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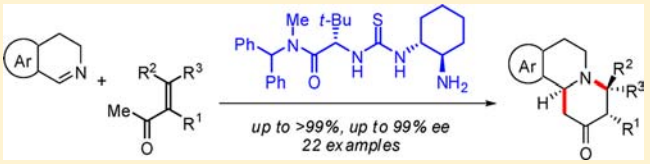
Enantioselective Formal Aza-Diels–Alder Reactions of Enones with Cyclic Imines Catalyzed by Primary Aminothioureas

Mathieu P. Lalonde, Meredeth A. McGowan, Naomi S. Rajapaksa, and Eric N. Jacobsen*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

Supporting Information

ABSTRACT: A highly enantio- and diastereoselective synthesis of indolo- and benzoquinolizidine compounds has been developed through the formal aza-Diels–Alder reaction of enones with cyclic imines. This transformation is catalyzed by a new bifunctional primary aminothiourea that achieves simultaneous activation of both the enone and imine reaction components.



INTRODUCTION

Chiral indolo- and benzoquinolizidine frameworks reside within a wide assortment of biologically active natural products and synthetic pharmaceutical compounds (Figure 1).[1,2] Among

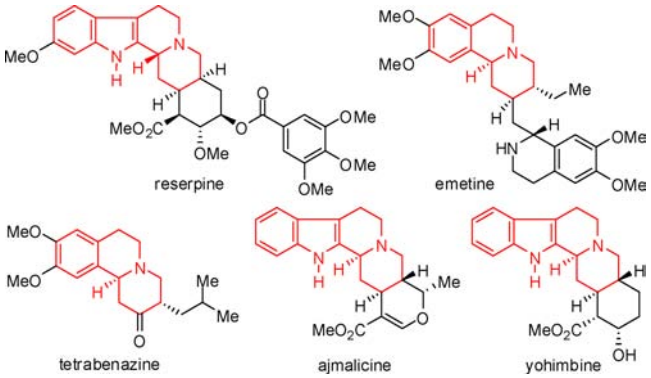
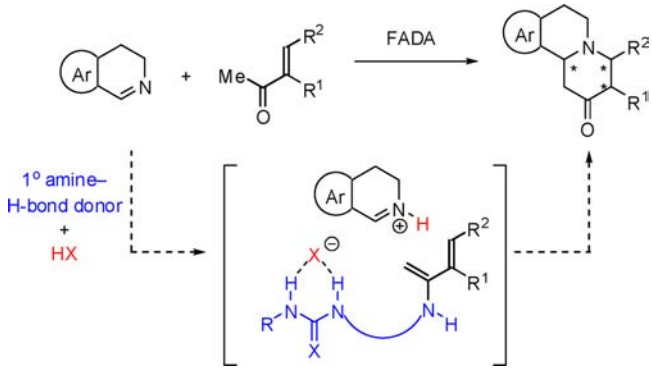


Figure 1. Selected examples of bioactive indolo- and benzoquinolizidine derivatives.

laboratory approaches to access structurally and stereochemically complex members of this class of heterocycles, formal aza-Diels–Alder (FADA) reactions between enones and cyclic imines (Scheme 1) are particularly attractive from the perspective of convergency, resulting in the concomitant formation of a C–C and C–N bond and up to four new stereocenters.[3,4] A proline-based protocol for enantioselective FADA reactions involving dihydro-β-carbolines has been described by Itoh and co-workers,[5] but the scope of this method has proven to be very limited.[6,7] We describe here the discovery of a new primary aminothiourea catalyst with broad scope for the highly enantio- and diastereoselective synthesis of indolo- and benzoquinolizidine derivatives through the formal [4 + 2] cycloaddition between enones and cyclic imines.

Our approach to catalysis of the FADA reaction was premised on the possibility of a cooperative mechanism, with specific acid activation of the imine combined with activation of

Scheme 1. FADA Reactions of Enones and Cyclic Imines and Approach to Catalysis



the enone as the corresponding dienamine (Scheme 1). Ureas and thioureas have demonstrated broad utility as hydrogen-bond donor catalysts for additions to imines, inducing electrophile activation either by direct binding or indirectly by means of anion binding.[8,9] In addition, several studies have highlighted the utility of primary amines as enamine precursors in transformations that involve ketone and hindered aldehyde substrates.[10] On the basis of these precedents, we undertook an investigation of primary amine-containing hydrogen-bond donors as bifunctional catalysts for the enantioselective FADA reaction of enones and cyclic imines.

