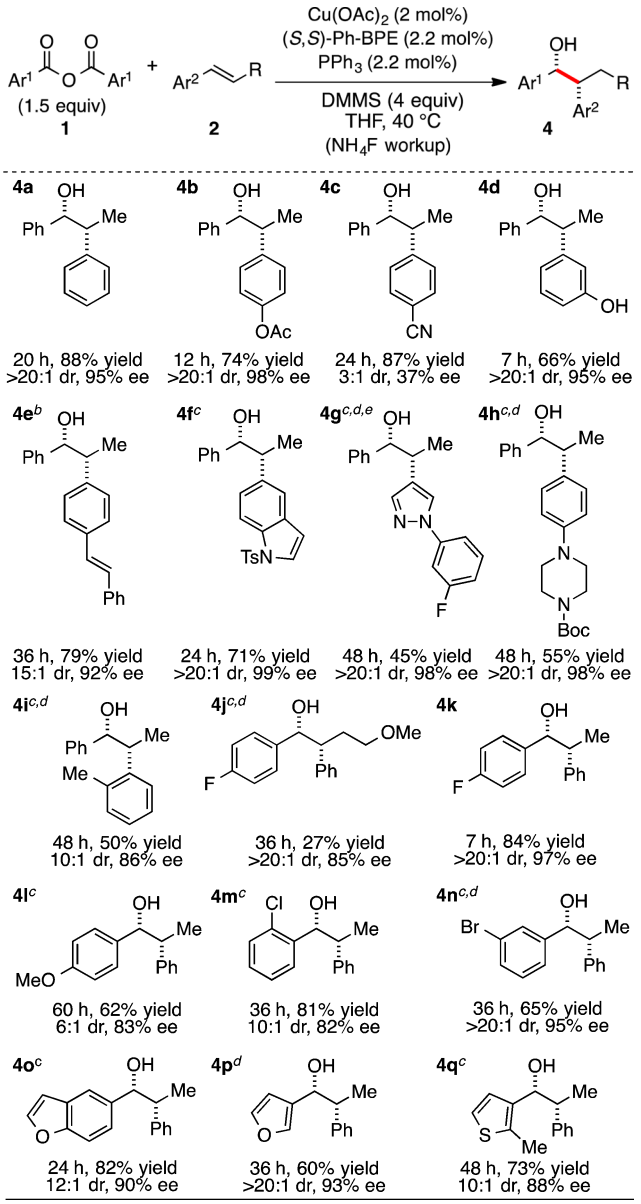


entry	L	PhCOX	yield, **4a** (%)	dr (syn:anti)	ee (%)
1	**L1**	**1a**	0	-	-
2	**L1**	**1b**	0	-	-
3	**L1**	**1c**	0	-	-
4	**L1**	**1d**	0	-	-
5	**L1**	**1e**	0	-	-
6	**L1**	**1f**	0	-	-
7	**L1**	**1g**	25	>20:1	-95
8	**L2**	**1g**	0	-	-
9	**L3**	**1g**	45	8:1	7
10	**L4**	**1g**	77	>20:1	94
11	**L4** + PPh_3	**1g**	91	>20:1	94



[a]Yields and dr determined by ^{1}H NMR analysis of crude reaction mixture; enantioselectivity determined of the purified alcohol product after treatment with NH_4F in MeOH.

Table 2. Alcohol Synthesis Substrate Scope[a]



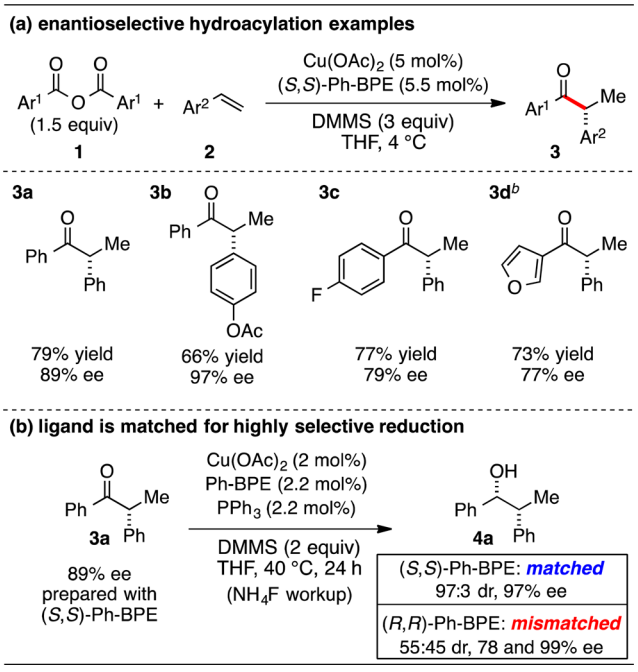
[a]All yields represent average isolated yields of two runs performed with 1 mmol of alkene; dr determined by ^{1}H NMR analysis of crude reaction material. [b]Reaction run at ambient temperature. [c]2.0 equiv of anhydride used. [d]4 mol % catalyst used. [e]Bz_2O added over 4 h, ^{1}H NMR yield, product isolated and characterized as the acylated alcohol.

