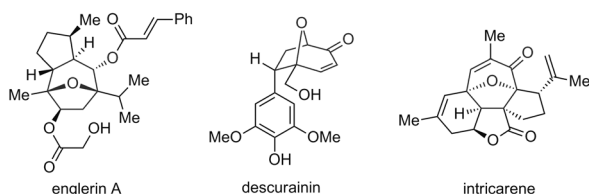


Catalytic Asymmetric Synthesis of 8-Oxabicyclooctanes by Intermolecular [5+2] Pirylium Cycloadditions**

Michael R. Witten and Eric N. Jacobsen*

Abstract: Highly enantioselective intermolecular [5+2] cycloadditions of pyrylium ion intermediates with electron-rich alkenes are promoted by a dual catalyst system composed of an achiral thiourea and a chiral primary aminothiurea. The observed enantioselectivity is highly dependent on the substitution pattern of the 5π component, and the basis for this effect is analyzed using experimental and computational evidence. The resultant 8-oxabicyclo[3.2.1]octane derivatives possess a scaffold common in natural products and medicinally active compounds and are also versatile chiral building blocks for further manipulations. Several stereoselective complexity-generating transformations of the 8-oxabicyclooctane products are presented.

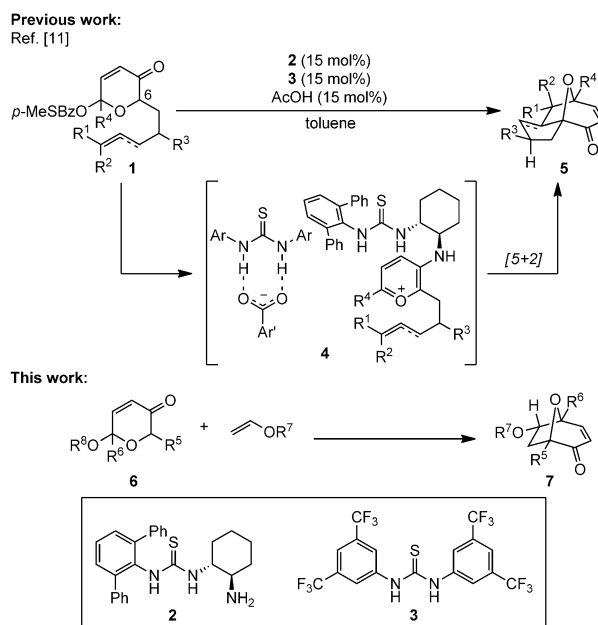
Chiral 8-oxabicyclo[3.2.1]octane architectures reside at the core of numerous natural products and biologically significant compounds (Scheme 1).^[1,2] Heterocycles of this class have also proven to be valuable intermediates in the stereoselective synthesis of oxygenated seven-membered carbocycles^[3]



Scheme 1. The 8-oxabicyclo[3.2.1]octane core in selected natural products.

and tetrahydrofuran derivatives.^[4] Successful stereoselective approaches to the 8-oxabicyclo[3.2.1]octane framework have relied on transition-metal-catalyzed [3+2] cycloadditions,^[5] [4+3] cycloadditions,^[6] diastereoselective [5+2] cycloadditions,^[7] and diastereoselective cascade cyclizations.^[8]

The [5+2] cycloaddition of a pyrylium ylide precursor with a C₂ dipolarophile (e.g. **6** to **7**, Scheme 2) provides a concise approach to the 8-oxabicyclo[3.2.1]octane frame-



Scheme 2. Enantioselective [5+2] cycloadditions. Bz = benzoyl.

