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A Cooperative Hydrogen Bond Donor/Brønsted Acid System for the Enantioselective Synthesis of Tetrahydropyrans

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Abstract

Carbocations stabilized by adjacent oxygen atoms are useful reactive intermediates involved in fundamental chemical transformations. These oxocarbenium ions typically lack sufficient electron density to engage established chiral Brønsted or Lewis acid catalysts, presenting a major challenge to their widespread application in asymmetric catalysis. Leading methods for selectivity operate primarily through electrostatic pairing between the oxocarbenium ion and a chiral counterion. A general approach to new enantioselective transformations of oxocarbenium ions requires novel strategies that address the weak binding capabilities of these intermediates. We demonstrate herein a novel cooperative catalysis system for selective reactions with oxocarbenium ions. This new strategy has been applied to a highly selective and rapid *oxa*-Pictet-Spengler reaction and highlights a powerful combination of an achiral hydrogen bond donor with a chiral Brønsted acid.

Graphical Abstract:

A novel, cooperative catalytic method for the asymmetric *oxa*-Pictet-Spengler reaction has been developed. This method, demonstrated in the synthesis of substituted tetrahydropyranoindoles, has enabled a six-step asymmetric synthesis of (–)-coixspirolactam C.

Keywords

cooperative catalysis; oxocarbenium ion; chiral phosphoric acid; hydrogen bonding; aryl urea

Oxygen-stabilized carbocations—oxocarbenium ions—are highly reactive intermediates in many established chemical transformations. These potent electrophiles are typically formed *in situ*, and the control of asymmetric induction in reactions of prochiral oxocarbenium ions

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remains a significant challenge in chemical synthesis. Unlike their nitrogen-stabilized counterparts—iminium ions—to which nucleophilic addition is typically governed by the dual application of hydrogen bonding and catalyst-substrate electrostatic interactions,^[1] oxocarbenium ions have been manipulated predominantly via electrostatic interactions (Fig. 1A).^[2] Prevailing perceptions regarding the relatively weak electrostatic interaction between organic oxocarbenium/counterion complexes have contributed to a dearth of methods for asymmetric oxocarbenium ion chemistry, though these notions have been challenged in recent years.^[3]

Pioneering work by Jacobsen detailed the ability of urea-based chiral anion-receptor catalysts to promote the enantioselective addition of silyl ketene acetals to oxocarbenium ions generated *in situ*.^[4] This report has been followed by several applications of chiral anion-binding catalysts in asymmetric reactions invoking oxocarbenium ion intermediates, though these reports are only known to be compatible with substrates that produce stabilized, conjugated ionic intermediates (e.g., benzylic or aromatic (pyrylium)-type intermediates).^[5]

Brønsted and Lewis acid catalysis are alternative approaches to generate chiral oxocarbenium ions, though the majority of these have similar limitations as anion-binding catalysis, or are constrained to cyclic frameworks.^[6] Notable exceptions include the use of novel highly constrained chiral imidodiphosphate-derived Brønsted acid catalysts pioneered by List, which uniquely engage non-stabilized oxocarbenium precursors in some cases through sequestration of the reactive intermediate.^[7] Several advances have also been made employing chiral nucleophiles with achiral oxocarbenium ion precursors.^[8]

Guided by our ongoing interest in cooperative catalysis and Prins-type heterocycle syntheses,^[9] we hypothesized that an alternative strategy to induce stereocontrol in oxocarbenium additions may be achieved by augmenting the presumed weak electrostatic ion-pairing interactions with favourable hydrogen bonds proximal to the oxocarbenium ion (Fig. 1B). This approach would enable the substrate to recruit chiral co-catalysts^[10] in a self-assembled motif, ultimately controlling the oxocarbenium ion geometry. To this end, we envisioned a reaction design including a hydrogen-bonding co-catalyst geared to cooperatively enhance, define, and prolong the lifetime of substrate-catalyst interactions.

