Catalytic Enantioselective Intermolecular [5+2] Dipolar Cycloadditions of a 3-Hydroxy-4-Pyrone-Derived Oxidopyrylium Ylide[§]

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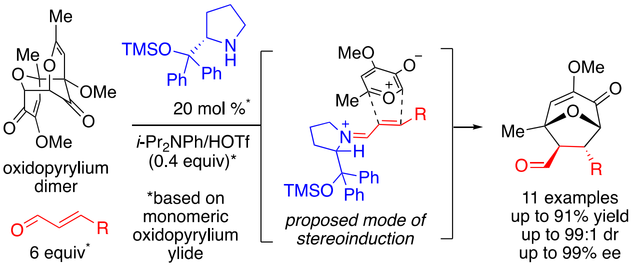
[§]Dedicated to Professor Paul A. Wender on the occasion of his 70th birthday.

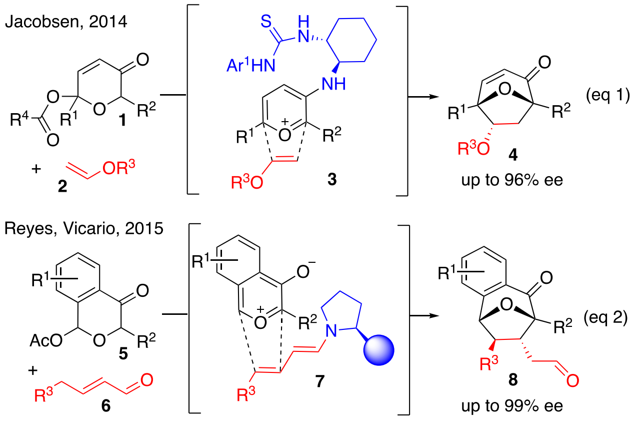


ABSTRACT: The first catalytic enantioselective [5+2] dipolar cycloaddition of a 3-hydroxy-4-pyrone-derived oxidopyrylium ylide is described. These studies leveraged the recently recognized ability of oxidopyrylium dimers to serve as the source of ylide, which was found to be key to increasing yields and achieving enantiomeric excesses up to 99%. General reaction conditions were identified for an array of α,β-unsaturated aldehyde dipolarophiles. Reaction products possess four stereocenters, and subsequent reduction introduced a fifth contiguous stereocenter with total stereocontrol.

The [5+2] dipolar cycloaddition of oxidopyrylium ylides enables facile access to the 8-oxabicyclo[3.2.1]octane scaffold,[1] and has been widely used in target-oriented synthesis.[2] In addition to being a prevalent substructure in bioactive natural products,[3] 8-oxabicyclo[3.2.1]octanes provide an entrée into functionalized tetrahydrofurans and cycloheptanes.[4-5] These two ring systems are of high interest to synthetic chemists, with the latter being relatively challenging to construct due to ring-strain and entropic considerations.[6]

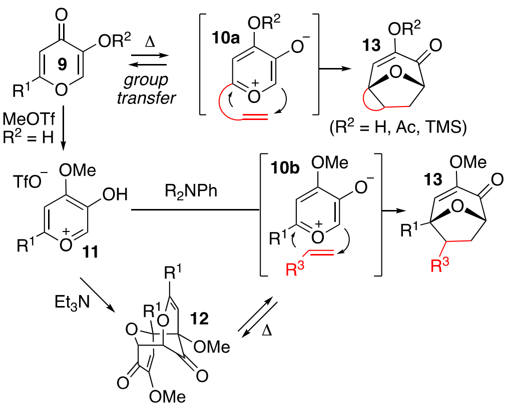
Despite the widespread utility of oxidopyrylium cycloadditions, including asymmetric variants of the reaction,[4b,7] catalytic enantioselective [5+2] dipolar cycloadditions of oxidopyrylium ylides have eluded the synthetic chemistry community until very recently. The first such reaction was intramolecular and was reported by Jacobsen and coworkers in 2011, and was subsequently adapted as an intermolecular process in 2014.[8] These reactions used a combination of enamine catalysis and a hydrogen-bonding catalyst to promote the asymmetric cycloaddition (eq 1, **Scheme 1**). In 2015, Reyes and Vicario reported the first catalytic enantioselective [5+2] dipolar cycloaddition of a benzopyrylium oxide via dienamine catalysis (eq 2).[9] These remain the only strategies for catalytic asymmetric oxidopyrylium cycloadditions published to date.

Scheme 1. Catalytic Asymmetric Intermolecular Oxidopyrylium Cycloadditions Employing Acyloxypyrans.



