

## Communication

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Christopher A. Discolo, Eric E. Touney, and Sergey V. Pronin

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# Catalytic asymmetric radical-polar crossover hydroalkoxylation

Christopher A. Discolo<sup>‡</sup>, Eric E. Touney<sup>‡</sup>, and Sergey V. Pronin<sup>\*</sup>

Department of Chemistry, University of California, Irvine, California 92697-2025, United States

Supporting Information Placeholder

**ABSTRACT:** Asymmetric intramolecular hydrofunctionalization of tertiary allylic alcohols is described. This metal hydride-mediated catalytic radical-polar crossover reaction delivers corresponding epoxides in good to high enantioselectivity and constitutes the first example of asymmetric hydrogen atom transfer-initiated process. A series of modified cobalt salen complexes has proven optimal for achieving good efficiency and asymmetric induction. Experimental data suggest that cationic cobalt complexes may be involved in the enantio-determining step, where cation– $\pi$  interactions in the catalyst contribute to the asymmetric induction.

Metal hydride-initiated radical reactions serve as a highly chemoselective means for Markovnikov hydrofunctionalization of under alkenes mild conditions.<sup>1,2</sup> The intermediate carbon-centered radicals generated upon hydrogen atom transfer (HAT)<sup>3</sup> to a carbon-carbon double bond can react with atom and group transfer reagents,<sup>4</sup> undergo addition to multiple bonds,<sup>5</sup> and participate in cross-coupling reactions<sup>6</sup> to introduce new functional groups and structural motifs. However, corresponding stereoselective processes are represented almost exclusively by the instances of stereochemical relay, including examples of auxiliarycontrolled hydration and hydrohydrazination of  $\alpha$ . $\beta$ unsaturated amides.<sup>2,7</sup> These limitations are not surprising due to the inherent challenge associated with enantiodifferentiation in prochiral alkyl radical intermediates.<sup>8</sup> In this context, early reports of a highly selective cis addition of putative cobalt(III) hydride intermediates<sup>9</sup> to 1,2-disubstituted alkenes involving rapid collapse of a radical pair in a solvent cage constitute the only relevant instances of efficient stereocontrol.<sup>10,11</sup> Here we show the first example of a highly enantioselective HAT-initiated hydrofunctionalization (Figure 1). This radical-polar crossover process is catalyzed by a series of modified cobalt salen complexes and allows for conversion of tertiary allylic alcohols to the corresponding enantioenriched epoxides. We present data suggesting that cationic cobalt complexes may be involved in the enantio-determining step,



**Figure 1.** Catalysis by alkylcobalt(IV) complexes allows for efficient asymmetric induction in HAT-initiated hydrofunctionalizations.

where cation– $\pi$  interactions in the catalyst contribute to the asymmetric induction. We also demonstrate the application of this chemistry in a formal Markovnikov hydrofunctionalization of tertiary allylic alcohols for enantioselective installation of trisubstituted stereocenters including those bearing amine, sulfide, and nitrile functionalities.

Building on the earlier work in the field,<sup>12</sup> we recently reported HAT-initiated radical-polar crossover reactions of tertiary allylic alcohols that afforded corresponding epoxides and semipinacol rearrangement products.<sup>13</sup> In that setting, the outcome of the hydrofunctionalization event was under strong catalyst control, which suggested participation of alkylcobalt complexes as electrophilic intermediates.<sup>14</sup> We reasoned that a proper choice of a scalemic chiral catalyst would allow for efficient enantioinduction provided that generation of the product could be limited to the putative alkylcobalt-based pathway. Initial experiments with tetrahydropyran derivative 1 and enantioenriched complex 4, which had previously proven competent in the HAT-initiated synthesis of epoxides,<sup>13</sup> delivered product **2** with low but measurable enantiomeric excess (Table 1). Extensive modifications experimentation with in the ethylenediamine-derived fragment led to identification of a series of o-biaryl-substituted complexes that delivered the desired product with improved levels of asymmetric induction. Thus, application of complex 5 delivered epoxide 2 with moderate enantioenrichment. Introduction of extended aromatic motifs in the *o*-biaryl substituent (e.g., complexes 6 and 7) allowed for significant enhancement of enantioselectivity and a complementary increase in the efficiency. Ultimately, dibenzofuran-containing complex 8

Table 1. Effect of the Catalyst Structure on theEnantioenrichment and Yield of Epoxide 2<sup>a,b</sup>



<sup>a</sup>Reaction time was 18 h, catalysts **4–8** were  $\geq$ 95% ee; see SI for details. <sup>b</sup>Yields were based on internal standard and determined by <sup>1</sup>H NMR, see SI for details. <sup>c</sup>Reaction with 0.5 mol% of catalyst **8** afforded 51% yield (65% conversion of alcohol **1**) after 48 h.

demonstrated optimal performance among the evaluated catalysts.<sup>15</sup> The process could also be conducted at low catalyst loadings without detrimental effects on the enantioselectivity, but required extended reaction times to achieve appreciable conversion of alcohol **1**.