For our initial investigations, we selected the *oxa*-Pictet-Spengler reaction^[11] as a test platform for our hypotheses. To date, only two examples of enantioselective *oxa*-Pictet-Spengler reactions have been reported.^[12] While highly selective, these reactions require several days to achieve acceptable conversions, which is likely attributable to the stability of on-cycle intermediates relative to the higher-energy oxocarbenium ions.^[12b] We recently developed a cooperative catalysis approach to generate oxocarbenium ions through the tandem isomerization-protonation of allyl ethers.^[13] Building on this approach, we set out to develop an asymmetric *oxa*-Pictet-Spengler reaction using tethered ethers as oxocarbenium ion precursors and aryl nucleophiles possessing hydrogen-bonding sites. Herein, we describe a novel cooperative catalytic system that exploits the hydrogen bonding capabilities of ureas in conjunction with a simple chiral phosphoric acid (CPA) catalyst^[14] to facilitate an exceptionally rapid, mild, and enantioselective intramolecular *oxa*-Pictet-Spengler reaction.

This reaction provides novel strategic routes to chiral, heterocyclic motifs that are prevalent in bioactive small molecules (Fig. 1C),^[15] exemplified by the application to the concise total synthesis of the natural product coixspirolactam C.^[16]

Our initial studies of tetrahydropyranoindole (THPI) precursor indole vinyl ethers examined the cyclization of the N-H species catalyzed by a CPA (Fig. 2, entry 1). These early studies found the resulting THPI was produced in low yield (27%), and the product exhibited little-to-no enantioenrichment (51:49 enantiomeric ratio [e.r.]). Based on early work demonstrating the hydrogen-bonding capabilities of CPAs,^[14a] we hypothesized the possibility of mapping the hydrogen bonding observed in iminium ion chemistries to oxocarbenium ions through the use of a pendent hydrogen bond donor (HBD). Initial screens including hydrogen bonding motifs on substrates showed promise (entries 2–3), and the use of R = *bis*-3,5-(trifluoromethyl)carboxamide on *gem*-dimethyl substrates led to an increased e.r. and yield of the product (67%, 68:32; entry 4).

With a new method established to recruit an optimal CPA via hydrogen bonding, we began to explore the capabilities of small molecule co-catalysts to modulate the presumed CPA/substrate complex. Given the Lewis basicity of the CPA phosphate, we anticipated that an exogenous HBD might coordinate to the CPA,^[17] allowing us to readily alter the steric and electronic parameters of the CPA.^[18] Gratifyingly, a screen of hydrogen-bonding additives furnished 1,3-*bis*(3,5-*bis*(trifluoromethyl) phenyl)urea,^[19] which afforded the product in 89% yield with 97:3 e.r. (entry 6). Notably, *the optimal reaction was complete in under 15 minutes (vs 12+ h for the non-HBD processes)*. Omission of the substrate-bound carboxamide is substantially detrimental to this cyclization, dramatically reducing yield and selectivity, (entry 7) whereas blocking the H-bonding site of the indole *N*-carboxamide with a methyl group shut down the reaction altogether (entry 8), underscoring the importance of hydrogen bonding for the efficacy of this process.

With these optimal reaction conditions, we explored the scope of this method (Fig. 3). Halogen-substituted, electron-donating, and electron-deficient indoles were well tolerated in this cyclization exhibiting good to excellent yields with excellent e.r. It is important to note that (5-F)- and (5-CF₃)-substituted indole substrates (**2g** and **2m**) performed admirably, as these electron-withdrawn substitutions have not been shown to generate the corresponding products using other enantioselective approaches.^[12a, 20] Similarly, the 7-methyl product **2h** and oxepine **2j** were smoothly synthesized, though with reduced e.r. We were additionally pleased to find that our optimized conditions efficiently promoted the formation of desmethyl products **2k–2m** with no erosion in enantioselectivity, though with diminished yield presumably due to the absence of Thorpe-Ingold angle compression.^[21] Finally, subjecting terminal vinyl ether analogues of **1** to the cyclization likewise afforded methyl-substituted pyranoindoles in good yield and excellent e.r. (**2n**, **2o**). This cyclization chemistry can also operate in tandem with other synthetic operations, permitting a one-pot ternary catalytic transformation of allyl ether **3** to **2a** via the intermediacy of an iridium hydride catalyst, in 55% yield with 87:13 e.r. (Scheme 1A). While isomerization proceeds at the reaction temperature, the cyclization was found to be slow; it is possible that the urea and CPA coordinate to the iridium catalyst at these temperatures, disrupting the critical H-bonding interactions and reducing reaction efficacy.