RESULTS AND DISCUSSION

A series of thioureas of the general structure **1** was evaluated for catalysis of the FADA reaction between dihydro-β-carboline **2a**[11] and commercially available enone **3a** (Table 1). Systematic variation of the amide, amino acid, and diamine components of the catalyst (e.g., entries 1–6)[12] led to the determination that the primary amino functional group was essential for catalysis

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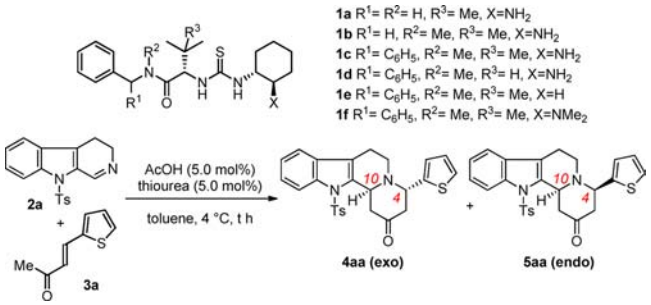
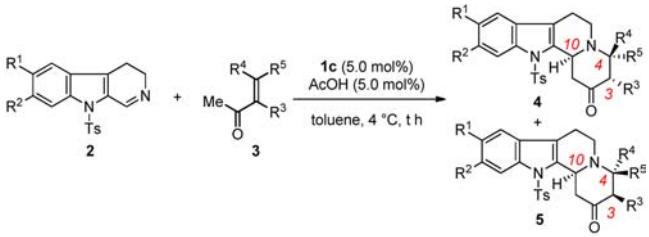
Table 1. Catalyst Optimization Studies[a]



entry	catalyst	t (h)	yield[b] (%)	dr[c] (**4aa**:**5aa**)	ee[d] (%) (**4aa**/**5aa**)
1	**1a**	72	67	2.1:1	88/95
2	**1b**	52	75	3.2:1	88/95
3	**1c**	60	89	9.4:1	99/97
4	**1d**	48	77	3.7:1	94/98
5	**1e**	72	0	–	–
6	**1f**	60	0	–	–
7[e]	**1c**	60	6	5.6:1[f]	94/90
8[g]	**1c**	60	92	5.6:1	97/96
9[h]	**1c**	72	68	9.2:1	99/99

[a]Unless noted otherwise, reactions were conducted using **2a** (0.1 mmol, 1.0 equiv), **3a** (2.0 equiv), **1a**–**f** (5.0 mol %), and AcOH (5.0 mol %) at 4 °C in anhydrous toluene ([**2a**] = 0.1 M). The notation **4xy** refers to the FADA adduct derived from imine **2x** and enone **3y**. [b]Isolated yield of diastereomerically pure **4aa** following purification by flash column chromatography. [c]Determined by HPLC analysis of the unpurified reaction mixture. [d]Determined by HPLC analysis of pure, isolated product diastereomers using commercial chiral columns. [e]Reaction carried out with 0 equiv of AcOH. [f]Calculated based on the isolated yields of each diastereomer. [g]Reaction carried out with 5.0 mol % BzOH instead of AcOH. [h]Reaction carried out with 1.2 equiv of **3a**.

Table 2. Primary Aminothiourea-Catalyzed FADA Reactions of Enones and Substituted 9-Tosyl-3,4-dihydro-β-carboline Imines[a]



2a: R^1=R^2=H
2b: R^1=Cl, R^2=H
2c: R^1=H, R^2=OMe

3a: R^3=R^4=H, R^5=2-C_4H_3S
3b: R^3=R^4=H, R^5=C_6H_5
3c: R^3=R^4=H, R^5=*p*-$MeOC_6H_5$
3d: R^3=R^4=H, R^5=*p*-$(CH_3)_2NC_6H_5$
3e: R^3=R^4=H, R^5=*p*-BrC_6H_5
3f: R^3=R^4=H, R^5=*p*-$CF_3C_6H_5$
3g: R^3=R^4=H, R^5=4-C_5H_4N
3h: R^3=R^4=H, R^5=2-C_4H_3O
3i: R^3=R^4=H, R^5=3-C_4H_3O
3j: R^3=R^4=H, R^5=*n*-C_3H_7
3k: R^3=R^4=H, R^5=*i*-C_3H_7
3l: R^3=R^4=H, R^5=*t*-C_4H_9
3m: R^3=Et, R^4=R^5=H
3n:
3o: R^3=H, R^4=R^5=Me

