Communication

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An Enantioselective Cross Dehydrogenative Coupling Catalysis Approach to Substituted Tetrahydropyrans

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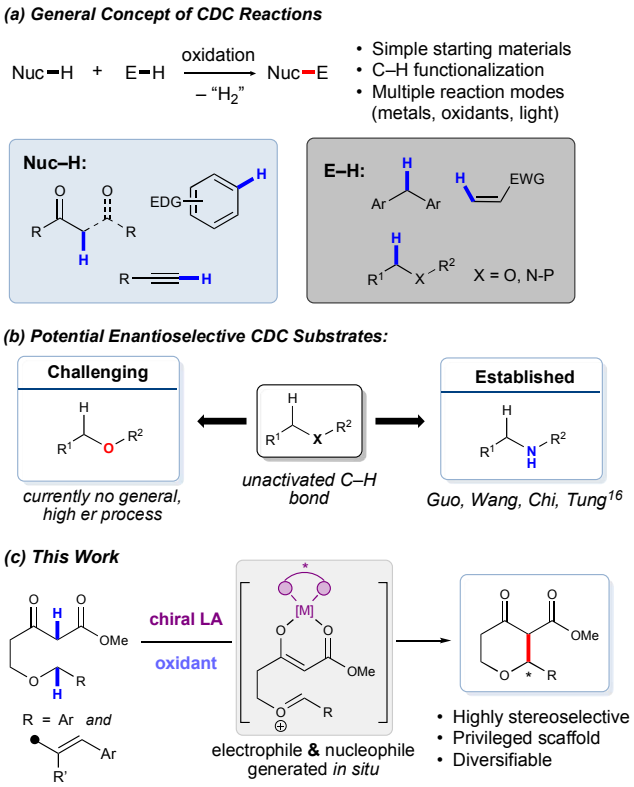
An enantioselective cross-dehydrogenative coupling (CDC) reaction to access tetrahydropyrans has been developed. This process combines *in situ* Lewis acid activation of a nucleophile in concert with the oxidative formation of a transient oxocarbenium electrophile, leading to a productive and highly enantioselective CDC. These advances represent one of the first successful applications of CDC for the enantioselective couplings of unfunctionalized ethers. This system provides efficient access to valuable THP motifs found in many natural products and bioactive small molecules.

Tetrahydropyrans (THPs) are key structural elements in numerous bioactive natural products and medicinally relevant compounds.[1] Due to the prevalence of THPs, multiple stereoselective processes have been developed for their construction, including Prins cyclizations,[2] hetero-Diels-Alder reactions,[3] and intramolecular nucleophilic conjugate additions.[4] Established methods to construct THPs in an enantioselective fashion typically focus on conjugate additions[5] or activation by enamine/iminium intermediates,[6] two approaches that are deployed extensively in total synthesis. Inspired by natural product targets of interest in our laboratory, as well as small molecules possessing intriguing biological activity, we envisioned a complementary and direct method for the enantioselective synthesis of substituted tetrahydropyran-4-ones. We have disclosed the use of β-hydroxy dioxinones as nucleophiles with aldehydes and isatins to undergo mild and stereoselective cyclizations in the presence of catalytic Lewis or Brønsted acids to access enantioenriched THPs.[7] Our efforts in this area have enabled total syntheses of various natural products including exiguolide,[8] neopeltolide,[9] okilactomycin,[10] and other naturally occurring compounds containing THPs.[11] Conceptually, moving beyond preformed nucleophiles such as dioxinones to simple β-ketoester systems presents opportunities for enantiocontrol, most likely through two-point/chelate binding, but also requires different activation modes to operate simultaneously in a single reaction flask.