Both of these prior studies leveraged carboxylate elimination of acyloxypyran to generate reactive oxidopyrylium ylides, which is the method most commonly associated with oxidopyrylium [5+2] cycloadditions.[1,2] A less studied intermediate to oxidopyrylium ylides are 3-hydroxy-4-pyrones (**9, Scheme 2**), which are classically converted to the active oxidopyrylium ylides through thermal group transfer (**9** → **10a**) and trapped by a tethered alkene or alkyne.[5a,10] Intermolecular 3-hydroxy-4-pyrone-based oxidopyrylium cycloadditions, on the other hand, can be performed by first converting the pyrone to 3-hydroxy-4-methoxypyrylium triflate salts (**11**), and then deprotonating them with aniline bases in the presence of the dipolarophile.[11] We further adapted this intermolecular reaction through our recent discovery that oxidopyrylium dimers (**12**) can be used as the source of the oxidopyrylium ylide, thereby eliminating conjugate acid and residual base present in the *in situ* deprotonation protocol.[12] 3-Hydroxy-4-pyrone-based oxidopyrylium ylides (**10a/b**) are inherently electron rich due to the presence of an added donor oxygen, and as such are known to react preferentially with electron poor dipolarophiles.[11a, 12c] Thus, unlike prior catalytic asymmetric intermolecular processes wherein oxidopyrylium ylides reacted with electron rich dipolarophiles (Scheme 1), 3-hydroxy-4-pyrone-derived oxidopyrylium ylides were viewed as an ideal ylide with which to develop an asymmetric oxidopyrylium cycloaddition reaction employing electron poor dipolarophiles accessible through iminium catalysis.[13]

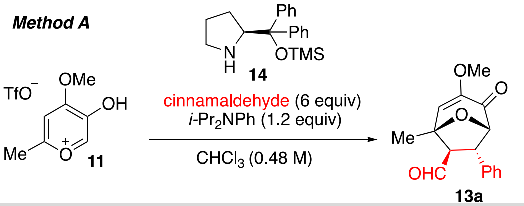
Scheme 2. Overview of 3-Hydroxy-4-pyrone-Based Oxidopyrylium Cycloaddition.



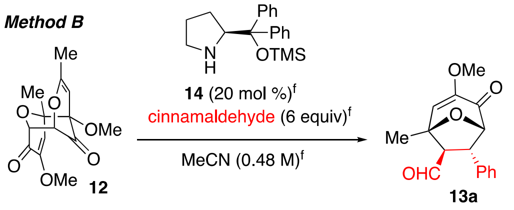
Early studies revealed that commercially available catalyst **14** was capable of promoting an enantioselective reaction between salt **11** and cinnamaldehyde upon addition of i-Pr$_2$NPh (method A, **Table 1**), generating product in high ee and dr, albeit in prohibitively low yields at rt (entry 1). Efforts to improve yields by raising the temperature from rt to 50 °C led to significant deterioration of both enantio- and diastereoselectivity (entry 2). After extensive optimization,[14] the best results were obtained in acetonitrile by doubling the loading of catalyst, which at room temperature generated the product in excellent ee and outstanding dr, but still in only 45% yield after 7 days (entry 3). We thus turned our attention to dimer **12** as the source of oxidopyrylium ylide (method B, Table 1).

When **12** was subjected to comparable reaction conditions, no conversion was observed, even at 50 °C (entry 4). This was not surprising given that catalytic acid is generally necessary to promote iminium ion formation, and that initial studies revealed no background reaction between **12** and cinnamaldehyde at this temperature (result not shown). What was surprising, however, was that the addition of catalytic benzoic acid led only to trace amounts of products (entry 5). Given the promising results with **11** and base, anilinium triflate was reintroduced into the reaction mixture through the addition of stoichiometric i-Pr$_2$NPh and TfOH (entries 6-9). Adjustment of time and temperature resulted in much higher product yields and comparable enantioselectivities relative to those obtained with salt **11**. In the absence of catalyst, some background reaction was observed (entry 10), demonstrating that the anilinium triflate promotes racemic background reaction. The equivalents of additives were reduced to achieve a concentration of anilinium triflate that promoted iminium activation, while not detrimentally catalyzing the racemic background reaction, which gave nearly enantiopure products (entry 11).[14]

Table 1. Representative Results from Asymmetric Oxidopyrylium Cycloaddition Optimization Studies.



entry	14 (mol %)	*t* (d)	temp (ºC)	yield (%)[a]	ee (%)[b]	dr [c]
1[d]	20	7	rt	9	90	16:1
2	20	0.1	50	47	67	5:1
3[e]	40	7	rt	45	97	33:1