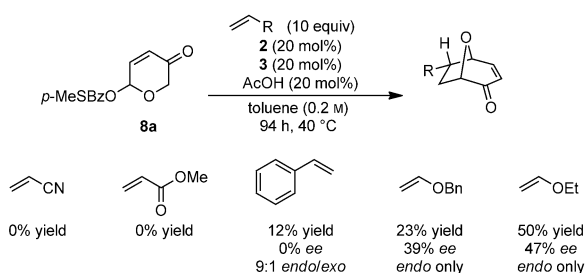
work, while also embedding a reactive α,β -unsaturated ketone in the bicyclic core.^[9,10] The products can thus be subjected to stereoselective elaboration to afford a diverse array of chiral structures in just one or two steps (see below). We reported recently that a dual catalyst system consisting of the chiral primary amine **2** and the achiral thiourea **3** catalyzes enantioselective intramolecular [5+2] cycloadditions of alkenylpyranones of structure **1** through the proposed intermediacy of thiourea-complexed aminopyrylium salts (**4**, Scheme 2).^[11–13] While this method enables the preparation of a range of complex tricyclic products, the corresponding intermolecular reaction would provide more general access to 8-oxabicyclo[3.2.1]octane derivatives from simpler and more accessible starting materials.^[14] However, initial efforts to effect intermolecular variants of these reactions proved unsuccessful (< 40% ee).^[11] Here, we disclose that closer examination of this reaction manifold has revealed striking substrate structure-enantioselectivity effects and has led to the successful development of highly enantioselective intermolecular [5+2] cycloadditions.

The racemic pyranone **8a** (Scheme 3), which is superficially analogous to pyranone substrates **1** identified as optimal for the intramolecular reaction,^[11] was examined initially as a model substrate for the study of the intermolecular cycloaddition. Treatment of **8a** with a series of

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Scheme 3. Screen of 2 π components.

terminal alkenes under the dual catalyst conditions developed in the original study revealed that the electronic properties of the 2 π component had a strong effect on reactivity.^[15] Electron-deficient olefins such as acrylonitrile and methyl acrylate were completely inert; styrene displayed measurable but low reactivity to afford racemic product; electron-rich olefins such as benzyl vinyl ether and ethyl vinyl ether underwent cycloaddition with higher conversions and encouraging enantioselectivity. The observation that a nucleophilic 2 π reactant is required in the catalytic reaction is consistent with a mechanism involving a cationic, electron-poor aminopyrylium intermediate analogous to **4** (Scheme 2) rather than an ambiphilic, zwitterionic oxidopyrylium intermediate.^[9f,g]

It proved possible to affect the enantioselectivity of the intermolecular cycloaddition reaction to a remarkable degree through relatively subtle modifications to the structure of the pyrylium precursor. All substrates shown to undergo intramolecular [5+2] cycloadditions with high enantioselectivity in the original study possessed a linkage to the 2 π component through the 6-position of the pyranone (**1**, Scheme 2).^[11] The possibility that the presence of a 6-substituent might affect the enantioselectivity in the intermolecular reaction was evaluated by comparing the reaction of **8a** with that of methylated pyranone **9a** (Table 1, entries 1 and 2).^[15] The dramatic improvement in the enantioselectivity observed with methylated derivative **9a** suggests a critical role of that substituent in controlling the transition-structure geometry in the catalytic reaction (see below).

Table 1: Reaction optimization.^[a]

8a: R = H, R' = *p*-MeSBz
9a: R = Me, R' = *p*-MeSBz
9b: R = Me, R' = *p*-(NO₂)Bz
9c: R = Me, R' = *p*-FBz
9d: R = Me, R' = 3,4,5-F₃Bz

Entry	Substrate	<i>t</i> [h]	Yield ^[b] [%]	ee ^[c] [%]
1	8a	48	53	47
2	9a	48	55	90
3	9b	48	63	94
4	9c	48	65	93
5	9d	48	73	92
6 ^[d]	9d	72	75	96

10: R = Me
11: R = H

[a] Reactions were performed on a 0.07 mmol scale. [b] Determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by HPLC using commercial columns with chiral stationary phases. [d] 5 equiv ethyl vinyl ether, room temperature.

