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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Direct Formation of Oxocarbenium Ions under Weakly Acidic Conditions: Catalytic Enantioselective Oxa-Pictet–Spengler Reactions

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Supporting Information

ABSTRACT: Two catalysts, an amine HCl salt and a bisthiourea, work in concert to enable the generation of oxocarbenium ions under mild conditions. The amine catalyst generates an iminium ion of sufficient electrophilicity to enable 1,2-attack by an alcohol. Catalyst turnover is achieved by amine elimination with concomitant formation of an oxocarbenium intermediate. The bisthiourea catalyst accelerates all of the steps of the reaction and controls the stereoselectivity via anion binding/ion pair formation. This new concept was applied to direct catalytic enantioselective oxa-Pictet–Spengler reactions of tryptophol with aldehydes.

Oxocarbenium ions are key intermediates in a range of synthetically important transformations. Because of their generally high reactivities and lack of basic sites suitable for interaction with chiral Lewis acids or hydrogen-bond donors, the development of catalytic enantioselective methods involving oxocarbenium intermediates poses significant challenges. Nevertheless, a number of creative approaches have been reported, the majority of which rely on the formation of oxocarbenium ions from acetals[1] or enol ethers.[2] Oxidative methods are also known.[3,4] Most catalytic enantioselective transformations reported to date feature cyclic and relatively stable pyrylium- or (iso)chroman-type oxocarbenium ions. Direct condensation of an alcohol with an aldehyde has only rarely been applied in the context of asymmetric catalysis.[5] Various reactions capable of providing valuable products via the intermediacy of oxocarbenium ions have not yet been realized in catalytic enantioselective fashion. For instance, progress in developing catalytic enantioselective oxa-Pictet–Spengler reactions has remained limited.[6,7] No highly enantioselective variants exist, and no direct approach from tryptophols and aldehydes has emerged. Here we report a new concept for asymmetric catalysis that enables the formation of oxocarbenium ions under mild, weakly acidic conditions. This dual catalysis strategy is applied to direct catalytic enantioselective oxa-Pictet–Spengler reactions.

We envisioned a new dual catalysis approach[8] for the generation of oxocarbenium ions under weakly acidic conditions. Our strategy is outlined in Figure 1 using the oxa-Pictet–Spengler reaction as an example and a pyrrolidinium salt and a generic chiral thiourea as model catalysts. With the proper choice of X^- in an apolar solvent, the catalysts likely

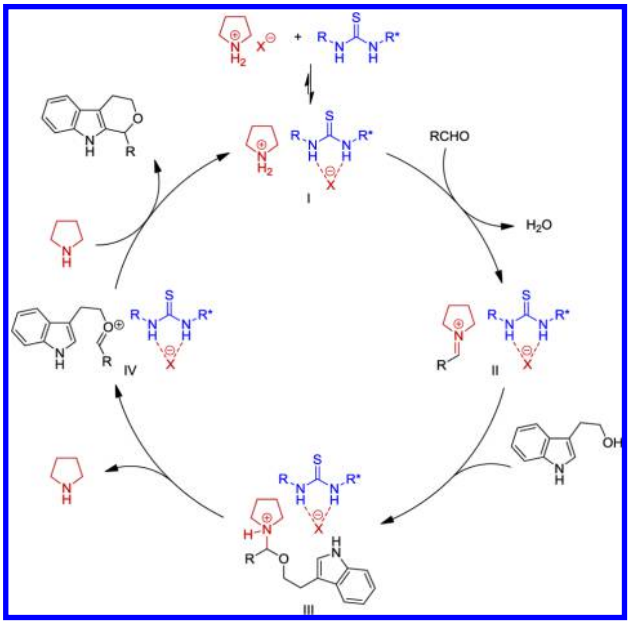


Figure 1. Proposed catalytic cycle.

interact and exist predominantly as ion pair **I**. Condensation with an aldehyde results in the formation of iminium ion pair **II**, which is subsequently attacked by an alcohol to generate *N*,*O*-acetal intermediate **III**. Elimination of the neutral amine catalyst furnishes oxocarbenium intermediate **IV**, which cyclizes to form the product. In this scenario, the enantiodetermining step is controlled entirely by the thiourea catalyst, which acts as a chiral anion receptor.[9−12]