entry	imine	enone	t (h)	yield of **4**[b] (%)	dr[c] (**4**:**5**)	ee[d] (%) (**4**/**5**)
1	**2a**	**3a**	60	90	9.4:1	99/97
2	**2a**	**3b**	48	95	18:1	99/n.d.
3	**2a**	**3c**	72	87	7.6:1	99/99
4	**2a**	**3d**	312	57	1.3:1	99/99
5[e]	**2a**	**3e**	48	91	10:1	99/n.d.
6	**2a**	**3f**	30	92	13:1	98/n.d.
7	**2a**	**3g**	48	96	>19:1	98/n.d.
8	**2a**	**3h**	48	84	4.2:1	96/99
9	**2a**	**3i**	48	81	4.5:1	99/99
10	**2a**	**3j**	55	91	>19:1	98/n.d.
11	**2a**	**3k**	60	>99	>19:1	98/n.d.
12	**2a**	**3l**	192	90	>19:1	97/n.d.
13[f]	**2a**	**3m**	192	88	7.0:1	95/92
14[g]	**2a**	**3n**	48	87	>19:1	99/n.d.
15[h]	**2a**	**3o**	408	50	–	92/n.d.
16	**2b**	**3j**	48	88	>19:1	97/n.d.
17	**2c**	**3j**	48	87	>19:1	97/n.d.

[a]Unless noted otherwise, reactions were conducted using **2** (0.3 mmol, 1.0 equiv), **3** (2.0 equiv), **1c** (5.0 mol %), and AcOH (5.0 mol %) at 4 °C in anhydrous toluene ($[\mathbf{2}]_0$ = 0.1 M). [b]Yields of isolated diastereomerically pure product following flash column chromatography on silica gel. [c]Determined by chiral HPLC analysis of the unpurified reaction mixture. [d]Determined by HPLC analysis of pure, isolated product diastereomers using commercial chiral columns (see SI). [e]Absolute configurations of **4ae** and **5ae** were determined via X-ray crystallography. The stereochemistry of all other adducts is assigned by analogy. [f]**1c** (20 mol %), AcOH (20 mol %), 23 °C. [g]**1c** (10 mol %), AcOH (10 mol %), 23 °C. [h]Incomplete conversion after 408 h.

(entries 5 and 6) and that the steric properties of the amide exerted a significant influence on stereoselectivity. Ultimately, tertiary amide derivative **1c** was shown to be optimal for the generation of the exo cycloadduct **4aa** with respect to both diastereo- and enantioselectivity. A crucial role of a weak Brønsted acid additive was also established: In the absence of catalytic AcOH, very low turnover of the thiourea catalyst was observed, although the enantioselectivity remained high (entry 7). A beneficial role of added AcOH has been observed in other primary aminothiourea-catalyzed reactions[10] and may be ascribed to acceleration of the condensation and/or hydrolysis steps integral to the enamine catalysis cycle. Additionally, thiourea-assisted, specific acid activation of the imine (Scheme 1, X = OAc) represents another potential role of the acid cocatalyst.[13] Consistent with this hypothesis, the identity of the carboxylic acid was found to have a measurable influence on the enantioselectivity of the transformation (AcOH vs BzOH, entries 3 and 8). Finally, improved product yields were obtained using an excess of enone (Table 1, entries 3 vs 9), as this served to curtail the effects of product inhibition.[14]

Under the optimized conditions outlined above, primary aminothiourea **1c** displays broad scope in FADA reactions between dihydro-β-carboline derivatives and conjugated enones [Table 2; see Supporting Information (SI) for additional substrates]. High yields of highly enantioenriched adducts were obtained with enones bearing β-aryl and heteroaryl substituents (entries 1–9) and linear and branched alkyl substituents (entries 10–13) as well as cyclic enones (entry 14). Longer reaction times and/or higher catalyst loadings were required for α-substituted (entries 13, 14) and electron-rich β-aryl substituted enones (entry 4), presumably due to slower imine/enamine formation with the aminothiourea catalyst.