Further improvement in both the enantioselectivity and the yield of the cycloaddition reaction was achieved through electronic tuning of the leaving group on the pyranone. While the *p*-thiomethylbenzoate leaving group had been identified as optimal in the intramolecular reaction, electron-deficient analogues **9b–d** were found to be advantageous in the intermolecular manifold (entries 3–5).^[16] In particular, 3,4,5-trifluorobenzoate derivative **9d** provided the best balance of reactivity and enantioselectivity, and further improvement in the *ee* values could be achieved by carrying out the reaction at ambient temperature and decreasing the amount of ethyl vinyl ether from 10 to 5 equivalents relative to pyranone (entry 6).

Having thus established viable parameters for effecting highly enantioselective intermolecular [5+2] cycloadditions of a pyrylium ion precursor, an investigation of the reaction substrate scope was carried out (Table 2).^[17] Pyranones bearing longer alkyl chains at the 6-position also undergo cycloaddition with ethyl vinyl ether with high enantioselectivity (entry 2); however β -branching in the side chain has a deleterious effect on reactivity (entries 3 and 4). Cycloadducts bearing siloxymethylene groups could be accessed in

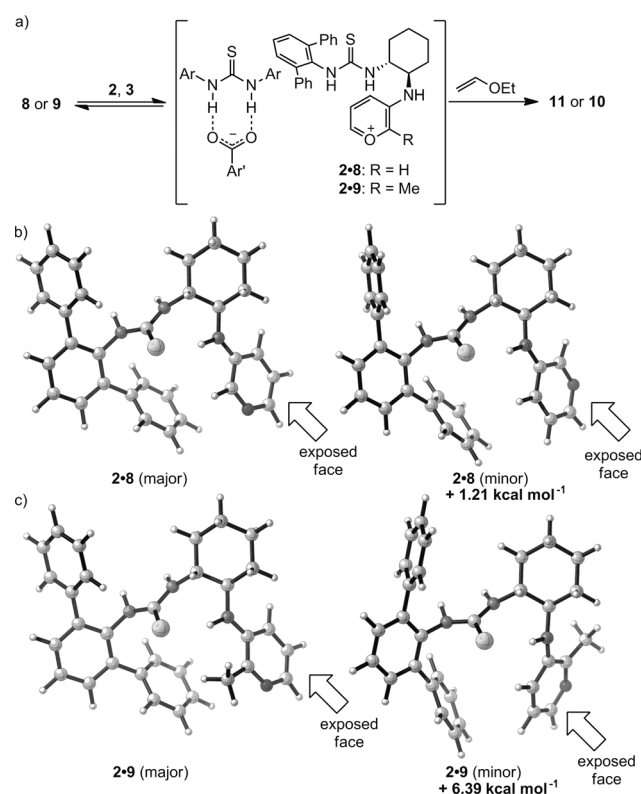


Table 2: Substrate scope.^[a]

Entry	Substrate	R ³	Product	Yield [%]	ee ^[b] [%]
1 ^[c,f]	 9d	Et	 10	69	96
2	 12	Et	 13	59	90
3 ^[c]	 14	Et	 15	22	88
4	 16	Et	 17	26	67
5	 18	Et	 19	64	86
6 ^[c,d]	 20	Et	 21	95	64
7	 22	Et	 23	75	89
8 ^[c]	 9d	Bn	 24	88	89
9 ^[e]	 9d	MOM	 25	54	91

[a] Reactions were performed on a 0.2 mmol scale. Yields of isolated products after chromatography on silica gel. For details on substrate synthesis, see the Supporting Information. [b] Determined by HPLC using commercial columns with chiral stationary phases. [c] 15 mol % **2** + 15 mol % **3**. [d] 96 h at 0 °C. [e] 10 equiv vinyl ether. [f] The absolute configuration of a derivative of **10** was determined by X-ray crystallography (see the Supporting Information), and that of all other products was assigned by analogy. MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl, Bn = benzyl.

moderate-to-good enantioselectivity under the catalytic conditions (entries 5–7). Products of this type have found extensive synthetic applications.^[3a,d,7a,c,f] Benzyl vinyl ether (entry 8) and (methoxymethoxy)ethene (entry 9) were also used successfully as 2 π components in the cycloaddition reaction, thereby affording products with readily cleavable ethers. However, styrene derivatives remain poorly reactive in reactions with **9d**, with the resultant cycloadducts formed

