

Direct Enantioselective Brønsted Acid Catalyzed *N*-Acyliminium Cyclization Cascades of Tryptamines and Ketoacids

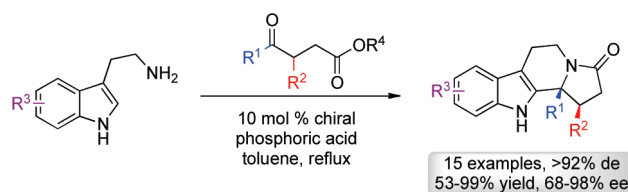
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ABSTRACT



A direct enantio- and diastereoselective *N*-acyliminium cyclization cascade through chiral phosphoric acid catalyzed condensation of tryptamines with γ - and δ -ketoacid derivatives to provide architecturally complex heterocycles has been developed. The reaction is technically simple to perform, atom-efficient, and broad in scope. Employing 10 mol % of (*R*)-BINOL derived chiral phosphoric acids in refluxing toluene allowed the polycyclic product materials to be generated in good yields (53–99%) and moderate to high enantioselectivities (68–98% ee).

N-Acyliminium ion cyclization reactions are powerful for the construction of nitrogen-containing heterocyclic ring systems.¹ When these are incorporated into cascade sequences,² powerful strategies for the one-pot production of polycyclic reaction products emerge. In a contribution to this field, we recently described the development of an enantioselective *N*-acyliminium ion cyclization reaction under chiral Brønsted acid catalysis. Reaction of various enol lactones **1** with tryptamine derivatives **2** in the presence of binol phosphoric acid (BPA) catalysts in refluxing toluene gave polycyclic products **3** in good to excellent yields and

high enantiomeric excess (Scheme 1). The reaction was found to be general for a range of substituted tryptamine derivatives and enol lactones made in a prior step or *in situ* via gold-catalyzed cycloisomerization of alkynoic acids.³

Although successful, the work was hampered by the need to form the enol lactone starting materials, and in some cases this was nontrivial. It was recognized that a direct method beginning with commercially available or readily prepared keto esters or keto acids **II** would circumvent these problems

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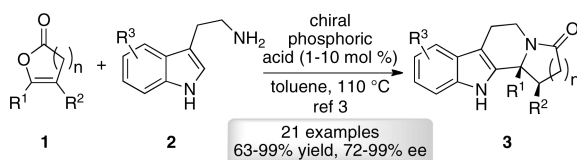
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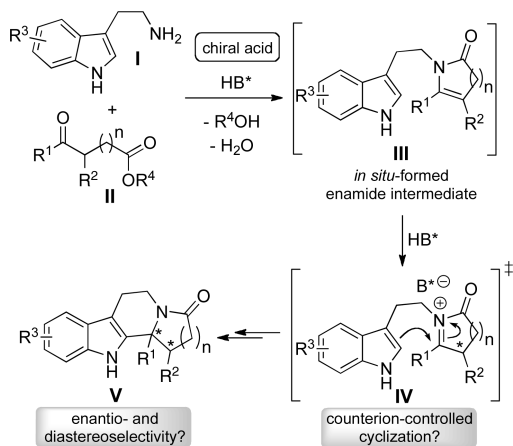
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Scheme 1. Enantioselective *N*-Acyliminium Cyclization Cascades under BPA Catalysis



and also allow the chemistry to be extended to spirocyclic products. Initial condensation of the tryptamine **I** with **II** would generate an imine which under Brønsted acid catalysis should condense with the ester resulting in the formation of an enamide intermediate **III**. On protonation by HB* in a low-polarity solvent, tight ion pairing of the *N*-acyliminium ion with the chiral conjugate base of the Brønsted acid should occur.^{4,5} Provided there is sufficient ordering and effective facial differentiation in this ion pair, attack of the pendant indole nucleophile should give rise to enantioselectivity in the (irreversible) cyclization step.⁶ With at least three points of diversity, numerous polycyclic structures **V** bearing additional stereogenic centers, functionality, and spectator groups could be readily accessed (Scheme 2). This would

Scheme 2. Proposed Direct BPA-Catalyzed Enantioselective Dehydrative *N*-Acyliminium Ion Cyclization Cascade



enable the repeated application of the method in target or library synthesis. Herein we report our findings.