Brief exploration of the substrate scope identified a

 Table 2. Preliminary Substrate Scope of the HAT-Initiated

 Enantioselective Hydrofunctionalization<sup>a</sup>









<sup>a</sup>0.05 M of allylic alcohol; see SI for details. <sup>b</sup>Reaction time was 18 h. <sup>c</sup>Yields were based on internal standard and determined by <sup>1</sup>H NMR. <sup>d</sup>Yield of isolated material for characterization purposes was 48%. <sup>e</sup>Absolute configuration was determined by X-ray crystallographic analysis. <sup>f</sup>Reaction time was 48 h. <sup>g</sup>At –60 °C. <sup>h</sup>Yield of isolated material for characterization purposes was 38%. <sup>i</sup>Epoxide was not observed.

series of cyclic dialkyl(vinyl)carbinols that successfully participated in our enantioselective HAT-initiated hydro-functionalization. Thus, derivatives of tetrahydropyran and piperidine (products **2**, Table 1, and

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9–11. Table 2) and their bicyclic counterparts (products 12 and 13) underwent conversion to the corresponding epoxides with good to high levels of asymmetric induction. Single-crystal X-ray analysis of product 11 established the absolute configuration of the newly formed stereocenter to be R, which is likely shared with other enantioenriched epoxides obtained in this study. Similarly good performance was observed with various functionalized cyclohexanes (products 14-20). Simple cyclohexanes including those containing only alkyl substituents (products 21–23) produced low to moderate degrees of enantioinduction. Application of acyclic substrates was unsuccessful (e.g., product 24). Attempted reactions of cycloalkanols containing fiveand seven-membered rings led to the corresponding semipinacol rearrangement products (e.g., 25 and 26),<sup>16</sup> which were produced with low levels of stereocontrol.

Analysis of the differential activation parameters in the hydrofunctionalization of allylic alcohol 1 in the presence of catalysts **5–8** revealed that enantioselectivity was enthalpically controlled and the magnitude of differential enthalpy correlated positively with the expanse of the aromatic moieties (Table 3).<sup>17</sup> This enthalpic gain

 Table 3. Eyring Analysis of Enantioselectivity in the

 Hydrofunctionalization of Allylic Alcohol 1<sup>a</sup>

ОН	5 mol% <i>catalys</i> 3 equiv. <b>3</b> 3 equiv. PhSiH <sub>2</sub> M (CD <sub>3</sub> ) <sub>2</sub> CO		Me OTf Me He He He He
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catalyst	R-squared	⊿⊿H <sup>‡</sup> (kcal/mol)	∆∆S <sup>‡</sup> (cal/mol•K)
5	0.98	-1.82 ± 0.07	-4.9 ± 0.2
6	0.99	-3.28 ± 0.07	-9.5 ± 0.2
7	0.99	-5.38 ± 0.27	$-17.2 \pm 0.9$
8	0.99	-6.54 ± 0.23	$-20.7 \pm 0.7$

<sup>a</sup>Based on six data points per catalyst, T = 233-292 K, see SI for details.

was attenuated by the corresponding increase in the differential entropy terms observed across the series of catalysts 5–8. These data are in principle consistent with a simple steric explanation that increasing the size of the arene fragment leads to destabilization of the minor transition state assembly in the enantio-determining step. However, current understanding of the electronic structure of relevant cobalt complexes also suggests an intriguing possibility for the role of stabilizing noncovalent interactions in the observed effects. Previous computational studies spectroscopic and of alkylcobalt(IV) glyoximates, porphyrins, and corrins as well as cobalt(III) salen derivatives indicate that radical cations resulting from ligand-to-metal charge transfer can contribute to the electronic structure.<sup>18,19</sup> We therefore proposed that cationic cobalt complexes may experience cation– $\pi$  interactions between the radical cation of the salen motif and the biaryl substituents of the ethylenediamine-based fragment (Figure 2).<sup>20</sup> In this setting, extension of the participating arenes would lead to more stabilizing interactions and their energetic benefits would be manifested enthalpically.<sup>21</sup> We found that enantioselectivity correlated strongly with both the polarizability and the quadrupole moment of the aromatic hydrocarbons correspon-



**Figure 2.** Representation of a radical cation of the putative alkylcobalt(IV) intermediate derived from catalyst **8** and substrate **1** (**L** is likely to be solvent). Red dotted lines indicate the proposed cation– $\pi$  interactions between the radical cation of the salen motif and the biaryl substituents.

ding to the varied substituents in complexes 5-7.22 Since the strength of cation $-\pi$  interactions should primarily be a function of electrostatic and dispersion forces,<sup>23,24</sup> the observed correlations between the underlying physical properties and the degree of asymmetric induction suggest that cation- $\pi$  interactions contribute to the improved stereochemical outcomes. Should the effect of the substituents be largely steric in nature, such significant correlations would not be expected.<sup>17,25</sup> This proposal is also consistent with the observation that introduction of electron-rich arenes results in additional enhancement of enantioselectivity (e.g., compare complexes 7 and 8).<sup>26</sup> We note that continued expansion of the aromatic moieties (e.g., introduction of pyrenyl and triphenylenyl groups) becomes detrimental to the performance of the catalyst. We attribute this effect to increasing steric interactions between the biaryl fragments and the bulky tert-butyl substitutents of the hydroxynaphthaldehyde-derived motif, which could lead to disruption of the cation $-\pi$  interactions.