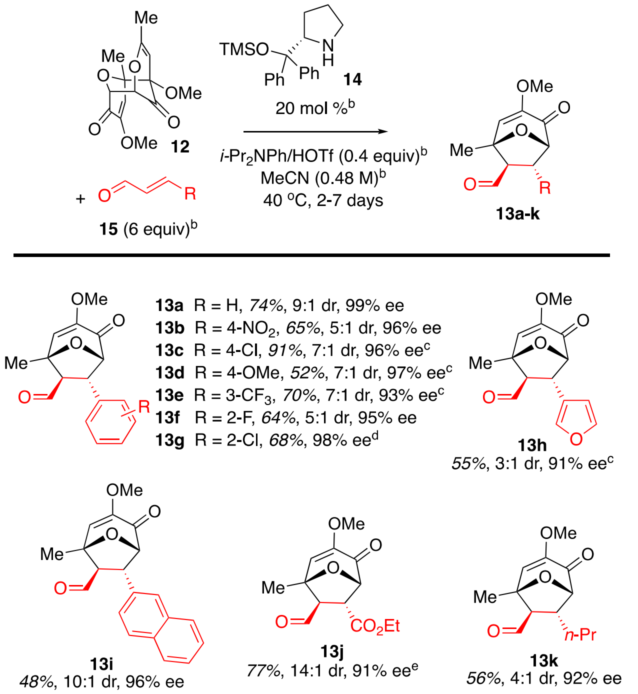
entry	additive (equiv)[f]	*t* (d)	temp (ºC)	yield (%)[a]	ee (%)[b]	dr [c]
4[g]	-	7	50	nr	--	--
5[g]	BzOH (0.2)	4	50	trace	--	--
6	i-Pr$_2$NPh (1.0) TfOH (1.0)	7	rt	32	95	10:1
7	i-Pr$_2$NPh (1.0) TfOH (1.0)	2	35	42	93	6:1
8[d]	i-Pr$_2$NPh (1.0) TfOH (1.0)	2	40	82	94	7:1
9	i-Pr$_2$NPh (1.0) TfOH (1.0)	2	45	91	89	6:1
10[h]	i-Pr$_2$NPh (1.0) TfOH (1.0)	4	40	8	--	1.5:1
11	i-Pr$_2$NPh (0.4) TfOH (0.4)	2	40	78	99	9:1
12	TfOH (0.4)	2	40	41	98	8:1

[a] Isolated yield. [b] Determined by chiral phase HPLC. [c] Determined by ^{1}H NMR. [d] Average of 2 experiments. [e] Solvent was MeCN. [f] Equivalents and

concentrations reported relative to monomeric ylide for consistency to method A. [g] Solvent was $CHCl_3$. [h] In the absence of **14**.

It is, at present, unclear why *N*,*N*-diisopropylanilinium triflate serves as an efficient additive for the reaction, whereas benzoic acid does not. Assuming that both additives are capable of catalyzing iminium ion formation, one hypothesis is that the greater nucleophilicity of the resulting benzoate, relative to both *i*-Pr_2NPh and triflate, may promote side reactions such as demethylation of the oxidopyrylium ylide (i.e., via loss of methoxide or methyl ether cleavage),[12b-c] thereby inhibiting desired reactivity. Confirming the importance of a non-nucleophilic conjugate base, TfOH alone as an additive did promote the cycloaddition reaction with comparable enantio- and diastereoselectivities, however lower yields were observed due to decomposition (entry 12).

Scheme 3. Substrate Scope Studies.[a]



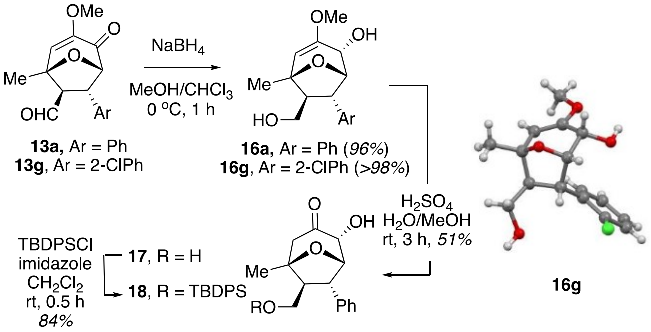
[a] Yields reflect isolated yields, with dr determined by ^1H NMR, and ee determined by chiral phase HPLC. [b] Equivalents and concentrations reported relative to monomeric ylide. [c] Reaction run at 35 °C. [d] Single diastereomer. [e] Reaction run for 11 days at -25 °C.