A preliminary reactivity study was performed using equimolar quantities of commercially available racemic

methyl 2-(2-oxocyclohexyl)acetate ($\pm$)-**4a** and tryptamine **2a**. Under conditions similar to those in our previous report,³ 10 mol % of 3,3'-bis(triphenylsilyl) BPA **5a** was employed as the catalyst in refluxing toluene for 24 h.⁷ Pleasingly the anticipated β -carboline product **3a** was formed in good yield and good enantiomeric excess (ee 83%) as a single diastereoisomer (>98:2 dr) (Table 1, entry 1). Furthermore, under

Table 1. Proof of Principle, Catalyst Screen, and Reaction Condition Optimization^a

entry	R	4	R ¹	catalyst	5	temp (°C)	time (h)	yield (%)	ee (%) ^a
1	Me	a	SiPh ₃	BPA	a	110	24	80	83
2	Et	b	SiPh ₃	BPA	a	110	24	77	82
3	H	c	SiPh ₃	BPA	a	110	24	77	81
4	H	c	3,5-(CF ₃) ₂ Ph	BPA	b	110	24	95	63
5	H	c	2,4,6-(ⁱ Pr) ₃ Ph	BPA	c	110	24	87	14
6	H	c	anthracenyl	BPA	d	110	24	95	43
7	H	c	9-phenanthryl	BPA	e	110	48	99	53
8	H	c	<i>p</i> -NO ₂ Ph	BPA	f	110	24	86	57
9	H	c	SiMe ₃	BPA	g	110	48	89	74
10	H	c	SiPh ₃	H ₈ -BPA	h	110	24	63	82

^a Determined by HPLC analysis using a chiral column (see Supporting Information for details).

identical reaction conditions, both the analogous ethyl ester and carboxylic acid substrates gave **3a** with similar levels of enantiocontrol and efficiency (Table 1, entries 2 and 3). With these initial results in hand, a catalyst screen (probing variation to the BINOL scaffold and the substituents at the 3 and 3' positions) was carried out using racemic acid ($\pm$)-**4c** and tryptamine **2a** to identify the most promising one in terms of reaction speed, efficiency, and enantiocontrol (Table 1, entries 3–10). Pleasingly, all of the screened acid catalysts efficiently facilitated the cyclization cascade with reaction times of between 24 and 48 h. Enantioselectivity was observed in all cases, but the optimal control arose from (*R*)-TPS-BPA (entry 3, 81% ee, 77% yield) and (*R*)-H₈-TPS-BPA (entry 10, 82% ee, 63% yield). The optimal conditions employed equimolar quantities of ($\pm$)-**4c** and **2a** at 0.0048 M in refluxing toluene with the BPA at 10 mol %.⁸

(4) For recent reviews on asymmetric organocatalysis by H-bond donors and Brønsted acids, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Doyle, A.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (d) Terada, M. *Chem. Commun.* **2008**, *35*, 4097. (e) Terada, M. *Synthesis* **2010**, *12*, 1929.

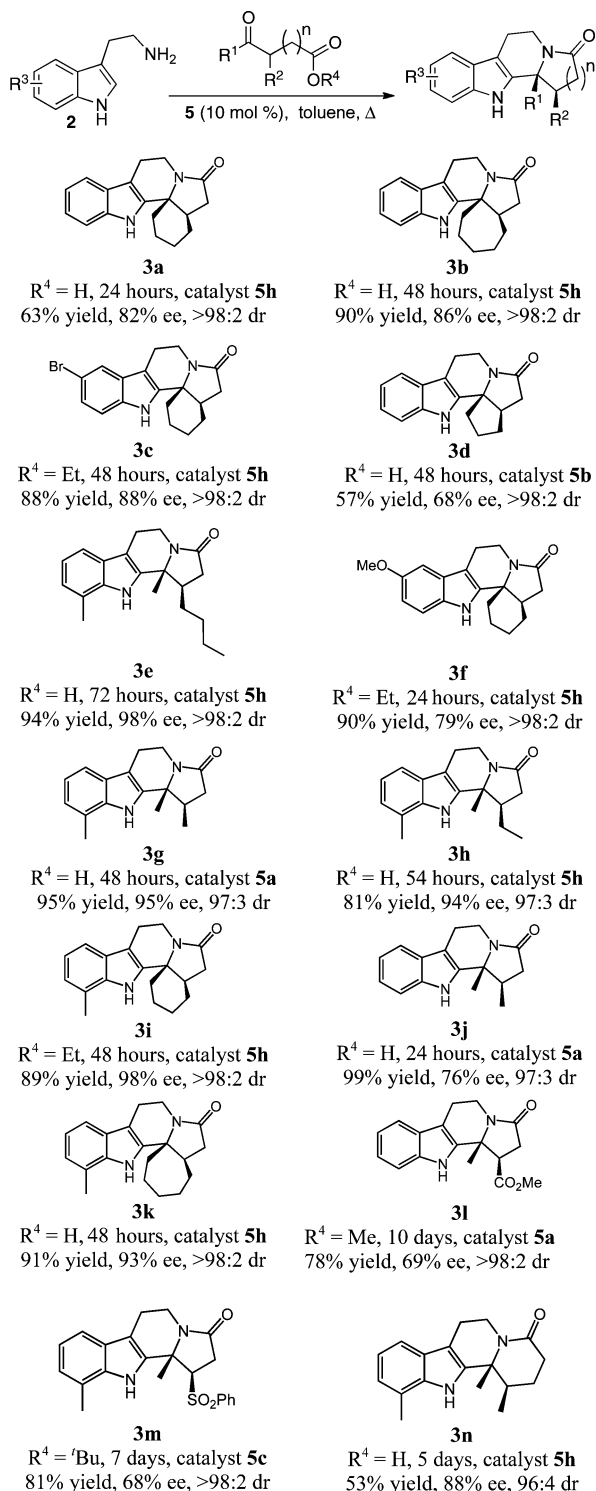
(5) For recent examples of chiral counterion-induced enantioselection in *N*-acyliminium ion reactions, see: (a) Li, G.; Kaplan, M. J.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2010**, *12*, 1960. (b) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 2553. (c) Rueping, M.; Lin, M.-Y. *Chem.-Eur. J.* **2010**, *16*, 4169.