The amine catalyst[13,14] has to fulfill three crucial requirements. First, the amine must be sufficiently nucleophilic to generate the requisite iminium ion. Second, the iminium ion must possess the necessary electrophilicity to facilitate 1,2-attack by a weakly nucleophilic alcohol. Finally, the amine must be an excellent leaving group. Although common in achiral settings[15] and harkening back to classic work by Knoevenagel,[16] examples of asymmetric iminium catalysis in which turnover of the catalyst is achieved by elimination are rare.[17,18] The anion-binding catalyst, while primarily responsible for controlling the stereochemical outcome, enhances the electrophilicity of

Received: May 20, 2016
Published: July 11, 2016

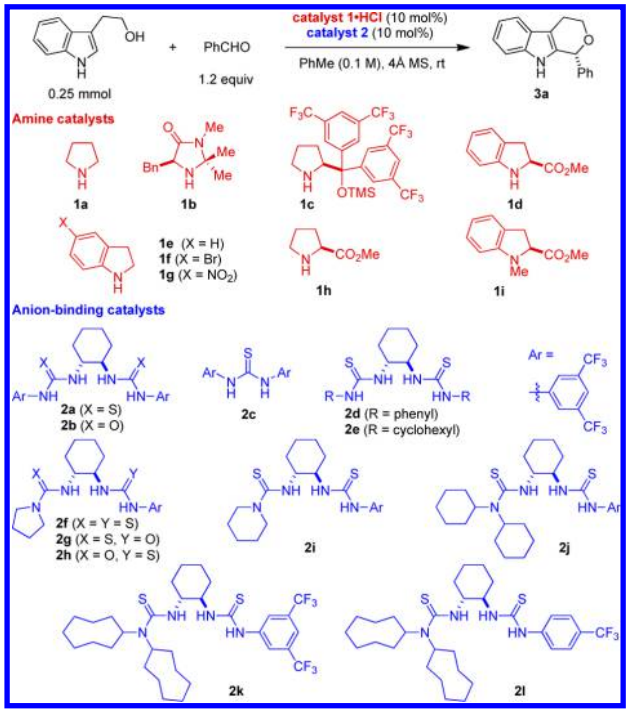
DOI: 10.1021/jacs.6b05225
J. Am. Chem. Soc. 2016, 138, 9053−9056

iminium ion **II**.[19] It likely also increases the leaving group aptitude of the amine in **III**.

Tryptophol and benzaldehyde were selected as model substrates to test the proposed oxa-Pictet–Spengler reaction (Table 1). As expected, no reaction was observed in the absence of any additives (entry 1). The Nagasawa catalyst **2a**[20] was initially tested in combination with various amine HCl salts. No reaction was observed with **1a**·HCl or widely used catalysts **1b**·HCl[13d] and **1c**·HCl[21] (entries 2–4). The failure of **1b** and **1c** is not necessarily surprising, considering that they were specifically designed to minimize 1,2-addition. Remarkably, (*S*)-indoline-2-carboxylic acid methyl ester (**1d**·HCl) used in concert with **2a** facilitated rapid formation of the desired product **3a** in excellent yield with notable ee (entry 5).[22] Virtually identical results were obtained with **1d**·HCl prepared in situ (entry 6). A number of other amine HCl salts were tested, but none provided further improvements (entries 7–11). Interestingly, (±)-**1d** provided results very similar to those with enantiopure **1d** (entry 7). Achiral 5-nitroindoline (**1g**) performed almost at the same level (entry 10).[23] These results strongly suggest that the amine catalyst is not involved in the enantiodetermining step of the reaction. Catalyst **1i**, which is incapable of forming iminium ions, was tested to rule out the possibility that the amine salt simply acts as a buffered source of HCl.[24] Indeed, while a small amount of **3a** was obtained with 29% ee, the reaction was extremely sluggish (entry 12). Use of **1d**·HCl as the only catalyst resulted in an extremely slow reaction and racemic **3a** (entry 13). A rapid albeit racemic reaction was observed in the presence of the achiral Schreiner catalyst **2c**[25] (entry 14). Entries 1–14 clearly highlight the need for both an electronically fine-tuned amine catalyst and a chiral anion-receptor catalyst.