Scheme 1. CDC Processes and Reaction Design

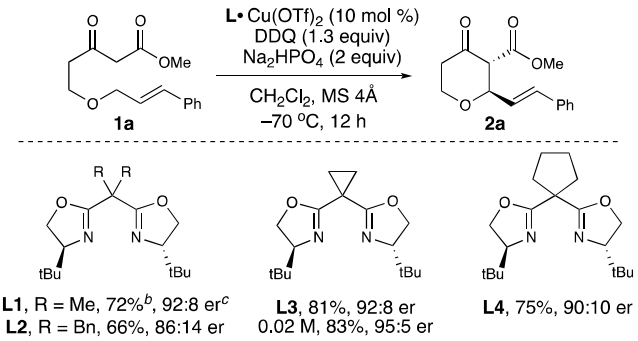


Cross-dehydrogenative coupling (CDC) reactions have emerged as powerful approaches to forge C–C bonds from inert C–H bonds.[12] As a subset of C–H functionalization processes,[13] CDC reactions are attractive because they do not require prefunctionalized starting materials, relying instead on oxidative

activation followed by net loss of H_2 to facilitate C–C bond formation. Specifically, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) a strong oxidizing agent, promotes the formation of stabilized carbocations by benzylic and allylic C–H bond activation, and subsequent C–C bond formation.[14] Mechanistically, DDQ mediated CDC reactions proceed via single electron transfer to form stabilized radical cations, followed by hydrogen atom abstraction to form the electrophilic coupling partner (e.g., oxocarbenium ion, iminium ion). Floreancig has effectively demonstrated that DDQ activation can facilitate racemic access to carbocycles and heterocycles via the oxidation of allylic ethers.[15] Although enantioselective CDC reactions have been reported during the last decade,[16] there is a dearth of highly enantioselective CDC reactions using oxocarbenium ion electrophiles in contrast to a plethora of enantioselective CDC reactions using iminium electrophiles (Scheme 1b).[17] A major challenge to this approach is successfully integrating strongly oxidative conditions for oxocarbenium ion formation (e.g., DDQ) with stereodefining catalysts necessary for nucleophile activation (e.g., chiral Lewis acids) to a) promote a productive reaction, and b) induce stereocontrol around a transient, highly reactive oxocarbenium ion. Herein we report an enantioselective CDC of β-ketoesters with oxocarbenium ions to access substituted tetrahydropyrans with high yields and enantioselectivity through a merged chiral Lewis acid/oxidation strategy (Scheme 1c).

We initiated our investigations of this chiral Lewis acid/oxidant process using β-ketoester substrate **1a** and found that Cu(II)-bisoxazoline (BOX) complex **L1**•$Cu(OTf)_2$ gave the desired product **2a** as the sole diastereomer in 72% yield and 92:8 er at –70 ºC (Scheme 2). Additional screening with chiral BOX ligands **L2–L5** identified ligand **L3** as optimal, furnishing **2a** in 83% yield and 95:5 er upon further reaction dilution to 0.02 M. Finally, substrates bearing more sterically encumbered esters were screened with no improvement in observed stereoselectivity (see Supp. Info.).

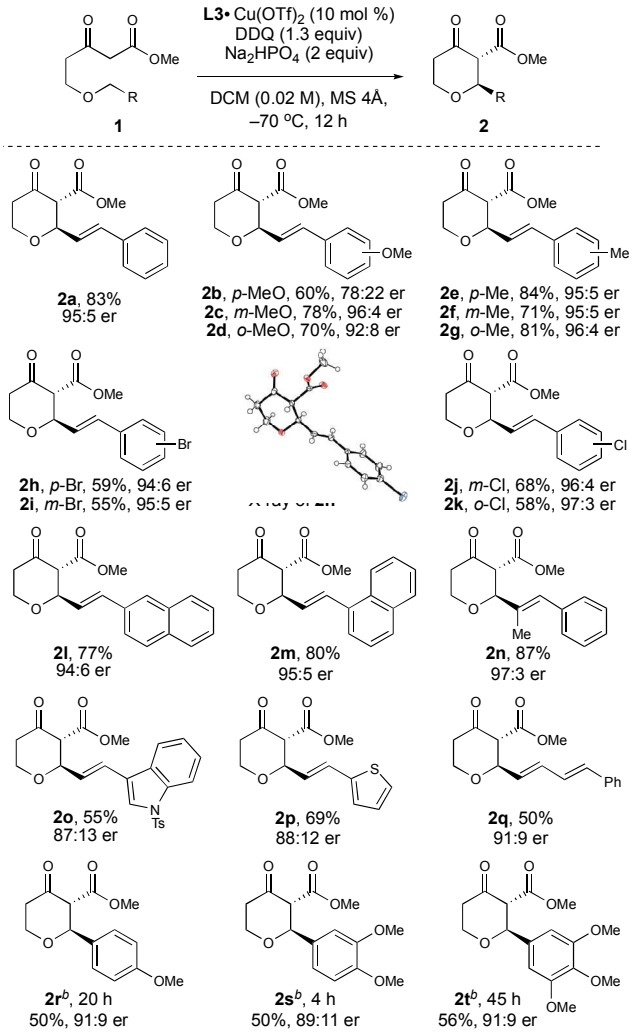
Scheme 2. Ligand Screening for CDC Reactions[a]