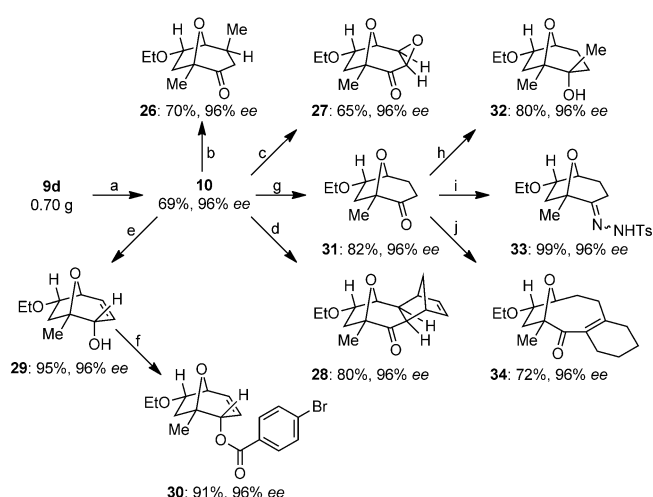
with very low (<15%) *ee* values. Enamines and polysubstituted vinyl ethers also proved to be poor substrates, the former undergoing hydrolysis under the reaction conditions and the latter exhibiting very low reactivity.^[15]

We sought to elucidate the basis for the significant difference in enantioselectivity between the reactions of pyranones **8** and **9** (e.g. Table 1, entries 1 and 2) as a possible path toward gaining insight into the mechanism of stereoinduction in these reactions. The formation of the adduct **2·9** (Figure 1a) was confirmed by mass spectrometric analysis of a reaction mixture sampled prior to addition of the vinyl ether component.^[15] The lowest energy structures of the two aminopyrylium ions **2·8** and **2·9** were located computationally (Figure 1b,c left).^[18] Rotation about the C(sp²)-N bond in each structure and reoptimization then yielded ground-state structures in which the opposite face of the aminopyrylium ion is exposed (Figure 1b,c right).^[19] In the minor conformer of **2·9**, a steric interaction between the methyl substituent and the catalyst's cyclohexyl backbone causes a significant distortion and energetic penalty (>6 kcal mol⁻¹ relative to the major conformer). That steric interaction is absent if the methyl group is omitted (Figure 1c), resulting in a much smaller energy difference between the conformations of **2·8**. We propose that the methyl substituent in **9** thus enforces a dominant reactive conformation of the aminopyrylium ion adduct, which results in a more highly enantioselective cycloaddition pathway.

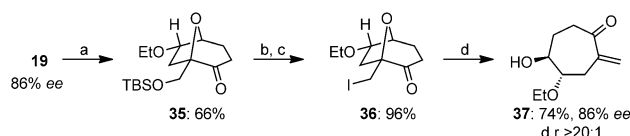
The 8-oxabicyclooctane cycloadducts possess several functional group handles for potential elaboration (Scheme 4). The synthesis of **10** was carried out successfully on 0.70 g batches of starting material under the conditions described in Table 2 to give cycloadduct in 69% yield and 96% *ee*. Products resulting from conjugate addition (**26**), epoxidation (**27**),^[20] Diels–Alder reaction (**28**),^[21] or Luche reduction (**29**) and subsequent acylation (**30**) were all generated as single diastereomers within detection limits. The cycloadduct **10** can also be subjected to hydrogenation to another key intermediate, saturated ketone **31**.^[22] This heterocycle undergoes Grignard addition stereoselectively to afford tertiary alcohol **32**. Tosylhydrazone **33**, which is primed to undergo Shapiro or Bamford–Stevens reactions, can also be readily synthesized from intermediate **31**. Finally, σ -bond insertion of cyclohexyne yields an unusual 9,6-fused ring system (**34**) in a single step.^[23]

The oxygen bridge of the 8-oxabicyclo[3.2.1]octane framework can also be cleaved reductively. In the case of iodide **36**, this results in formation of an interesting seven-membered product possessing an exocyclic enone (Scheme 5).^[24] As in all of the previous examples, the product was generated as a single diastereomer and without compromise of the optical purity of the initial cycloadduct.