Consistent with the well-known tendency of ureas to be poorer anion receptors than the corresponding thioureas,[26] catalyst **2b** provided a reduced reaction rate and low ee (entry 15). Surprisingly, **2d** and **2e**, both of which are substantially more electron-rich than **2a** and thus expected to be poorer anion receptors, provided significant improvements in ee (entries 16 and 17). A possible rationale is that one thiourea acts as an anion receptor while the other engages in interactions with the substrate. These considerations and results from a broad screen of other catalysts[24] led us to the realization that the most efficient catalysts feature both an electron-deficient and an electron-rich thiourea. The presence of two *N*-H protons on the electron-rich thiourea is not required. In fact, catalyst **2f** afforded further improvements (entry 18). Replacement of either thiourea in **2f** for a urea provided inferior results. However, while exchange of the electron-deficient thiourea (anion binding site) for a urea (catalyst **2g**) only had a minor effect (entry 19), dramatic loss of reactivity and selectivity ensued when the electron-rich thiourea was replaced. Moreover, the sense of enantioinduction with **2h** was opposite to that with **2f** (entry 20). Increasing the size of the secondary amine component proved beneficial (entries 21–23) as did exchanging the 3,5-bis(trifluoromethyl)phenyl group for 4-trifluoromethylphenyl (entry 24).[27] A further increase in enantioselectivity was achieved at a lower substrate concentration (entry 25). At −30 °C, **3a** was obtained in 90% yield with 91% ee (entry 26).[28] While **2l** was capable of promoting the title reaction using only HCl as the cocatalyst, the reaction rate was dramatically reduced (entry 27). In addition, the formation of unidentified byproducts was noted.

Table 1. Optimization of the Reaction Conditions



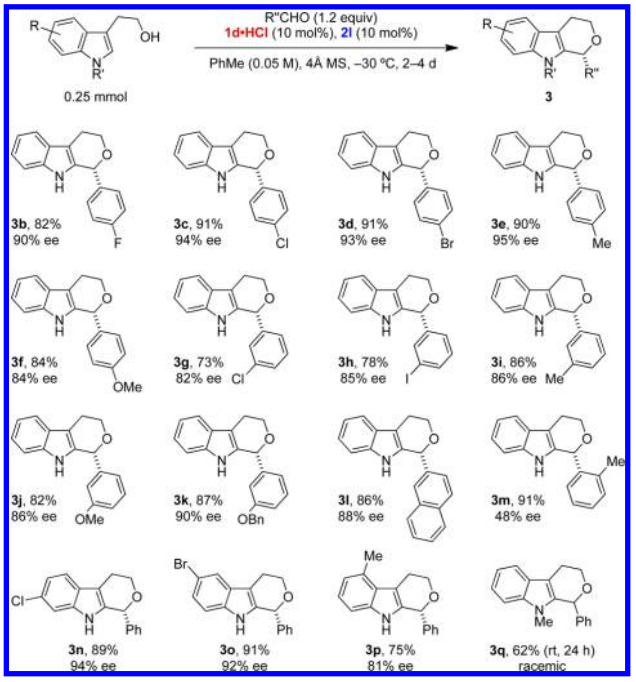
entry	catalyst **1**·HCl	catalyst **2**	time (h)	yield (%)	ee (%)
1	–	–	24	0	–
2[a]	**1a**	**2a**	24	0	–
3	**1b**	**2a**	24	trace	ND
4[a]	**1c**	**2a**	24	0	–
5	**1d**	**2a**	1	91	33
6[a]	**1d**	**2a**	1	90	33
7	(±)-**1d**	**2a**	2	85	34
8[a]	**1e**	**2a**	24	0	–
9[a]	**1f**	**2a**	24	8	31
10[a]	**1g**	**2a**	1	82	26
11	**1h**	**2a**	24	trace	ND
12	**1i**	**2a**	48	13	29
13	**1d**	-	24	14	0
14	**1d**	**2c**	1	88	0
15	**1d**	**2b**	3	39	−8
16	**1d**	**2d**	2	90	50
17	**1d**	**2e**	2	90	61
18	**1d**	**2f**	2	88	66
19	**1d**	**2g**	2	88	55
20	**1d**	**2h**	24	34	−24
21	**1d**	**2i**	2	90	66
22	**1d**	**2j**	2	91	70
23	**1d**	**2k**	2	88	75
24	**1d**	**2l**	2	90	79
25[b]	**1d**	**2l**	3	91	84
26[b,c]	**1d**	**2l**	48	90	91
27[b]	–[d]	**2l**	24	64	81

[a]**1**·HCl was prepared in situ from **1** and HCl (4 M in dioxane). [b]The reaction was run at 0.05 M concentration. [c]The reaction was run at −30 °C. [d]10 mol % HCl (4 M in dioxane) was used as the cocatalyst.