[a]The reactions were performed with **1a** (0.2 mmol), **L**•$Cu(OTf)_2$ (10 mol %), DDQ (0.26 mmol), Na_2HPO_4 (0.4 mmol), and MS 4Å (250 mg) in CH_2Cl_2 (0.04 M). Absolute configuration of **2a** was determined based on X-ray crystal analysis of **2h**.[18] [b]Yield of isolated product. [c]Determined by chiral-phase SFC analysis.

After optimization the basic asymmetric CDC reaction with β-ketoester **1a**, the general scope was explored (Table 1). When the aromatic ring on the cinnamyl ether was substituted with electron-donating groups at its *para*, *meta*, or *ortho* position, the reactions provided desirable tetrahydropyran-4-ones **2c–2g** in high yields and stereoselectivity with exception of **2b**. We observed that substrate **1b** possessing a *p*-methoxycinnamyl group produced side products due to over-oxidation. Furthermore, reaction of **1b** without a Cu(II) catalyst produced *rac*-**2b** in 70% yield in only 1 hour, suggesting the competitive background reaction of this highly reactive substrate also contributed to the observed reduction in stereoselectivity.

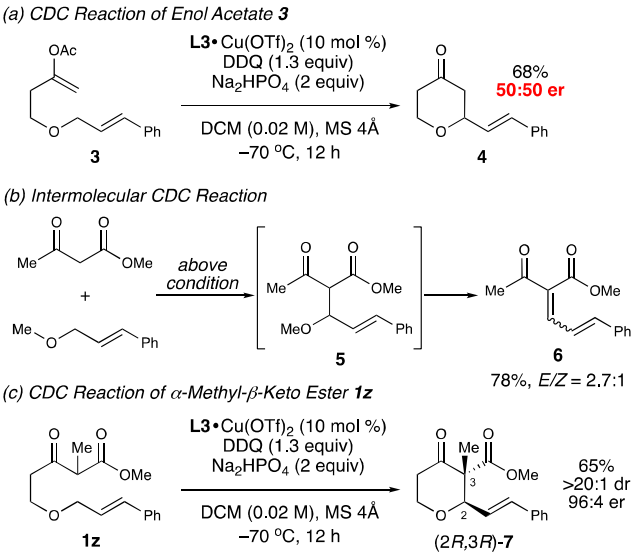
Table 1. Substrate Scope of β-Keto Esters 1[a]



[a]See Supp. Info. for reaction details. Er determined by chiral-phase SFC analysis. Products **2** were obtained with >20:1 dr (trans/cis). [b]Performed at –30 ºC.

We then evaluated substrates substituted with electron-withdrawing groups at *para*, *meta*, and *ortho* positions. The reactions of **1h–1k** provided desired products **2h–2k** in moderate yields and high stereoselectivity. The results showed that high yields and stereoselectivity were observed for **1l** and **1m** containing naphthyl groups. The reaction of **1n** containing a trisubstituted cinnamyl alkene afforded **2n** in 87% yield and 97:3 er, while heteroaryl and conjugated ethers **1o–1q** gave tetrahydropyran-4-ones **2o–2q** in somewhat decreased yields and stereoselectivities. A survey of benzyl ethers revealed that only 4-methoxy-substituted substrates **1r–1t** were capable of producing desired products **2r–2t** with high stereoselectivity and moderate yield. Under the current conditions, we have not observed productive reactions using propargylic, unsubstituted allylic, alkyl, or ether substrates leading to tetrahydrofurans (i.e., 5 atom tether length). Instead, over-oxidation, resulting in 2,3-dihydropyran-4-one, or no oxidation is observed (see Supp. Info.). However, with this successful proof of concept, investigations with various oxidation methods and Lewis acids to engage an even larger range of substrate classes are ongoing.

