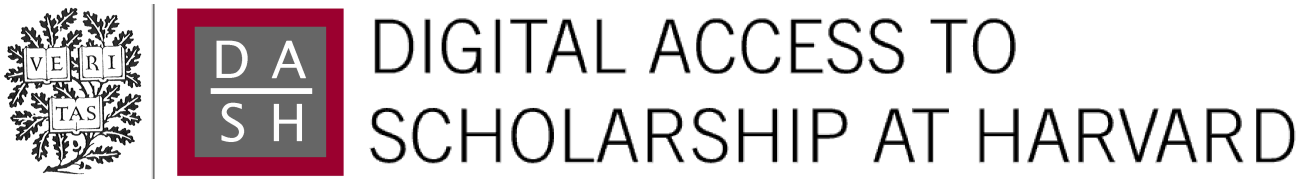

Dual Catalysis in Enantioselective Oxidopyrylium-Based [5+2] Cycloadditions

Dual Catalysis in Enantioselective Oxidopyrylium-Based [5+2] Cycloadditions

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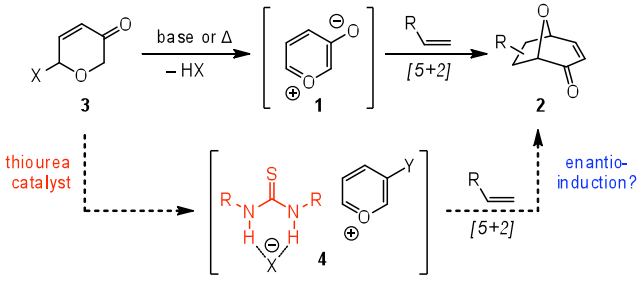
Supporting Information Placeholder

ABSTRACT: A new method is reported for effecting catalytic enantioselective intramolecular [5+2] cycloadditions based on oxidopyrylium intermediates. The dual catalyst system consists of a chiral primary aminothiourea and a second achiral thiourea. Experimental evidence points to a new type of cooperative catalysis with each species being necessary to generate a reactive pyrylium ion pair which undergoes subsequent cycloaddition with high enantioselectivity.

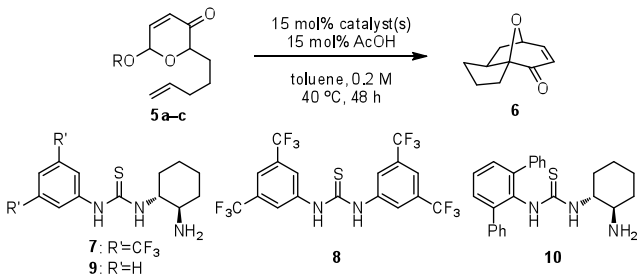
The [5+2] dipolar cycloaddition of oxidopyrylium ylides (**1**, Scheme 1) and two-carbon dipolarophiles generates complex, chiral 8-oxabicyclo[3.2.1]octane architectures **2**.[1] In addition to being a structural motif common to numerous natural products,[2] such cycloadducts have proven to be highly valuable intermediates in the synthesis of functionalized seven-membered carbocycles[3] and tetrahydrofuran derivatives.[4] Despite the utility of this [5+2] cycloaddition and its widespread use in organic synthesis,[5] asymmetric examples have thus far been limited to diastereoselective variants,[6] and there are currently no catalytic enantioselective methods that engage reactive pyrylium intermediates in cycloaddition chemistry.[7] Herein we report a dual-catalyst system consisting of a chiral primary aminothiourea and an achiral thiourea that promotes an intramolecular variant of the title reaction with high enantioselectivity. Experimental evidence points to a new type of cooperative mechanism of catalysis.[8]

Scheme 1. Oxidopyrylium cycloadditions and proposed mode of catalysis



It has been shown recently that small-molecule chiral hydrogen-bond donor catalysts can serve as anion abstractors and binders in the generation and enantioselective transformation of highly reactive cationic intermediates,[9] and we became interested in the potential application of the principle of anion-binding catalysis to oxidopyrylium formation and cycloaddition. These intermediates are generally accessed by thermolysis of the corresponding acetoxypyranone **3** (X = OAc, Scheme 1),[10] or by reaction of **3** with an amine base.[11] Upon elimination of acetic acid, reactive **1** has been shown to undergo [5+2] cycloadditions with both electron-rich and electron-poor dipolarophiles.[12] We hypothesized that a urea or thiourea catalyst might induce ionization of an appropriate leaving group from **3** or a tautomeric form thereof, to give pyrylium **4**. Our efforts thus focused on identifying an appropriate precursor to this species (i.e. X in **3**) as well as the best mode for activation and asymmetric induction in subsequent [5+2] cyloadditions.