(6) For recent organocatalyzed enantioselective additions of indoles to *N*-acyliminium ions, see: (a) Rueping, M.; Nachtsheim, B. J. *Synlett* **2010**, *1*, 119. (b) Peterson, E. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6328. (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. For addition of pyrroles, see: (d) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577. For related additions to sulfenamide iminiums, see: (e) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485. For additions to sulfonyliminiums, see: (f) Sun, F.-L.; Zheng, X.-J.; Gu, Q.; He, Q.-L.; You, S.-L. *Eur. J. Org. Chem.* **2010**, 47.

(7) For pioneering studies on chiral phosphoric acid catalysis, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Uruguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

With optimal reaction conditions established, the scope of the reaction with respect to the tryptamine and the keto acid (or ester) was investigated (Scheme 3). Cyclopentanone,

Scheme 3. Scope of the Direct Enantioselective BPA-Catalyzed *N*-Acyliminium Ion Cyclization Cascade

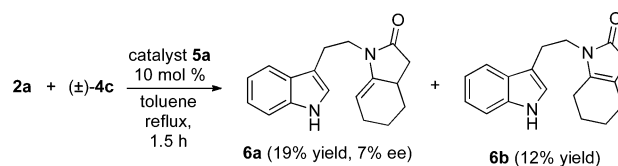


cyclohexanone and cycloheptanone derived γ -keto acids or esters were all good substrates, giving the desired β -carbo-

lines in good yields, as single diastereomers (>98:2 dr), with moderate to high enantioselectivities (**3a–d**, **3f**, **3i**, **3k**). Acyclic γ -keto acids (R^1 and $R^2 = \text{alkyl}$) also partook in the reaction under the same conditions to form the fused lactams with high diastereoselectivities ($\geq 97:3$ dr) and moderate to high enantioselectivities (**3e**, **3g,h**, **3j**). Substrates bearing electron-withdrawing groups α to the ketone were also successful in yielding the expected tetracycle (**3l,m**). Tryptamines bearing methoxy, bromide, or methyl groups were reactive, but 7-methyl tryptamine gave rise to the highest levels of enantioinduction. Notably, in all cases the diastereoselectivity in the reaction was excellent. When applied to a δ -keto acid, a slightly modified procedure afforded six-membered fused lactam product **3n** with good diastereo- and enantioselectivity.

Single crystal X-ray analysis established the absolute and relative stereochemistry of **3c** and the relative stereochemistry of **3g**.⁹ The absolute and relative stereochemistry of **3l** was established by comparison of its NMR spectroscopic data, specific rotation, and HPLC retention times with the literature data.³ Although the origin of enantioselectivity has yet to be determined, we believe the high diastereoselectivity in the enantioenriched product is a result of a *dynamic kinetic asymmetric cyclization* and arises through a combination of strong substrate control in the cyclization and a fast epimerization via a prochiral cyclic enamide intermediate (see Scheme 2).^{3,10} It was discovered that when tryptamine **2a** was reacted with ($\pm$)-**4c** in the presence of **5a** in refluxing toluene, after a short reaction time, two isomeric enamides **6a** and **6b** could be isolated (Scheme 4). The chiral enamide

Scheme 4. Identification of Reaction Intermediates in the Cyclization Cascade



6a was found to have an insignificant enantiomeric excess (7% ee) compared to **3a** formed under the same conditions but with a longer reaction time (83% ee).