We recognized compound **2n** as a potential precursor to coixspirolactam C (**6**)—a natural product isolated from adlay bran that demonstrates mild inhibitory activity against lung and colon cancer cell lines ($IC_{50} = 30\text{--}50\text{ }\mu\text{g/mL}$).^[16] As THPI **2n** exhibits all of the requisite carbon atoms of coixspirolactam C—and most of the desired connectivity—we envisioned a concise synthetic route to the product enabled by our cooperative methodology. Subjecting **2n** (synthesized from tryptophol in 3 steps) to *N*-bromosuccinimide under acidic conditions furnished a 20:1 mixture of spirocycles **4** and **5** as single diastereomers.^[22] Acylated spirocycle **4** was smoothly converted to the free spirooxindole (**5**) by application of lithium hydroxide in $\text{CH}_2\text{Cl}_2/\text{MeOH}$. X-ray analysis confirmed the desired relative stereochemistry of the molecule, and established the absolute stereochemistry of the intermediate (Scheme 1B). This heterocyclic substructure is also present in several bioactive products,^[23] yet there are surprisingly few published methods to access these spirooxindole derivatives.^[24] Studies to oxidize **2n** directly to the natural product through C–H functionalization logic^[25] required examination of multiple oxidation conditions. Ultimately, subjecting **5** to *tert*-butyl hydroperoxide and diacetoxyiodobenzene in nitromethane oxidized the substrate to the desired lactone (**6**, 46% yield)^[26] which matched the spectra (NMR, HRMS) reported for the natural product, but with opposite optical rotation value ($[\alpha]_D^{25} -20.1^\circ$ ($c = 0.074$, MeOH) vs reported $+5.9^\circ$), thus supporting the absolute stereochemical assignment of the natural product.^[27] The overall route comprises the first synthesis of coixspirolactam C in only 6 steps and confirms the reported connectivity.^[16a]

As a result of our experimental observations that the inclusion of a hydrogen bonding urea provides dramatic enhancements to yield, selectivity, and rate, we propose the following reaction pathway (Scheme 2). The substrate recruits the urea and CPA by hydrogen bonding to form a proto-assembled complex. Subsequently, the CPA protonates the substrate enol ether, producing an oxocarbenium ion **I** that is rapidly trapped by the indole C3 position for form spirocyclic intermediate **II**.^[28] Spirocyclic intermediate **II** undergoes a cationic 1,2-shift to produce the final connectivity through the indole C2 position. Deprotonation of the resulting tricycle restores aromaticity and furnishes the THPI product.

The CPA-urea co-catalyst system reported here provides both a greater reactivity and higher levels of selectivities for this transformation involving an oxocarbenium ion. The overall reaction provides access to a family of THPIs that can be further elaborated to achieve syntheses of members of a pharmacologically active family of spirooxindole natural products.^[16b, 23] This reaction manifold represents a new application of cooperative catalysis, and holds potential for new and selective asymmetric transformation involving oxocarbenium ions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References:

- [1]. Kobayashi S, Ishitani H, Chem. Rev 1999, 99, 1069–1094. [PubMed: 11749440]
- [2]. Knowles RR, Jacobsen EN, Proc. Natl. Acad. Sci. U. S. A 2010, 107, 20678–20685. [PubMed: 20956302]
- [3]. (a)Brak K, Jacobsen EN, Angew. Chem. Int. Ed 2013, 52, 534–561;(b)Milo A, Neel AJ, Toste FD, Sigman MS, Science 2015, 347, 737–743. [PubMed: 25678656]
- [4]. Reisman SE, Doyle AG, Jacobsen EN, J. Am. Chem. Soc 2008, 130, 7198–7199. [PubMed: 18479086]
- [5]. (a)Burns NZ, Witten MR, Jacobsen EN, J. Am. Chem. Soc 2011, 133, 14578–14581; [PubMed: 21848300] (b)Yeung CS, Ziegler RE, Porco JA, Jr., Jacobsen EN, J. Am. Chem. Soc 2014, 136, 13614–13617; [PubMed: 25213353] (c)Kennedy CR, Lehnher D, Rajapaksa NS, Ford DD, Park Y, Jacobsen EN, J. Am. Chem. Soc 2016, 138, 13525–13528; [PubMed: 27704810] (d)Visco MD, Attard J, Guan Y, Mattson AE, Tetrahedron Lett. 2017, 58, 2623–2628.
- [6]. (a)Zhang QW, Fan CA, Zhang HJ, Tu YQ, Zhao YM, Gu P, Chen ZM, Angew Chem Int Ed Engl 2009, 48, 8572–8574; [PubMed: 19816900] (b)Coric I, Vellalath S, List B, J. Am. Chem. Soc 2010, 132, 8536–8537; [PubMed: 20527773] (c)Moquist PN, Kodama T, Schaus SE, Angew. Chem. Int. Ed 2010, 49, 7096–7100;(d)Sun Z, Winschel GA, Borovika A, Nagorny P, J. Am. Chem. Soc 2012, 134, 8074–8077; [PubMed: 22545651] (e)Lu C, Su X, Floreancig PE, J. Org. Chem 2013, 78, 9366–9376; [PubMed: 23968162] (f)Hsiao CC, Liao HH, Sugiono E, Atodiresei I, Rueping M, Chemistry 2013, 19, 9775–9779; [PubMed: 23744744] (g)Kim JH, Coric I, Palumbo C, List B, J. Am. Chem. Soc 2015, 137, 1778–1781; [PubMed: 25636054] (h)Gheewala CD, Hirschi JS, Lee WH, Paley DW, Vetticatt MJ, Lambert TH, J. Am. Chem. Soc 2018, 140, 3523–3527. [PubMed: 29485273]
- [7]. Lee S, Kaib PS, List B, J. Am. Chem. Soc 2017, 139, 2156–2159. [PubMed: 28169541]
- [8]. (a)Rueping M, Volla CM, Atodiresei I, Org. Lett 2012, 14, 4642–4645; [PubMed: 22913599] (b)Maity P, Srinivas HD, Watson MP, J. Am. Chem. Soc 2011, 133, 17142–17145; [PubMed: 21988178] (c)Zhang H, Zhu L, Wang S, Yao ZJ, J. Org. Chem 2014, 79, 7063–7074; [PubMed: 25006993] (d)Terada M, Li F, Toda Y, Angew. Chem. Int. Ed 2014, 53, 235–239(e)Zi W, Toste FD, J. Am. Chem. Soc 2013, 135, 12600–12603. [PubMed: 23957763]
- [9]. (a)Wang MH, Cohen DT, Schwamb CB, Mishra RK, Scheidt KA, J. Am. Chem. Soc 2015, 137, 5891–5894; [PubMed: 25929160] (b)Murauski KJR, Walden DM, Cheong PH-Y, Scheidt KA, Adv. Synth. Catal 2017, 359, 3713–3719. [PubMed: 30473657]
- [10]. Bhadra S, Yamamoto H, Chem. Rev 2018, 118, 3391–3446. [PubMed: 29570284]
- [11]. Larghi EL, Kaufman TS, Eur. J. Org. Chem 2011, 2011, 5195–5231.
- [12]. (a)Zhao C, Chen SB, Seidel D, J. Am. Chem. Soc 2016, 138, 9053–9056; [PubMed: 27396413] (b)Das S, Liu L, Zheng Y, Alachraf MW, Thiel W, De CK, List B, J. Am. Chem. Soc 2016, 138, 9429–9432. [PubMed: 27457383]
- [13]. (a)Lombardo VM, Thomas CD, Scheidt KA, Angew. Chem. Int. Ed 2013, 52, 12910–12914; (b)Ascic E, Ohm RG, Petersen R, Hansen MR, Hansen CL, Madsen D, Tanner D, Nielsen TE, Chemistry 2014, 20, 3297–3300. [PubMed: 24616060]
- [14]. (a)Parmar D, Sugiono E, Raja S, Rueping M, Chem. Rev 2014, 114, 9047–9153; [PubMed: 25203602] (b)Xu H, Zuend SJ, Woll MG, Tao Y, Jacobsen EN, Science 2010, 327, 986–990. [PubMed: 20167783]
- [15]. Nasir NM, Ermanis K, Clarke PA, Org. Biomol. Chem 2014, 12, 3323–3335. [PubMed: 24744139]
- [16]. (a)Lee MY, Lin HY, Cheng F, Chiang W, Kuo YH, Food Chem. Toxicol 2008, 46, 1933–1939; [PubMed: 18331775] (b)Chung CP, Hsu CY, Lin JH, Kuo YH, Chiang W, Lin YL, J. Agric. Food Chem 2011, 59, 1185–1194. [PubMed: 21284381]
- [17]. Zhang Z, Schreiner PR, Chem. Soc. Rev 2009, 38, 1187–1198. [PubMed: 19421588]
- [18]. (a)for select examples of hydrogen-bond donor catalysis see: Borovika A, Tang P-I, Klapman S, Nagorny P, Angew. Chem. Int. Ed 2013, 52, 13424–13428;(b)Pace WH, Mo D-L, Reidl TW, Wink DJ, Anderson LL, Angew. Chem. Int. Ed 2016, 55, 9183–9186;(c)Palo-Nieto C, Sau A, Williams R, Galan MC, J. Org. Chem 2017, 82, 407–414; for an example of an HBD-mediated