Table 1. Reaction optimization



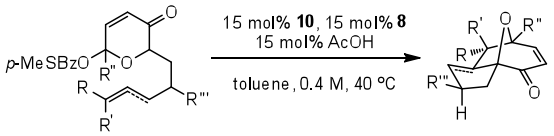
entry	substrate (R=)	catalyst(s)	yield (%)[a]	ee (%)[b]
1[c]	**5a** (Ac)	**7**	37	21
2[c]	**5a** (Ac)	**7** + **8**	44	67
3	**5a** (Ac)	**7** + **8**	53	67
4	**5a** (Ac)	**9** + **8**	41	66
5	**5a** (Ac)	**10** + **8**	30	88
6	**5b** (Bz)	**10** + **8**	56	91
7	**5c** (*p*-MeSBz)	**10** + **8**	72	91
8[d]	**5c** (*p*-MeSBz)	**10** + **8**	76	91

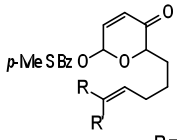
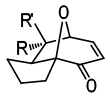
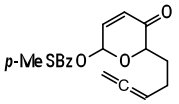
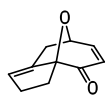
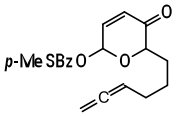
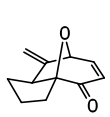
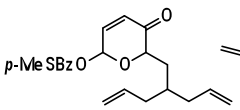
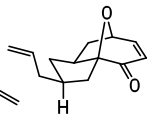
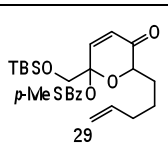
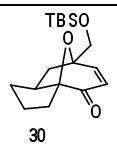
Reactions performed on a 0.05 mmol scale. [a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Determined by HPLC using commercial chiral columns. [c] No added AcOH. [d] Conditions: 10 mol% **10** + **8**, 0.4 M.

Racemic acetoxypyranone **5a**[11] was chosen for initial exploratory and ensuing optimization studies. The desired reaction was found to take place in the presence of a variety of chiral thiourea derivatives in combination with stoichiometric triethylamine, but no stereoinduction was observed in the formation of cycloadduct **6**.[13] In contrast, bifunctional primary aminothiourea **7**[14] induced formation of **6** with low levels of enantioselectivity in the absence of exogenous base (Table 1, entry 1). An unexpected but ultimately significant observation resulted from a broad screen of additives, with achiral thiourea catalyst **8**[15] dramatically improving the reaction enantioselectivity (entry 2). The addition of acetic acid as a second co-catalyst provided a measurable yield enhancement, with no effect on product ee (entry 3). Other achiral or chiral hydrogen-bond donors (including the urea analogue of **8**) proved less beneficial as additives. Whereas the electron-poor bistrifluoromethyl anilide group is found to be an optimal chiral catalyst feature in a growing number of enantioselective thiourea-

promoted reactions,[16] phenylthiourea **9** (entry 4) was found to be comparable to **7**. This prompted an exhaustive examination of the effect of aryl substitution on the aminothiourea catalyst,[13] and led to the identification of **10**, which bears a 2,6-diphenylanilide component, as the most enantioselective aminothiourea catalyst (entry 5). The diminished reactivity displayed by **10** was overcome by utilizing substrate **5b** containing a benzoate-leaving group (entry 6). Upon exploring various substituents on the benzoate a further enhancement was observed with *para*-thiomethylbenzoyl substrate **5c** (entry 7). This improved reactivity is likely not a result of better leaving group or hydrogen-bond accepting ability, as *para*-thiomethyl substitution has no effect on the acidity of benzoic acid ($\sigma_{para} = 0.0$[17]). This effect may instead be a result of the lower solubility in toluene of the *para*-thiomethylbenzoic acid byproduct (as compared to benzoic or acetic acid), which precipitates during the course of the reaction. Finally, increasing the reaction concentration further improved the rate, allowing for the loadings of **10** and **8** to be reduced with this parent substrate (entry 8).