Scheme 3. CDC Reaction Extension



Attempts to access enantioenriched tetrahydropyran-4-ones without the β-ketoester were unsuccessful, as enol acetate **3** provided racemic **4** in 68% yield (Scheme 3a). This observation supports the hypothesis that the β-ketoester is crucial for stereoselectivity by coordination with the Cu(II)/BOX catalyst. In an attempt to probe whether an enantioselective *intermolecular* CDC reaction was possible, cinnamyl methyl ether was exposed to methyl acetoacetate in the presence of **L3•**Cu(OTf)$_2$ to afford **5** (Scheme 3b). Although the intermediate oxocarbenium ion could potentially undergo both 1,2- and 1,4-addition, the 1,2-addition adduct **5** was observed (as detected by NMR spectroscopy). Unfortunately, attempts to isolate **5** have been unsuccessful, due to facile elimination of the β-methoxy group to form enone **6** (2.7:1 *E*/*Z* mixture). Lastly, we evaluated α-methyl-β-ketoester **1z**, which would forge a quaternary C-center (Scheme 3c). To our satisfaction, the reaction of **1z** provided the desired (2*R*,3*R*)-**7** in 65% yield (>20:1 dr, 96:4 er)[23] which provides a roadmap for future intermolecular asymmetric CDC reactions.

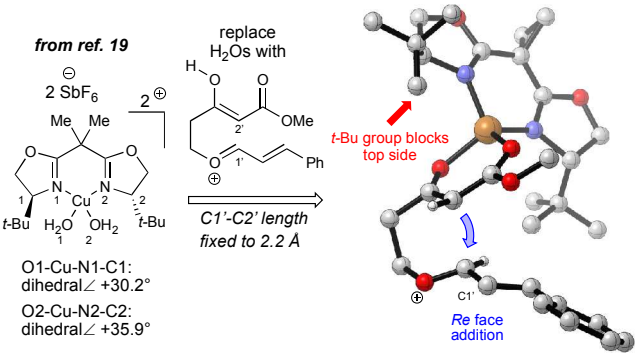
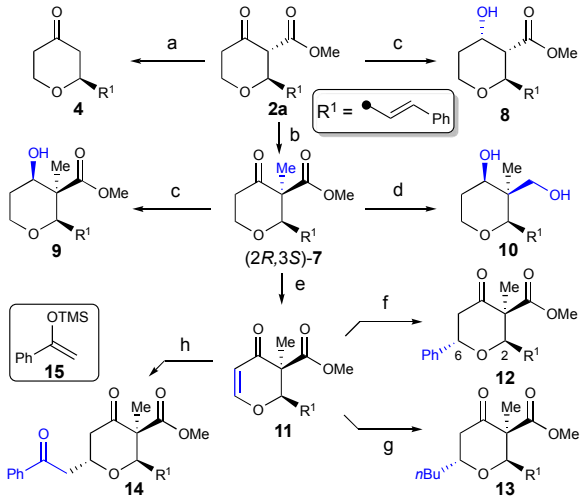


Figure 1. Stereochemical induction model with **1a**/DDQ intermediate (see Supp. Info. for details)

The stereochemical model of the reaction with **1a**, Cu(II)/BOX and DDQ is based on a reported X-ray crystal structure of [**L1**•Cu(H_2O)$_2$](SbF$_6$)$_2$ by replacement of H_2O ligands with the oxocarbenium ion of **1a** (Figure 1).[19] With the oxidized substrate bound to the Cu(II) center via bidentate chelation, the bulky *tert*-butyl group of the **L3**•Cu(II) complex shields the top face of the bound substrate (*Si* face) which in turn places the transient oxocarbenium ion below. During the reaction, the metal-bound enol(ate) adds to the *Re* face of the oxocarbenium ion via a pseudo chair-like conformation to provide product **2a** with *S* configuration at the C1' position, consistent with observed stereochemistry. This model also supports the observed relative C1'-C2' *trans* relationship of the products.