In summary, the catalytic, asymmetric, intermolecular [5+2] pyrylium cycloadditions developed in this study provide



Scheme 4. Derivatization reactions. Reaction conditions: a) **2** (15 mol %), **3** (15 mol %), AcOH (15 mol %), ethyl vinyl ether, toluene; b) Me_2CuLi , Et_2O ; c) $t\text{BuOOH}$, NaHCO_3 , H_2O , MeOH ; d) cyclopentadiene, ZnCl_2 , C_6H_6 ; e) $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, NaBH_4 , MeOH ; f) $p\text{-BrBzOH}$, DMAP, pyr., CH_2Cl_2 ; g) SiH_2Ph_2 , ZnCl_2 (10 mol %), $[\text{Pd}(\text{PPh}_3)_4]$ (2 mol %), CHCl_3 ; h) MeMgI , Et_2O ; i) H_2NNHTs , THF, H_2O ; j) cyclohexenylphenyl iodonium tetrafluoroborate, KOEt_3 , THF. All products are isolated in d.r. > 20:1. DMAP = 4-dimethylaminopyridine, pyr. = pyridine, Ts = toluene-4-sulfonyl.



Scheme 5. Stereocontrolled preparation of cycloheptanone **37**. Reaction conditions: a) SiH_2Ph_2 , ZnCl_2 (10 mol %), $[\text{Pd}(\text{PPh}_3)_4]$ (2 mol %), CHCl_3 ; b) AcOH, HCl, THF, H_2O ; c) I_2 , PPh_3 , imidazole, C_6H_6 ; d) Zn, MeOH.

multifunctional chiral building blocks that are immediate precursors to a wide range of compound classes. Studies into the mechanism of catalyst cooperativity, as well as extension of the principle into other transformations, are the focus of continuing efforts in this laboratory.

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- [1] For example, Englerin A: a) R. Ratnayake, D. Covell, T. T. Ransom, K. R. Gustafson, J. A. Beutler, *Org. Lett.* **2009**, *11*, 57–60; Descurainin: b) K. Sun, X. Li, W. Li, J. Wang, J. Liu, Y. Sha, *Chem. Pharm. Bull.* **2004**, *52*, 1483–1486; Intricarene: c) J. Marrero, A. D. Rodríguez, C. L. Barnes, *Org. Lett.* **2005**, *7*, 1877–1880; Anthecularin: d) A. Karioti, H. Skaltsa, A. Linden, R. Perozzo, R. Brun, D. Tasdemir, *J. Org. Chem.* **2007**, *72*, 8103–8106; Cortistatin A: e) S. Aoki, Y. Watanabe, M. Sanagawa, A.