DOI: 10.1021/jacs.6b03086
J. Am. Chem. Soc. 2016, 138, 5821–5824

aryl halides (**4k**, **4m**, and **4n**), are compatible with this transformation. With electron-neutral and electron-rich aryl alkenes, alcohol products are typically formed in moderate to good yield (45−88%) with >20:1 dr and >95% ee. However, highly electron-deficient styrenes, such as 4-cyanostyrene (**4c**), led to products in good yield but with low selectivity, possibly due to racemization of the more acidic ketone intermediate formed upon hydroacylation. *ortho*- and *β*-Substitution is tolerated on the aryl alkene component (**4i** and **4j**), but product yields are decreased as direct anhydride reduction competes with hydrocupration of these more encumbered alkene substrates. For the anhydride component, electron-rich (**4l**), electron-poor (**4k**), and *ortho*-substituted (**4m**) substrates are all competent coupling partners. Furthermore, good yields and selectivities were obtained with a range of substrates containing heterocyclic fragments, including indoles (**4f**), pyrazoles (**4g**), piperazines (**4h**), benzofurans (**4o**), furans (**4p**), and thiophenes (**4q**). Under the current reaction conditions, alkyl carboxylic anhydrides do not engage in the coupling reaction and are instead directly reduced by the CuH catalyst, a current limitation of this system.

A useful feature of this methodology is the ability to selectively access chiral ketones or alcohols by controlling the relative rates of hydroacylation and carbonyl reduction. We have qualitatively observed that 1,2-reduction occurs more slowly than the hydroacylation process, and when the reaction is conducted at a lower temperature, ketone products can be isolated in good yields.[20] Scheme 2a shows several examples of this formal enantioselective hydroacylation protocol. With styrene, ketones are isolated with moderate to good enantioselectivity (77−89% ee) (**3a**, **3c**, and **3d**). Employing the more electron-rich 4-acetoxystyrene as a substrate enabled the respective ketone product to be produced with high enantioselectivity (**3b**, 97% ee).

Scheme 2. (a) Enantioselective Ketone Synthesis and (b) Reduction[a]



[a]All yields represent average isolated yields of two runs performed with 1 mmol of alkene. [b]Reaction run at ambient temperature.

At the outset of this project, we questioned whether the chirality of the L*CuH catalyst would be matched for both transformations (hydroacylation and 1,2-reduction). To examine this aspect, chiral ketone **3a**, which was produced in 89% ee using (*S*,*S*)-Ph-BPE ligand, was reduced under the standard reaction conditions using both antipodes of the Ph-BPE ligand.[21] The (*S*,*S*)-Ph-BPE system yielded alcohol in 97:3 dr with 97% ee, while the use of (*R*,*R*)-Ph-BPE ligand delivered alcohol in 55:45 dr with 78 and 99% ee, respectively. These results indicate that a matched/mismatched case is evident for ketone reduction and that the ligand used is stereomatched for hydroacylation and reduction. This phenomenon provides an opportunity for further enantioenrichment of the final alcohol product, as demonstrated with the typically high levels of enantiopurity (>90% ee) observed for the alcohol products in Table 2.[22]

In summary, we have developed a new protocol for the enantioselective reductive coupling of aryl alkenes with aryl carboxylic anhydrides for selective access to either chiral ketones or alcohols. This process is enabled through dual catalytic cycles wherein a chiral L*CuH catalyst first promotes enantioselective hydroacylation, while a slower diastereoselective ketone reduction process delivers the alcohol product with further enantioenrichment. A wide range of functional groups and heterocycles are tolerated, and ongoing work is aimed at expanding this methodology to less activated alkenes and aliphatic carboxylic acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03086.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Research reported in this publication was supported by the National Institutes of Health (GM46059). We thank the NIH for a postdoctoral fellowship for J.S.B. (GM112197) and the Danish Council for Independent Research, Technology and Production Sciences for a postdoctoral fellowship for E.A. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We also thank Drs. Michael Pirnot and Yiming Wang for advice on the preparation of this manuscript.

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