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Enantioselective Brønsted Acid-Catalyzed *N*-Acyliminium Cyclization Cascades

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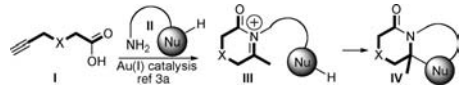
Bond formation through intramolecular attack on *N*-acyliminium ion electrophiles by π nucleophiles is a stalwart method for the construction of nitrogen-containing ring systems.[1] When this is incorporated into cascade sequences,[2] powerful strategies for the one-pot production of polycyclic reaction products emerge. To this end, we recently described a gold(I)-catalyzed reaction cascade of alkynoic acids **I** and amine-tethered π nucleophiles **II** for the direct synthesis of architecturally complex heterocyclic structures of type **IV** (Scheme 1).[3]

Scheme 1. Au(I)-Catalyzed *N*-Acyliminium Ion Cyclization Cascade



Proceeding by ring opening of in situ-formed enol lactones followed by dehydrative cyclization via *N*-acyliminium ion intermediates, this cascade was attractive for both library production and target synthesis. However, in the absence of any asymmetric controller, the overall sequence was restricted to the production of racemates. To address this limitation, we postulated that if the *N*-acyliminium ion **4** (Scheme 2, $R^2 = H$) were generated via a chiral Brønsted acid[4−6] (HA*)-catalyzed dehydrative condensation of an enol lactone **1** and an amine, such as tryptamine **2**, stereocontrol in the production of **5** could be imparted[7,8] during the enantiodetermining ring-forming step through tight ion pairing with the chiral counterion.[9] Also, this could potentially be extended to an enantio- and diastereoselective variant[10] (Scheme 2, $R^2 \neq H$) and coupled to a gold(I)-catalyzed cycloisomerization of alkynoic acid starting materials, allowing a powerful enantioselective multicatalyst reaction cascade. Herein we describe our findings.

Initially, a range of (*R*)-BINOL phosphoric acid [(*R*)-BPA] derivatives were screened for activity and enantioinduction in a model cyclization reaction of ketoamide **3a** (Table 1). In CH_2Cl_2 at room temperature with catalysts **6a**−**d** at 10 mol %, the reactions proceeded slowly to afford the desired tetracyclic product **5a** in >80% conversion after 1.5 to 10 days. The highest ee of 27% was obtained using 3,3′-bis(triphenylsilyl)BPA [(*R*)-TPS-BPA, **6d**]. A subsequent solvent, temperature, concentration, and catalyst survey revealed that a substrate concentration of 7 mM in boiling toluene with 10 mol % **6d** was optimal for the rapid synthesis of **5a** in high ee (Table 1, entry 7).

With the optimal reaction conditions in hand, we turned our attention toward the enantioselective *N*-acyliminium cyclization cascade. We first investigated the one-pot sequence starting directly with α-angelica lactone **1a** and tryptamine **2a** (Table 2, entry 1). Pleasingly, at 7 mM in boiling toluene in the presence of (*R*)-TPS-BPA **6d** (10 mol %),

Scheme 2. Concept of an Enantioselective *N*-Acyliminium Cyclization Cascade under Chiral Brønsted Acid Catalysis

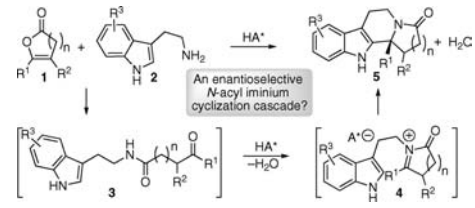
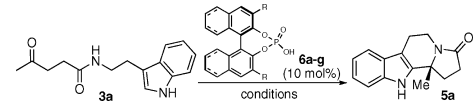


Table 1. Feasibility and Optimization Studies on Test Substrate **3a**



entry	R	catalyst	**6**	solvent	[3a] (mM)	temp	time	ee (%)[a]
1	H	BPA	**a**	CH_2Cl_2	50	rt	3 days	8
2	3,5-$(CF_3)_2$Ph	BPA	**b**	CH_2Cl_2	50	rt	36 h	15
3	4-NO_2Ph	BPA	**c**	CH_2Cl_2	50	rt	7 days	0
4	$SiPh_3$	BPA	**d**	CH_2Cl_2	50	rt	10 days	27
5	$SiPh_3$	BPA	**d**	toluene	50	rt	14 days	27
6	$SiPh_3$	BPA	**d**	toluene	35	50 °C	1 day	50
7	$SiPh_3$	BPA	**d**	toluene	7	110 °C	1 h	84
8	9-phenanthryl	BPA	**e**	toluene	7	110 °C	12 h	55
9	2,4,6-(^{i}Pr)$_3$Ph	BPA	**f**	toluene	7	110 °C	12 h	50
10	$SiPh_3$	H_8-BPA	**g**	toluene	7	110 °C	6 h	84

[a] Determined by HPLC using a Chiralcel OD column.

equimolar amounts of the reagents afforded cyclized product **5a** in quantitative yield and 84% ee after 2 h. With enantiocontrol transferring to the cyclization cascade, a range of substituted tryptamines (**2a**−**f**) incorporating electron-withdrawing and -donating substituents at positions 4, 5, 6, and 7 were then reacted with a range of five- and six-membered-ring singly or doubly substituted enol lactones (**1a**−**j**). Table 2 shows the results.