Table 2. Substrate scope

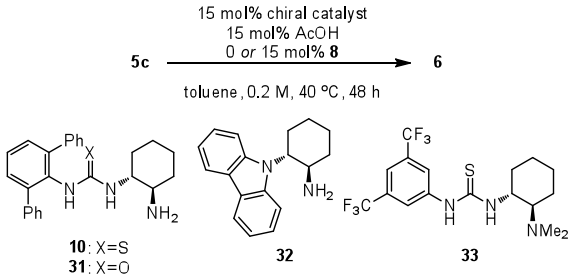


entry	substrate	product	time (h)	yield (%)[a]	ee (%)[b]
1[c,d]	 5c R = H, R' = H	 6	48	74	91
2	11 R = Me, R' = H	12	72	70	90
3	13 R = H, R' = Me	14	72	66	89
4	15 R = Me, R' = Me	16	96	51	89
5	17 R = H, R' = Ph	18	72	48	86
6	19 R = CO_2Et, R' = H	20	72	66	90
7[e]	21 R = CO_2Me, R' = Me	22	96	37	80
8[c,d]	 23	 24	72	54	95
9	 25	 26	72	42	88
10[d]	 27	 28	72	77	90
11	 29	 30	72	70[f]	89[f]

[a] Isolated yields after chromatography on silica gel. [b] Determined by HPLC using commercial chiral columns. [c] 10 mol% **10** + **8**. [d] The absolute stereochemistry of **24** and derivatives of **28** and **6** were determined by X-ray crystallography and that of all other products was assigned by analogy. [e] 20 mol% **10** + **8**. [f] Determined on the free alcohol.

With optimal catalytic conditions in hand, an examination of the substrate scope was undertaken (Table 2). Substitutions at the olefin terminus were tolerated (entries 2–7), despite a diminishment of reactivity occurring upon increased substitution (entries 4 and 7). Allenes are viable cycloaddition substrates (entries 8 and 9), however alkyne-bearing substrates proved unreactive under the current set of conditions. Other viable substrates include those bearing substitution on the tether connecting the dipole and dipolarophile as in diallyl substrate **27** (entry 10), or on the pyranone ring as in **29** (entry 11). Product **30** bears a siloxymethylene unit commonly found in synthetically useful oxidopyrylium cycloadducts.[18] Substrate variations that were not tolerated include methylation at the internal position of the olefin as well as a homologue of substrate **5c** containing an additional methylene in the tether. Initial efforts to extend this system to an asymmetric intermolecular variant have been met with only moderate success.[13]

Table 3. Catalyst structure-activity relationship study



entry	catalyst	0 mol% **8** yield (%)[a]	0 mol% **8** ee (%)[b]	15 mol% **8** yield (%)[a]	15 mol% **8** ee (%)[b]
1	**10**	32	72	72	91
2	**31**	7	n.d.	58	71
3	**32**	7	n.d.	58	–85
4	**33**	10	n.d.	11	n.d.

Reactions performed on a 0.05 mmol scale. [a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Determined by HPLC using commercial chiral columns.

In order to probe the possible roles of the different components in this dual thiourea catalyst system, a series of reactions were run with different bifunctional chiral catalysts in the presence and absence of **8** (Table 3). A clear and dramatic cooperative effect is observed between the optimal catalysts as evidenced by the poorer results obtained without achiral catalyst **8** (entry 1). A beneficial effect of **8** has also been reported recently in proline-catalyzed transformations, where its primary role appears to be as a phase-transfer catalyst to solubilize proline in the non-polar media.[19] Such a role is unlikely in the present system, as all components of this oxidopyrylium-based cycloaddition reaction are initially soluble in toluene (*vide supra*).