A range of aromatic aldehydes readily participated in oxa-Pictet–Spengler reactions (Scheme 1). Electronically diverse substituents were readily accommodated at the para and meta positions. The introduction of an ortho substituent led to a drop in enantioselectivity (product **3m**). A number of

DOI: 10.1021/jacs.6b05225
J. Am. Chem. Soc. 2016, 138, 9053–9056

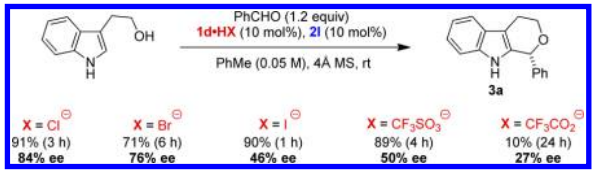
Scheme 1. Substrate Scope



substituted tryptophols also provided products in good yields and enantioselectivities. Interestingly, the presence of an indole *N*-H proton was found to be a strict requirement. Product **3q**, derived from *N*-Me tryptophol, was formed more sluggishly and was obtained in racemic form.

To firmly establish the role of catalyst **2l** as an anion receptor, different salts of **1d** were evaluated (Scheme 2). While

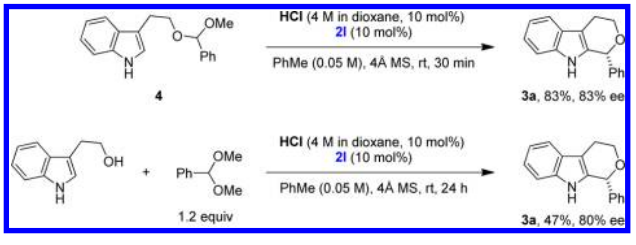
Scheme 2. Effect of the Counteranion



chloride, bromide, iodide, and triflate all provided reactive systems, chloride furnished the highest ee. On the other hand, iodide facilitated the fastest reaction. The use of trifluoroacetate dramatically retarded the reaction rate.

Experiments designed to provide evidence for the involvement of oxocarbenium ion intermediates are summarized in Scheme 3. Exposure of mixed acetal **4** to 10 mol % HCl (added as a 4 M solution in dioxane) and 10 mol % catalyst **2l** provided product **3a** in rapid fashion and nearly identical selectivity as observed before (cf. Table 1, entry 25). The same catalyst

Scheme 3. Evidence for the Intermediacy of Oxocarbenium Ions



combination also facilitated the reaction between tryptophol and benzaldehyde dimethyl acetal. In this instance, the reaction was significantly slower, and product **3a** was recovered with slightly diminished ee.

The high levels of enantioselectivity observed for a range of substrates are consistent with the existence of a tight ion pair between the bisthiourea–anion complex and the oxocarbenium ion. Multiple non-covalent interactions likely exist between the ions. While the chloride anion is almost certainly engaged in hydrogen-bonding interactions with the electron-deficient thiourea,[29] the electron-rich thiourea may be involved in interactions with the substrate. For instance, the thiourea sulfur atom could act as a hydrogen-bond acceptor, increasing the nucleophilicity of the indole moiety via a S···H–N interaction.

In summary, we have outlined a new dual catalysis concept for the direct generation of oxocarbenium ions from aldehydes and alcohols, enabling catalytic enantioselective oxa-Pictet–Spengler reactions under weakly acidic conditions. A new amine catalyst and a novel bisthiourea catalyst were identified in the course of this study. The two catalysts work in concert and fulfill crucial roles in the efficient generation of the oxa-Pictet–Spengler products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05225.

Experimental procedures and characterization data (PDF)

Crystallographic data for **3d** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based in part upon work supported by the National Science Foundation under Grant CHE-1300382. We thank Dr. Tom Emge (Rutgers University) for crystallographic analysis.

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(27) With the analogue of catalyst **2l** in which the electron-rich thiourea was replaced with the corresponding urea, only trace amounts of product were observed within 24 h.

(28) Under otherwise identical conditions with 5-nitroindoline (**1g**) in place of **1d**, product **3a** was obtained in 75% yield with 89% ee following a reaction time of 72 h.

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DOI: 10.1021/jacs.6b05225
J. Am. Chem. Soc. 2016, 138, 9053–9056