The scope of the aminothiourea methodology with respect to the imine component includes both electron-deficient and -rich dihydro-β-carbolines (Table 2, entries 16 and 17). Substituted 3,4-dihydroisoquinolines (**6**) also underwent FADA reactions with enone **3j** in the presence of catalyst **1c** to generate chiral benzoquinolizidine frameworks in high yield, dr, and ee, although higher catalyst loadings were required for this imine substrate class (Table 3).[15]

Examination of the data in Table 2 reveals a trend where FADA adducts bearing electron-rich C4 substituents are obtained in relatively low diastereomeric ratios (e.g., entries

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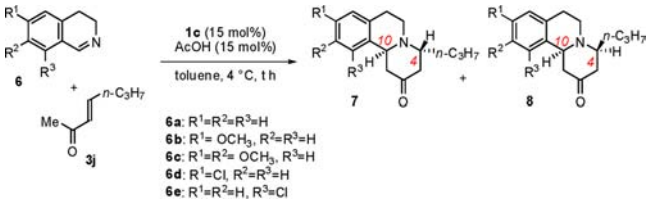
Table 3. Primary Aminothiourea-Catalyzed FADA Reactions of Enones and 3,4-Dihydroisoquinolines[a]



entry	imine	t (h)	yield[b] (%) (7)	dr[c] (7:8)	ee[d] (%) (7)
1[e]	6a	60	88	>19:1	92
2	6b	48	89	16:1	91
3[f]	6c	48	>99	17:1	92
4	6d	72	93	>19:1	92
5	6e	48	88	15:1	91

[a]Unless otherwise noted, reactions were conducted using **6** (0.2 mmol, 1.0 equiv), **3j** (1.5 equiv), **1c** (15 mol %), and AcOH (15 mol %) at 4 °C in anhydrous toluene ([**6**] = 0.1 M). [b]Yields of isolated diastereomerically pure product following flash column chromatography on silica gel. [c]Determined by chiral HPLC analysis of the unpurified reaction mixture. [d]Determined by chiral HPLC analysis of pure, isolated product diastereomers. [e]**6a** (0.4 mmol scale). [f]**6c** (0.35 mmol scale).

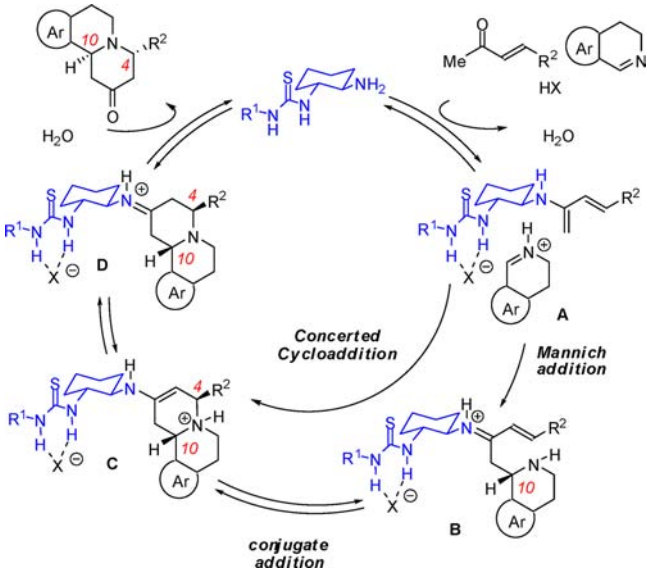
4, 8, and 9). In order to determine whether diastereoselectivity is under kinetic or thermodynamic control, diastereomerically pure adduct **4ad** was subjected to the reaction conditions in the presence of 1 equiv of enone **3d** for 4 d.[16] A product ratio of 6.3:1 (**4ad**:**5ad**) was determined.[17,18] However, a crossover experiment conducted between diastereomerically pure adduct **4aa** and enone **3j** yielded none of the possible crossover product **4aj**, indicating that the overall reaction is not reversible.[19] Instead, the observed decrease in the product diastereomeric ratio suggests that during the course of the reaction, kinetic adducts **4** can undergo epimerization at C4 to thermodynamic adducts **5**,[20] but that the C10 center is formed irreversibly.