Instead, we propose that the function of **8** in the pyrylium cycloaddition reaction is as a carboxylate-binding agent (Figure 1A),

acting cooperatively with **10** to generate the reactive ion pair **34**. Compound **31**, the urea analog of **10**, displays very low reactivity in the absence of **8**,[20] but does serve as a moderately enantioselective co-catalyst in conjunction with **8** (Table 3, entry 2). While the thiourea component of the optimal catalyst **10** therefore does influence the reaction enantioselectivity even in the presence of **8** (compare entries 1 and 2), it is not necessary for obtaining reactivity or high ee. Thus, the combination of primary aminocarbazole **32** and thiourea **8** is an effective catalyst system, catalyzing the selective formation of **6** in 85% ee (entry 3). It is significant that catalysts **10** and **32** induce cycloaddition with opposite senses of enantiocontrol (*vide infra*). Consistent with the notion that an H-bond donor catalyst is needed to induce ionization to the pyrylium ion, primary aminocarbazole **32** is virtually unreactive in the absence of **8** (entry 3). Tertiary aminothiourea **33**[21] is unreactive both in the presence and absence of **8** (entry 4), pointing to the necessity of a primary amine for catalytic activity. These observations with basic tertiary aminothiourea **33** as well as the fact that acetic acid increases the rate of reaction are consistent with an operative enamine catalysis mechanism. Condensation between the amine of the catalyst and the ketone of the substrate is expected to yield a dienamine after tautomerization. Hydrogen-bond donor-mediated benzoate abstraction would then generate a catalyst•pyrylium adduct **34** poised to undergo the intramolecular cycloaddition.

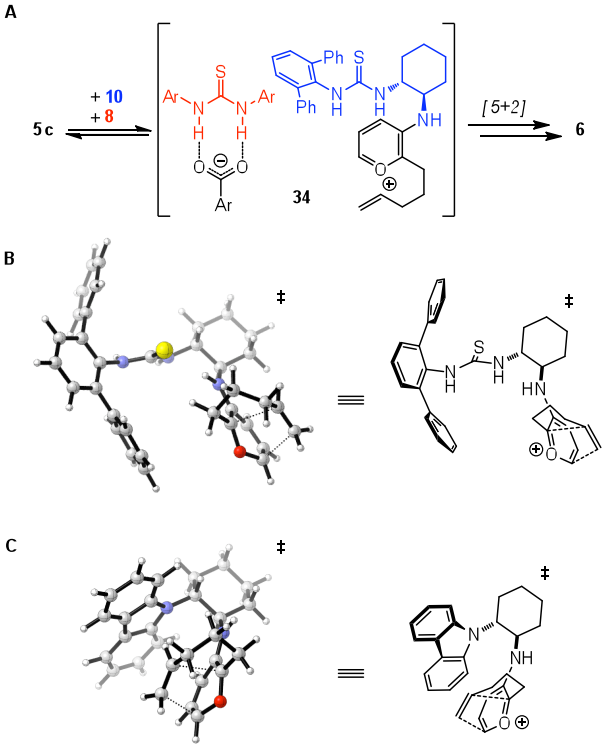


Figure 1. (A) Proposed role for thiourea catalysts **10** and **8**. Calculated lowest energy cycloaddition transition structures at the B3LYP/6-31G(d) level of theory for (B) **10**•pyrylium, and (C) **32**•pyrylium.

With the goal of evaluating the viability of aminopyrylium **34** in the cycloaddition chemistry induced by the catalyst combination of **10** and **8**, a computational frontier molecular orbital analysis[22] of a variety of dipolarophiles and of oxido-, amido-, and aminopyryliums (**4**, Y = O^-, NH^-, NH_2, respectively, Scheme 1) was performed and compared with observed trends in intermolecular cycloadditions. The dominant HOMO-LUMO interactions between each of the three hypothetical pyrylium species and alkenes of varying electronic properties were thereby predicted.[13] With an oxido- or amidopyrylium, either the HOMO or the LUMO of the dipole can be more relevant to cycloaddition depending on the dipolarophile, in line with the experimental observation that oxidopyrylium dipolar intermediates undergo reaction with either electron-rich or electron-deficient alkenes.[5c,12] Alternatively, the LUMO of an aminopyrylium was predicted to be the MO relevant to cycloaddition in all cases, consistent with our observation that intermolecular reactions under thiourea-catalyzed conditions only proceed with electron-rich dipolarophiles containing a high HOMO.[13] The results thus point towards an aminopyrylium – and not an oxido- or amidopyrylium – as the relevant intermediate in the thiourea-catalyzed reactions described herein.