When tryptamine **2a** was used, the enantioselectivities ranged from 83 to 87% and the reaction yields from 70 to 99% (entries 1−5). Adding substituents to the indole moiety resulted in enhanced enantioselectivity in all cases (85−99% ee; entries 6−16), with the highest selectivities being observed with the phenyl-substituted lactone **1e** (87−99% ee; entries 5, 7, 11, 12, 13, and 16). Formation of a δ-lactam was also possible, however, the catalyst H_8-BPA (**6g**) was found to impart the highest levels of enantiocontrol (entry 17). To test its scale-up potential, the reaction cascade of 7-methyltryptamine **2f** and phenyl enol lactone **1e** was investigated at lower catalyst loadings. Pleasingly, employing 1 mol % **6d** yielded **5p** in 95% yield and 96% ee [see the Supporting Information (SI)].

With disubstituted enol lactones (**1g**−**j**), we were pleasantly surprised to observe only one of the two possible diastereoisomers in

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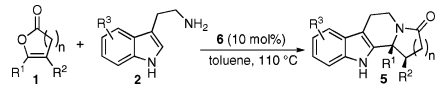
Table 2. Scope of the BPA-Catalyzed Cyclization Cascade



entry	R^1	R^2	n	1	R^3	2	6	time (h)	5	Yield (%)[a]	ee (%)[b]
1[c]	methyl	H	1	**a**	H	**a**	**d**	2	**a**	99	84
2	*n*-propyl	H	1	**b**	H	**a**	**d**	24	**b**	87	84
3	*n*-hexyl	H	1	**c**	H	**a**	**d**	12	**c**	70	83
4	*n*-dodecyl	H	1	**d**	H	**a**	**d**	12	**d**	74	83
5[c]	phenyl	H	1	**e**	H	**a**	**d**	36	**e**	78	87
6	methyl	H	1	**a**	4-Br	**b**	**d**	26	**f**	81	92
7	phenyl	H	1	**e**	4-Br	**b**	**d**	36	**g**	66	94
8	methyl	H	1	**a**	5-Br	**c**	**d**	12	**h**	99	86
9	*n*-propyl	H	1	**b**	5-Br	**c**	**d**	12	**i**	70	89
10[c]	*n*-hexyl	H	1	**c**	5-Br	**c**	**d**	24	**j**	66	88
11	phenyl	H	1	**e**	5-Br	**c**	**d**	44	**k**	65	90
12	phenyl	H	1	**e**	5-F	**d**	**d**	24	**l**	73	90
13	phenyl	H	1	**e**	6-F	**e**	**d**	24	**m**	64	89
14	methyl	H	1	**a**	7-Me	**f**	**d**	24	**n**	92	92
15	*n*-hexyl	H	1	**c**	7-Me	**f**	**d**	12	**o**	63	95
16	phenyl	H	1	**e**	7-Me	**f**	**d**	41	**p**	95	99
17	methyl	H	2	**f**	7-Me	**f**	**g**	96	**q**	82	85
18[d,e]	methyl	CO_2Me	1	**g**	H	**a**	**d**	130	**r**	74	75
19[d,e]	methyl	$P(O)(OMe)_2$	1	**h**	H	**a**	**f**	82	**s**	95	85
20[d,e]	*n*-pentyl	$P(O)(OMe)_2$	1	**i**	H	**a**	**f**	178	**t**	90	91
21[c,d,e]	methyl	SO_2Ph	1	**j**	7-Me	**f**	**f**	106	**u**	95	72

[a] Isolated yields. [b] Determined by CSP HPLC analysis. [c] See the SI for proof of stereochemistry. [d] Using 20 mol % catalyst. [e] One diastereomer was observed in the ^{1}H NMR spectrum of the crude reaction material.

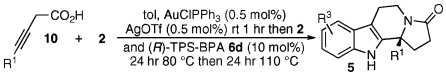
the reaction mixture, and high levels of enantioselectivity were achieved using either catalyst **6d** or **6f** (entries 18−21).