Scheme 4. Transformations of 2a

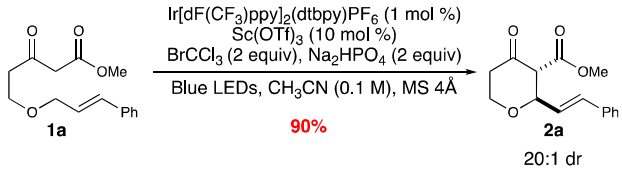


[a]Conditions: (a) DMF/H_2O, 130 ºC, 77% (b) MeI, NaH, 97%, 13:1 dr (c) L-selectride, 64% for **8**, 71% for **9** (d) $LiAlH_4$, 62% (e) Pd(TFA)$_2$, O_2, 67% (f) Rh(cod)$_2$BF$_4$, PhB(OH)$_2$, 75%, 20:1 dr (g) nBu$_2$CuLi, TMSCl, 76%, 20:1 dr (h) **15**, $InCl_3$, 93%, 10:1 dr

A practical advantage of this strategy is the ease of synthetically elaborating these β-keto esters (Scheme 4). Conventional heating in DMF/H_2O provided the decarboxylated product **4** in 77% yield, where methylation of **2a** gave 3,3-disubstituted tetrahydropyran-4-one (2*R*,3*S*)-**7** in excellent yield with 13:1 dr.[23] Exposure of β-ketoesters **2a** or **7** to L-selectride provided the corresponding tetrahydropyran-4-ol **8** or **9**, while $LiAlH_4$ reduction of **7** furnished diol **10**.[20] Functionalization of the 6-position of the **7** has also been demonstrated. First, cyclic enone **11** was prepared via dehydrogenation using 1 atm of O_2 in the presence of Pd(TFA)$_2$ in DMSO.[21] Rh(I)-catalyzed 1,4-addition of phenylboronic acid produced **12**,[22] and conjugate addition of an alkyl cuprate provided **13** as the *trans* diastereomers in both reactions.[20,23] Lastly, a Mukaiyama-Michael addition proceeded to afford **14** with 10:1 diasteromeric ratio.[23,24] Notably, while many synthetic methods exist for *cis*-2,6-tetrahydropyran structures,[25] there are far fewer preparations for *trans*-2,6-tetrahydropyrans.[26]

To substitute DDQ as a reagent, we investigated complementary oxidation processes to form the oxocarbenium ion. A recent report of photoredox catalysis being used to generate oxocarbenium ions[27] inspired us to leverage this approach and trap the oxocarbenium ion with our tethered carbon nucleophile. Gratifyingly, the use of Sc(OTf)$_3$, Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$, blue LEDs, and bromochloroform provided access to *rac*-**2a** in 90% yield (Scheme 5). To date, these photoredox conditions are not yet compatible with various chiral ligands to induce enantioselectivity.[28]

Scheme 5. Photoredox-Catalyzed CDC Reaction



In summary, a chiral Lewis acid-catalyzed intramolecular cross-dehydrogenative coupling of β-ketoesters has been developed. This oxidative process utilizes unfunctionalized starting materials to provide chiral 2-substituted tetrahydropyrans with excellent yields and stereoselectivity. The *in situ* generation of both nucleophilic and electrophilic partners specifically provides new opportunities for enantioselective oxocarbenium ion-driven reactions and CDC processes in general. Investigations in our laboratory towards leveraging this chiral Lewis acid/oxidation system with new substrate classes as well as the use of visible light mediated oxidation in asymmetric transformations are currently underway.

ASSOCIATED CONTENT

Supp. Info. Experimental procedures and spectroscopic, and crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) CCDC 1817530 (**2h**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystalographic Data Centre.
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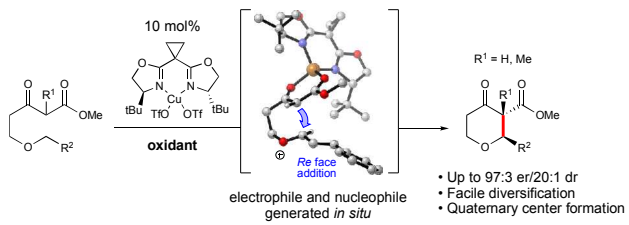
10 mol%
oxidant
Re face addition
electrophile and nucleophile generated in situ
R1 = H, Me
• Up to 97:3 er/20:1 dr
• Facile diversification
• Quaternary center formation