Analysis of structural features found in the wellperforming allylic alcohols (see Table 2) revealed additional correlations. The presence of properly positioned heteroatom-containing substituents appears to result in superior enantioselectivity during the epoxide formation. For example, functionalized epoxides **18–20** were produced with good enantioselectivities.<sup>27</sup> In contrast, epoxides **21–23** were obtained with significantly lower asymmetric induction under identical conditions, suggesting that steric factors are not the sole determinant in enantioselectivity. The superior outcomes observed with products **18–20** may stem from additional stabilizing interactions between the functionalized cyclohexane fragment and the radical cation of the cobalt salen motif in the enantio-determining step. Similar considerations should be applicable in the cases of products  $2, 9-17.^{28}$ 

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Taken all together, these observations suggest involvement of cationic cobalt complexes in the enantiodetermining step. For example, diastereomeric alkylcobalt(IV) intermediates may undergo kinetic resolution<sup>29</sup> during the intramolecular nucleophilic displacement (see equation 1). In this scenario, an increase in the cation– $\pi$  interactions in the catalyst would stabilize the electrophiles, leading to a later transition state and enhanced



enantioselectivity. Additional interactions between the heteroatom-containing substituents of the wellperforming substrates and the radical cation of the salen motif would have a similar effect on the displacement. Diastereomeric alkylcobalt(IV) intermediates may interconvert upon epimerization of the stereocenter bearing the homolytically-labile carbon-cobalt bond.<sup>30</sup> Relevant rearrangements of alkyl substituents in organocobalt complexes were previously demonstrated to proceed via a radical chain mechanism.<sup>31</sup> Formation of alkylcobalt(IV) intermediates may involve oxidation of the corresponding alkylcobalt(III) complexes,<sup>14</sup> which can be generated via HAT from the putative cobalt(III) hydride intermediates to alkenes followed by radical pair collapse.<sup>32,33</sup> An alternative scenario may involve enantio-determining diffusion of alkyl radicals into the solvent cage during the capture by cationic cobalt(III) complexes en route to the corresponding alkylcobalt(IV) intermediates.<sup>34–36</sup> Both scenarios are also consistent with the superior performance of polar solvents: cyclization of allylic alcohol 1 in the presence of catalyst 8 produces epoxide 2 only in 26% ee when acetone is replaced with dichloromethane.

Combination of our HAT-initiated cyclization of dialkyl(vinyl)carbinols with the well-established reactivity of trisubstituted epoxides in  $S_N2$  reactions provides an entry into a formal enantioselective hydrofunctionalization of tertiary allylic alcohols with Markovnikov selectivity. Thus, reaction of epoxide 11 with Boc-protected piperazine produced aminoalcohol 27 in high yield (Scheme 1). Related structural motifs previously found

#### Scheme 1. Derivatization of Epoxide 11



application in medicinal chemistry efforts.<sup>37</sup> Similar displacements with a thiolate, an allyl Grignard reagent, and Nagata's reagent delivered corresponding sulfide **28**, alkene **29**, and nitrile **30**, respectively, with good efficiency. In all cases, excellent levels of stereoinversion were observed, demonstrating potential of this approach in the enantioselective synthesis of polyfunctional building blocks.

In summary, we show the first example of a highly enantioselective HAT-initiated hydrofunctionalization catalyzed by a series of new cobalt salen complexes. Our observations are consistent with the proposed participation of alkylcobalt(IV) complexes, which accounts for strong catalyst control and allows for direct conversion of dialkyl(vinyl)carbinols to the corresponding scalemic epoxides. The experimental data suggest that cationic cobalt complexes may be involved in enantio-determining step, where cation $-\pi$  interactions in the catalyst contribute to the superior asymmetric induction obtained with the new cobalt salen derivatives. The radical-polar crossover reactivity described herein is expected to serve as a starting point for overcoming the challenges of absolute stereocontrol in the development of asymmetric HAT-initiated processes and for future studies of the mechanistic underpinnings associated with this fascinating class of chemical transformations.<sup>38</sup>

#### ASSOCIATED CONTENT

Experimental procedures, characterization data for new compounds, and CIF file for compound **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

## **Corresponding Author**

spronin@uci.edu

#### **Author Contributions**

<sup>‡</sup>These authors contributed equally.

#### Notes

The authors declare no competing financial interest.

#### ACKNOWLEDGMENT

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