tandem asymmetric Michael addition/oxa-Pictet Spengler process see: [PubMed: 28004941]
(d)Fan W-T, Li N-K, Xu L, Qiao C, Wang X-W, Org. Lett 2017, 19, 6626–6629. [PubMed:
29192792]

- [19]. Schreiner PR, Wittkopp A, Org. Lett 2002, 4, 217–220. [PubMed: 11796054]
[20]. Seayad J, Seayad AM, List B, J. Am. Chem. Soc 2006, 128, 1086–1087. [PubMed: 16433519]
[21]. Beesley RM, Ingold CK, Thorpe JF, J. Chem. Soc., Trans 1915, 107, 1080–1106.
[22]. Shavel J, Zinnes H, J. Am. Chem. Soc 1962, 84, 1320–1321.
[23]. Gao Z-H, Kong L-M, Zou X-S, Shi Y-M, Shang S-Z, Luo H-R, Liang C-Q, Li X-N, Li Y, Du X,
Xiao W-L, Sun H-D, Nat. Prod. Bioprospect 2012, 2, 249–254.
[24]. Galliford CV, Scheidt KA, Angew. Chem. Int. Ed 2007, 46, 8748–8758.
[25]. Davies HM, Du Bois J, Yu JQ, Chem. Soc. Rev. 2011, 40, 1855–1856. [PubMed: 21390392]
[26]. Zhao Y, Ang JQL, Ng AWT, Yeung YY, RSC Adv. 2013, 3, 19765–19768.
[27]. Attempts to obtain pure natural material to assess purity and the absolute value of the reported
+5.9° optical rotation were not successful. The original isolation paper only provides numerical
values for different NMR spectra and not full spectra to ascertain potential purity issues. Our
synthetic material is >95% pure as determine by NMR and HPLC techniques.
[28]. (a)Zheng C, Xia Z-L, You S-L, Chem 2018, 4, 1952–1966;(b)Bailey PD, Chem J Research-S
1987, 202–203.

A) asymmetric iminium and oxocarbenium ion chemistries

B) reaction concept

Proof of Concept:

C) bioactive THPIs and related compounds

Figure 1.

Existing strategies and proposed cooperative catalysis strategy for the control of addition facial selectivity to oxocarbenium ions.

Figure 2.

Optimization, scope, and applications. ^aSee SI for expanded optimization table. ^b10 mol % additive. ^cYields in table determined by NMR spectroscopy using trimethoxybenzene as an internal standard unless noted. ^dDesmethyl substrate, derived from tryptophol. ^eIsolated yield.

Figure 3.

Substrate scope. See SI for experimental details. Enantiomeric ratio determined by SFC analysis on chiral stationary phase.

A) ternary catalysis cascade

B) (-)-coixspirolactam C synthesis

Scheme 1.

A) ternary catalysis cascade B) (-)-coixspirolactam C synthesis

Scheme 2.
Proposed catalytic cycle