- Setiawan, N. Kotoku, M. Kobayashi, *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149; Hedyosumin C: f) Z.-S. Su, S. Yin, Z.-W. Zhou, Y. Wu, J. Ding, J.-M. Yue, *J. Nat. Prod.* **2008**, *71*, 1410–1413.
- [2] Compounds containing the chiral 8-oxabicyclo[3.2.1]octane core have been identified recently as psychoactive analogues of the tropane alkaloids with promising pharmaceutical potential: a) P. C. Meltzer, A. Y. Liang, P. Blundell, M. D. Gonzalez, Z. Chen, C. George, B. K. Madras, *J. Med. Chem.* **1997**, *40*, 2661–2673; b) P. C. Meltzer, S. Liu, H. S. Blanchette, P. Blundell, B. K. Madras, *Bioorg. Med. Chem.* **2002**, *10*, 3583–3591; c) P. C. Meltzer, O. Kryatova, D.-P. Pham-Huu, P. Donovan, A. Janowsky, *Bioorg. Med. Chem.* **2008**, *16*, 1832–1841.
- [3] a) P. A. Wender, H. Y. Lee, R. S. Wilhelm, P. D. Williams, *J. Am. Chem. Soc.* **1989**, *111*, 8954–8957; b) P. A. Wender, H. Kogen, H. Y. Lee, J. D. Munger, R. S. Wilhelm, P. D. Williams, *J. Am. Chem. Soc.* **1989**, *111*, 8957–8958; c) S. M. Bromidge, P. G. Sammes, L. J. Street, *J. Chem. Soc. Perkin Trans. 1* **1985**, 1725–1730; d) P. A. Wender, C. D. Jesudason, H. Nakahira, N. Tamura, A. L. Tebbe, Y. Ueno, *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977; e) P. A. Roethle, P. T. Hernandez, D. Trauner, *Org. Lett.* **2006**, *8*, 5901–5904; f) Y. Li, C. C. Nawrat, G. Pattenden, J. M. Winne, *Org. Biomol. Chem.* **2009**, *7*, 639–640; g) K. C. Nicolaou, Q. Kang, S. Y. Ng, D. Y.-K. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 8219–8222.
- [4] a) C. W. G. Fishwick, G. Mitchell, P. F. W. Pang, *Synlett* **2005**, 285–286; b) U. Murali Krishna, *Tetrahedron Lett.* **2010**, *51*, 2148–2150; c) A. A. Yadav, P. S. Sarang, G. K. Trivedi, M. M. Salunkhe, *Synlett* **2007**, 989–991; d) M. A. Ali, N. Bhogal, J. B. C. Findlay, C. W. G. Fishwick, *J. Med. Chem.* **2005**, *48*, 5655–5658.
- [5] a) S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417–1418; b) D. M. Hodgson, A. H. Labande, F. Y. T. M. Pierard, M. Á. Expósito Castro, *J. Org. Chem.* **2003**, *68*, 6153–6159; c) D. M. Hodgson, T. Brückl, R. Glen, A. H. Labande, D. A. Selden, A. G. Dossetter, A. J. Redgrave, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5450–5454; d) N. Shimada, M. Anada, S. Nakamura, H. Nimbu, H. Tsutsui, S. Hashimoto, *Org. Lett.* **2008**, *10*, 3603–3606; e) K. Ishida, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2010**, *132*, 8842–8843.
- [6] a) M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2058–2059; b) J. Huang, R. P. Hsung, *J. Am. Chem. Soc.* **2005**, *127*, 50–51.
- [7] a) P. A. Wender, K. D. Rice, M. E. Schnute, *J. Am. Chem. Soc.* **1997**, *119*, 7897–7898; b) F. López, L. Castedo, J. L. Mascareñas, *Org. Lett.* **2000**, *2*, 1005–1007; c) F. López, L. Castedo, J. L. Mascareñas, *Org. Lett.* **2002**, *4*, 3683–3685; d) U. Murali Krishna, K. D. Deodhar, G. K. Trivedi, *Tetrahedron* **2004**, *60*, 4829–4836; e) P. A. Wender, F. C. Bi, N. Buschmann, F. Gosselin, C. Kan, J.-M. Kee, H. Ohmura, *Org. Lett.* **2006**, *8*, 5373–5376; f) P. A. Wender, N. Buschmann, N. B. Cardin, L. R. Jones, C. Kan, J.-M. Kee, J. A. Kowalski, K. E. Longcore, *Nat. Chem.* **2011**, *3*, 615–619.
- [8] B. Li, Y.-J. Zhao, Y.-C. Lai, T.-P. Loh, *Angew. Chem.* **2012**, *124*, 8165–8169; *Angew. Chem. Int. Ed.* **2012**, *51*, 8041–8045.
- [9] For recent reviews, see a) V. Singh, U. Murali Krishna, Vikrant, G. K. Trivedi, *Tetrahedron* **2008**, *64*, 3405–3428; b) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 189–218; c) K. E. O. Ylijoki, J. M. Stryker, *Chem. Rev.* **2013**, *113*, 2244–2266; for pioneering reports, see d) J. B. Hendrickson, J. S. Farina, *J. Org. Chem.* **1980**, *45*, 3359–3361; e) P. G. Sammes, L. J. Street, *J. Chem. Soc. Chem. Commun.* **1982**, 1056–1057; f) P. G. Sammes, L. J. Street, *J. Chem. Soc. Perkin Trans. 1* **1983**, 1261–1265; g) P. G. Sammes, L. J. Street, *J. Chem. Res. Synop.* **1984**, 196–197.
- [10] Other than our earlier study (Ref. [11]), there is only a single report of an enantioselective [5+2] pyrylium cycloaddition