Based on these observations, we outline a catalytic cycle for the primary aminothiourea-catalyzed FADA reaction (Scheme 2).[21] In this proposal, activation of the enone is achieved by the catalyst through formation of the corresponding covalently bound dienamine, and simultaneously the imine is activated as a thiourea-bound iminium ion (**A**). Cyclization to intermediate **C** can then proceed by means of an irreversible concerted [4 + 2] cycloaddition or by a stepwise Mannich-conjugate addition, in which the C10 center is installed irreversibly. Tautomerization of enamine **C** to iminium ion **D**, followed by hydrolysis releases the FADA adduct and regenerates the aminothiourea catalyst. The diminished diastereomeric ratios of FADA adducts containing electron-rich C4 substituents can be ascribed to either or both of the mechanisms outlined in Scheme 3. An off-cycle retro-Mannich reaction of intermediate **D** or a potentially on-cycle β-elimination from tautomeric intermediate **C** would generate iminium ions **E** and **B**, respectively, which would both be stabilized by electron-rich C4 substituents. Ring closure from either of these iminium ion intermediates could result in the formation of thermodynamic FADA adducts via intermediates **C**′ or **D**′.

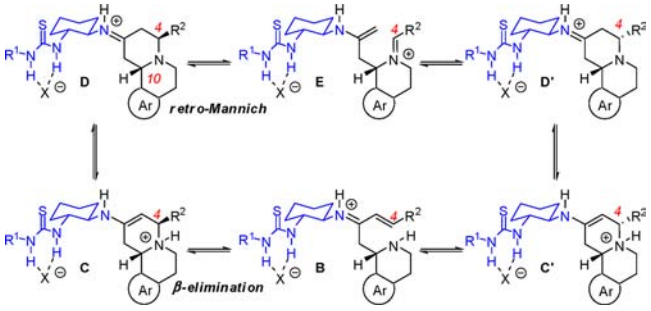
CONCLUSION

In conclusion, we have developed a primary aminothiourea-catalyzed FADA reaction of enones and cyclic imines for the enantioselective synthesis of a variety of stereochemically complex indolo- and benzoquinolizidine building blocks. The hydrogen-bond donor and primary amine are essential functional components of the optimal catalyst, allowing for dual activation of the reaction components. The application of this catalyst to the synthesis of alkaloid natural products is the subject of ongoing research.[22]

Scheme 2. Proposed Catalytic Cycle for the Formation of FADA Adducts



Scheme 3. Possible C4-Epimerization Pathways



ASSOCIATED CONTENT

Supporting Information

Catalyst optimization studies, complete experimental procedures, and characterization data for substrates and FADA products, ee and dr determination, and crystallographic data for compounds **4ae** and **5ae**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

jacobsen@chemistry.harvard.edu

Notes

The authors declare no competing financial interest.

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(6) Proline catalysis of the reaction of imine **2a** with three different enones has been reported (ref 5). High catalyst loadings (30−50 mol %) and large excess of enone (30 equiv relative to imine in two of the reported examples) were required to achieve acceptable yields of cyclization product.

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(11) **2a** was obtained from tryptamine in 75% overall yield over three steps. See SI.

(12) See SI for an expanded description of the catalyst and reaction optimization studies.

(13) This type of anion-binding catalysis has been invoked in other thiourea-promoted reactions of imines. See: Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887−890.

(14) The excess enone can be recovered quantitatively from the reaction mixture. See SI (Scheme S8) for a product inhibition study.

(15) Proline was found to be far inferior as a catalyst for FADA reactions involving dihydroisoquinolines. For example, reaction of imine **6d** with enone **3j** (entry 4 in Table 3) with 30 mol % proline afforded a 1.3:1 mixture of **7dj** and **8dj** in 66% and 46% ee, respectively.

(16) These conditions were chosen to mimic conditions toward the completion of the reaction, where there is one equivalent of unreacted enone remaining.

(17) The ee of the major diastereomer was 99% whereas that of the minor was 98.5%. Virtually no epimerization occurred when the analogous experiment was conducted with catalyst **1e**.

(18) Virtually no epimerization is observed in the absence of catalyst.

(19) FADA adduct **4aa** was recovered quantitatively and with a slight diminishment of dr (>99:1 to 99:1).

(20) Absolute configuration of **4ae** and **5ae**, determined via X-ray crystal structure analysis, confirms that epimerization occurs at C4.

(21) Girling, P. R.; Kiyoi, T.; Whiting, A. *Org. Biomol. Chem.* **2011**, *9*, 3105−3121.

(22) For example, catalyst **1c** has been applied successfully to the enantioselective total synthesis of reserpine: Rajapaksa, N. S.; McGowan, M. A.; Rienzo, M.; Jacobsen, E. N. *Org. Lett.* **2013**, DOI: 10.1021/ol400046n.