While the unprecedented intermediacy of aminopyryliums such as **34** agrees with the experimental and computational data described above, the reversal in the sense of enantioinduction observed using primary amine catalysts **10** and **32** in conjunction with achiral thiourea **8** was difficult to reconcile by any simple means. A computational analysis of transition structures for cycloadditions of the proposed **10**•pyrylium and **32**•pyrylium ions was therefore undertaken.[23] Although these simplified models do not take into account the counteranion, good correlation with experimental results were obtained. Of the multiple first-order saddle points that were located for each complex, the lowest energy transition structure leads to the observed major enantiomer of product (Figure 1B,C), and the second-lowest energy transition structure corresponds to the observed minor enantiomer in each case.[24]

In summary, we have identified a dual thiourea catalyst system for intramolecular oxidopyrylium [5+2] cycloadditions, providing enantioselective access to valuable tricyclic structures. Application of this reaction to the synthesis of biologically active small-molecules, further mechanistic studies into the origin of the catalyst cooperativity, and extension of the underlying principles to other multifunctional (thio)urea-catalyzed transformations are the focus of ongoing investigations.

ASSOCIATED CONTENT

Supporting Information. Full experimental procedures, syntheses of substrates and catalysts **10** and **32**, characterization data for all new compounds, NMR spectra for cycloaddition products, HPLC traces for scalemic cycloaddition products, geometries and energies of calculated stationary points, and crystallographic information. This material is available free of charge via the internet at http://pubs.acs.org.

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(13) See Supporting Information for details.

(14) For preparation and use, see reference 9g and references therein.

(15) (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217–220. (b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.*, **2003**, *9*, 407–414.

(16) For examples that include a direct comparison of different aryl thioureas, see: 9b, 9c, 9d, 9g, 9h, and 21.

(17) McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420–427.

(18) See references 3a, 5b, 6a, and 6d for examples.

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(20) In general, ureas are substantially weaker Brønsted acids than the corresponding thioureas, and accordingly also poorer H-bond donors: pK_a of *N,N′*-diphenylthiourea (DMSO) = 13.5, while *N,N′*-diphenylurea = 19.5: Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5903–5904.

(21) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.

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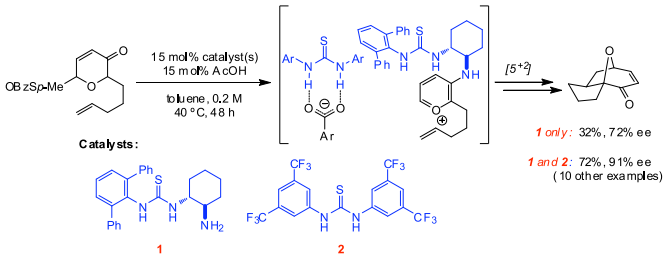
(23) B3LYP/6-31G(d) has been established as an appropriate level of theory for studying oxidopyrylium [5+2] cycloadditions: (a) López, F.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **2003**, *68*, 9780–9786. (b) Wang, S. C.; Tantillo, D. J. *J. Org. Chem.* **2008**, *73*, 1516–1523.

(24) Uncorrected electronic energy differences between the two lowest energy diastereomeric transition structures are 1.31 kcal/mol for **10**•pyrylium and 1.33 kcal/mol for **32**•pyrylium. See Supporting Information for structures.

(25) CYLview, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009; http://www.cylview.org.


OBzSp-Me
15 mol% catalyst(s)
15 mol% AcOH
toluene, 0.2 M
40 °C, 48 h
[5+2]
1 only: 32%, 72% ee
1 and 2: 72%, 91% ee
(10 other examples)
Catalysts:
1
2