When **6a** or **6b** were treated with 10 mol % of **5a** under the optimized conditions for the cascade, they both gave rise to the formation of **3a** in good yields and identical enantiomeric excess (83% ee). To gain further insight, racemic oxoamide ($\pm$)-**7** was synthesized via amide coupling between

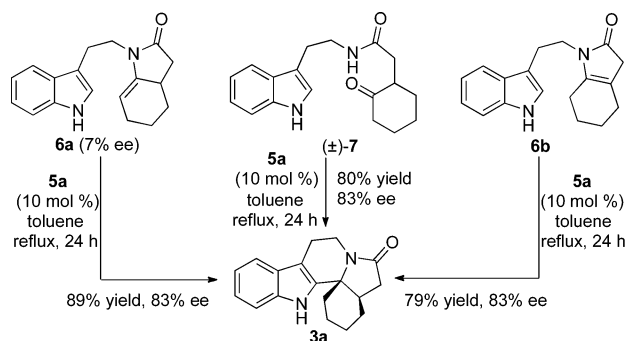
(8) As was observed in our previous studies (see ref 3), performing the reactions at 0.0048 M was found to be optimal for enantiocontrol.

(9) Crystallographic data (excluding structure factors) for **3c** and **3g** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 790998 and 790999) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

(10) For relevant discussions on dynamic kinetic asymmetric transformations, see: (a) Steinreiber, J.; Faber, K.; Griengl, H. *Chem.—Eur. J.* **2008**, *14*, 8060. See also: (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543.

tryptamine **2a** and racemic oxoacid ($\pm$)-**4c**. Treatment of ($\pm$)-**7** with 10 mol % of **5a** under the optimal cyclization conditions gave **3a** in good yield (80%) with 83% ee (Scheme 5).

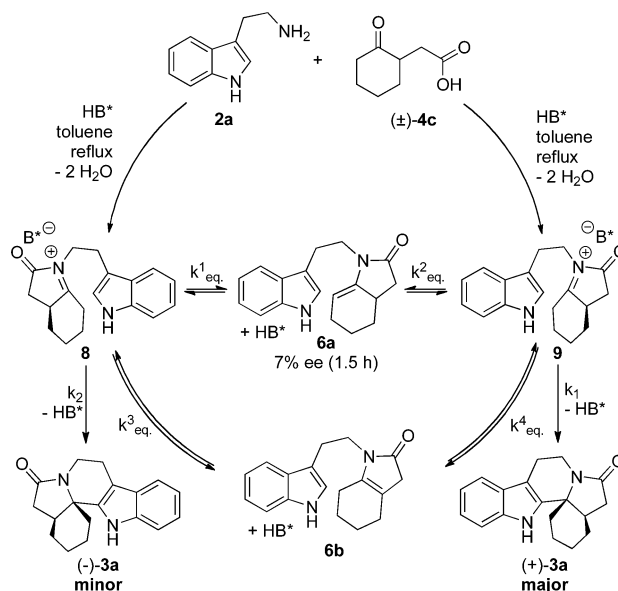
Scheme 5. Evidence for Passage through a Common *N*-Acyliminium Ion Intermediate in the Cyclization Cascade



On the basis of the outcomes of these experiments, we believe the enantiodetermining step in our cascade involves nucleophilic attack of the indole nucleophile on an *N*-acyliminium ion, and not an imine or iminium ion (followed by γ -lactam formation; see Supporting Information). Furthermore the most plausible mechanistic pathway would involve the initial formation of diastereomeric *N*-acyliminium salts **8** and **9** through condensation of the primary amine **2a** with racemic ketoacid ($\pm$)-**4c** (Scheme 6). As well as undergoing reversible deprotonation/reprotonation to the respective enantiomers of **6a**, these salts are able to rapidly interconvert via enamide intermediate **6b**, which allows epimerization of the tertiary stereogenic center. It would therefore be the relative rate of cyclization of each salt that determines the enantioselectivity and presumably k^1_{eq} , k^2_{eq} , k^3_{eq} , $k^4_{eq} \gg k_1 > k_2$.

In summary, a direct enantioselective chiral phosphoric acid catalyzed *N*-acyliminium ion cyclization cascade of tryptamines and ketoacid derivatives has been developed. The reaction is easy to perform and broad in scope and provides the polycyclic β -carboline products in good overall yields (53–99%) and moderate to high enantioselectivities

Scheme 6. Postulated Origins of Stereocontrol in the Reaction Cascade via a Dynamic Kinetic Asymmetric Cyclization



(68–98% ee). Further exploration and development work in this field is ongoing, as is the application of the chemistry to natural product synthesis. The results of these endeavors will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for compounds **3a–n**, **4**, **6a**, **6b**, and **7** and CIF files for compounds **3c** and **3g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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