- (product < 20% ee): D. M. Hodgson, P. A. Stuppel, C. Johnstone, *ARKIVOC* **2003**, vii, 49–58.
- [11] N. Z. Burns, M. R. Witten, E. N. Jacobsen, *J. Am. Chem. Soc.* **2011**, *133*, 14578–14581.
- [12] For a review of anion-binding asymmetric catalysis, see K. Brak, E. N. Jacobsen, *Angew. Chem.* **2013**, *125*, 558–588; *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561.
- [13] For preparation and use of catalyst **3**, see a) P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217–220; b) A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407–414.
- [14] For diastereoselective intermolecular [5+2] cycloadditions, see a) K. Tchabanenko, C. Sloan, Y.-M. Bunetel, P. Mullen, *Org. Biomol. Chem.* **2012**, *10*, 4215–4219; b) E. C. Garnier, L. S. Liebeskind, *J. Am. Chem. Soc.* **2008**, *130*, 7449–7458.
- [15] See the Supporting Information for details.
- [16] In Ref. [11], we proposed that the low solubility of the *p*-thiomethylbenzoic acid by-product was a crucial driving force in the intramolecular reaction. In contrast, 3,4,5-trifluorobenzoic acid is fully soluble under the reaction conditions employed in this study. The improved reactivity imparted by the 3,4,5-trifluorobenzoate group in **9d** relative to less electron-deficient analogues may be ascribed simply to its superior properties as a leaving group. However, the 3,4,5-trifluorobenzoate leaving group is inferior in the intramolecular reaction. See the Supporting Information for details.
- [17] For certain indicated substrates, catalyst loading could be reduced to 15 mol% **2** and 15 mol% **3** without detrimental effect on yield or enantioselectivity. In all other cases, this reduction in catalyst resulted in significantly diminished yields.
- [18] B3LYP/6-31G(d) has been established as an appropriate level of theory for studying [5+2] pyrylium cycloadditions; see a) F. López, L. Castedo, J. L. Mascareñas, *J. Org. Chem.* **2003**, *68*, 9780–9786; b) S. C. Wang, D. J. Tantillo, *J. Org. Chem.* **2008**, *73*, 1516–1523.
- [19] These calculations apply to the conformations of the aminopyrylium ground states prior to the cycloaddition step, rather than to the actual transition structures for cycloaddition. They are further simplified in that they omit the thiourea **3**-benzoate counteranion. Nonetheless, we propose that the pronounced energy difference calculated for the conformations of **2·9d** is expected to translate to the relevant cycloaddition transition structures that lead to the two enantiomers **10**.
- [20] K. A. Marshall, A. K. Mapp, C. H. Heathcock, *J. Org. Chem.* **1996**, *61*, 9135–9145.
- [21] V. Nair, G. Anilkumar, T. S. Sujatha, J. S. Nair, *Synth. Commun.* **1998**, *28*, 2549–2557.
- [22] D. A. Archer, S. M. Bromidge, P. G. Sammes, *J. Chem. Soc. Perkin Trans. 1* **1988**, 3223–3228.
- [23] C. M. Gampe, S. Boulos, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 4186–4189; *Angew. Chem. Int. Ed.* **2010**, *49*, 4092–4095.
- [24] N. Ohmori, *J. Chem. Soc. Perkin Trans. 1* **2002**, 755–767.
- [25] C. Y. Legault, *CYLview*, version 1.0b; Université de Sherbrooke, 2009; <http://www.cylview.org>.