Upon identification of optimal reaction conditions, an investigation into the substrate scope of this transformation ensued (**Scheme 3**). The reaction exhibited broad substrate compatibility, affording 8-oxabicyclo[3.2.1]octane products in all cases in moderate to high yields and dr, and in high ee. Both electron-rich and –poor benzene rings were tolerated (**13a-g**), as were heteroaromatic and polyaromatic R groups (**13h-i**), although an aromatic R group was not required for this transformation. Adjacent non-aromatic sp^2 centers, as in ester **13j**, were acceptable. Importantly, aliphatic enals were also suitable substrates (**13k**). Also notable is the tolerance of this cycloaddition reaction for steric bulk. The enal with the most hindered β-position, generated the corresponding product, **13g**, in comparable yield to other substrates, but in higher ee and as a single diastereomer.

Remarkably, despite the diversity of enals evaluated in this reaction, the conditions developed for **13a** proved general and, with only one exception (**13j**), did not require extensive reoptimization. Only a minor adjustment in temperature was necessary for certain substrates to achieve high ee's (**13c-e, 13h**), and there was no discernable trend as to which substrates would require these slightly modified conditions. While the reaction time, product yield, and ee all increased when these substrates were subjected to a slightly reduced reaction temperature, curiously, the dr of the products decreased in all cases, sometimes dramatically so. For example, **13c** and **13e** were each formed in 13:1 dr at 40 °C and in 7:1 dr at 35 °C, while **13h** was produced in 10:1 dr at 40 °C and in 3:1 dr at 35 °C. With enal **13j**, however, there was a significant uncatalyzed background reaction even at 0 °C, so low temperature conditions were employed. α-Methyl-*trans*-cinnamaldehyde was unreactive under the standard conditions after three days.

Representative subsequent transformations of the reaction products are shown in Scheme 4. Global reduction of **13** to provide **16** introduced another stereocenter. Diols **16g** and **16a** were produced in quantitative and nearly quantitative yield, respectively, and as a single diastereomer. Acidic hydrolysis of the methyl enol ether in **16a** revealed ketone **17** in 51% unoptimized yield. Finally, selective silyl protection of the primary alcohol afforded **18** in 84% yield. Reaction products, **13**, effectively contain three carbonyl groups (including one masked as an enol ether), which have been differentiated in **18** for further orthogonal elaboration.

Scheme 4. Elaboration of Oxabicyclo Scaffold.



The relative and absolute configurations of **13a** and **16g**, respectively, were established by X-ray crystallography.[15] X-ray crystallography also revealed that the major diastereomer is the exo diastereomer. Comparison of ^1H NMR data revealed that the exo diastereomer was the major diastereomer in all cases, and the exclusive diastereomer in the case of **13g**. Based on this data, a model for asymmetric induction using the oxidopyrylium ylide form is depicted in Figure 1. It cannot be ruled out, however, that the conjugated iminium ion reacts directly with dimer **12** or an intermediate.

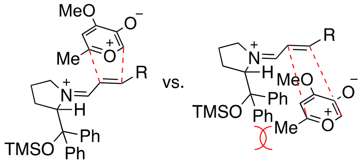


Figure 1. Proposed Mode of Asymmetric Induction.

In conclusion, the first catalytic enantioselective [5+2] dipolar cycloaddition employing 3-hydroxy-4-pyrone-based oxidopyrylium ylides was developed. This also represents the first catalytic enantioselective intermolecular oxidopyrylium cycloaddition of electron-deficient dipolarophiles, which were accessible via iminium catalysis, using a commercially available *L*-proline-derived catalyst. The oxidopyrylium ylide dimer reactant enabled use of substoichiometric quantities of strong acid (TfOH) and base (*N*,*N*-diisopropylaniline), which was critical to attain the best yields, selectivities, and reaction times. This transformation has a remarkable substrate scope with respect to the enal reactant, yet general reaction conditions that were optimal for nearly all enals were identified. This reaction generated 8-oxabicyclo[3.2.1]octanes with four contiguous stereocenters in 91-99% ee, and the exo adduct was the major diastereomer. Reaction products can be readily elaborated, including introduction of a fifth stereocenter.

ASSOCIATED CONTENT

Supporting Information

Supporting information includes detailed experimental procedures and ^{1}H and ^{13}C NMR spectra. These materials are available free of charge via the Internet at http://pubs.acs.org.

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(14) See the Supporting Information.

(15) CCDC 1567374 and 1567375 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.