The high levels of diastereo- and enantiocontrol with doubly substituted enol lactone substrates **1g**−**j** were notable and worthy of further investigation. With short reaction times, both ketoamide **3r** and the dehydrated prochiral enamide **7** could be isolated in significant quantities (see the SI). Identification of **7** as a key intermediate in the mechanistic pathway means that the high diastereo- and enantiocontrol observed in the reaction is consistent with fast, reversible formation of the diastereomeric *N*-acyliminium salts **8** and **9** followed by rate-determining ring closure (Scheme 3), where k_1 for production of (+)-**5r** is greater than k_2 for the production of (−)-**5r** because of matched substrate[11] and catalyst control.

Pleasingly, this enantioselective cascade was compatible with an in situ enol lactone-forming gold(I)-catalyzed cycloisomerization of alkynoic acids **10** (Table 3).[3a,12] Thus, when alkynoic acids **10b**−**d** were treated with gold(I) triflate triphenylphosphine (0.5 mol %) and then tryptamines **2a**, **2c**, and **2f** in the presence (*R*)-TPS-BPA **6d** (10 mol %), the multicatalyst cascade products were isolated in good yields and with high ee's.[13]

Work to expand and apply these findings is ongoing, and the results will be reported in due course.

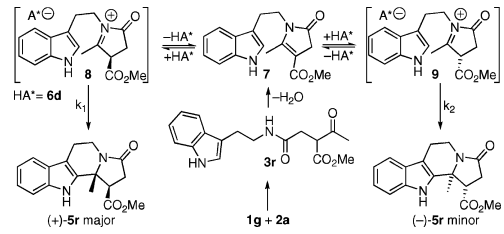
Table 3. Au(I) and Chiral Brønsted Acid Multicatalyst Cascade



entry	R^3	2	R^1	10	5	yield (%)[a]	ee (%)[b]
1	H	**a**	*n*-propyl	**b**	**b**	79	84
2	H	**a**	*n*-hexyl	**c**	**c**	92	83
3	H	**a**	*n*-dodecyl	**d**	**d**	87	83
4	5-Br	**c**	*n*-propyl	**b**	**i**	77	89
5	5-Br	**c**	*n*-hexyl	**c**	**j**	77	88
6	5-Br	**c**	*n*-dodecyl	**d**	**v**	82	89
7	7-Me	**f**	*n*-propyl	**b**	**w**	96	95
8	7-Me	**f**	*n*-hexyl	**c**	**o**	84	95
9	7-Me	**f**	*n*-dodecyl	**d**	**x**	81	95

[a] Isolated yields. [b] Determined by CSP HPLC analysis.

Scheme 3. Proposed Mechanistic Pathway



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Supporting Information Available: Experimental procedures, spectral data for **1**, **2**, **3a**, **5**, **7**, and **10**, and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(2) For selected reviews, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(3) (a) Yang, T.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 12070. Also see: (b) Yang, T.; Ferrali, A.; Campbell, L.; Dixon, D. J. *Chem. Commun.* **2008**, 2923.

(4) 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) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.

(5) 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.

(6) For selected examples illustrating the high levels of enantioselectivity using chiral Brønsted acid organocatalysis, see: (a) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (b) Martin, N. J. A.; Ozores, L.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 8976. (c) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016. (d) Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122. (e) Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001. (f) Kang, Q.; Zheng, X.-J.; You, S.-L. *Chem.—Eur. J.* **2008**, *14*, 3539. (g) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609.

(7) For examples of the related asymmetric Pictet−Spengler reaction under chiral Brønsted acid catalysis, see: (a) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086. (b) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745. (c) 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. (d) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405. For a thiourea-catalyzed example, see: (e) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887.

(8) For examples of *N*-acyliminium cyclizations using chiral thiourea catalysts, see: (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (b) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577.

(9) For examples of chiral counterion-mediated asymmetric catalysis, see: (a) García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363. (b) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (c) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (d) Rueping, M.; Antonchick, A. P.; Brickmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903.

(10) For discussions of 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.

(11) The same diastereoisomer is the sole reaction product using PTSA (cat).

(12) For selected examples of tandem (or dual) metal/organocatalysis, see: (a) Chercheja, S.; Rothenbücher, R.; Eilbracht, P. *Adv. Synth. Catal.* **2009**, *351*, 339. (b) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-H. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (c) Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6954. (d) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (e) Sorimashi, K.; Terada, M. *J. Am. Chem. Soc.* **2008**, *130*, 14452. (f) Ref 9d. (g) Ref 9c. (h) Komanduri, V.; Krische, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 16448.

(13) A repeat of the reaction between **2a** and **10d** with AgOTf (0.5 mol %) and **6d** (10 mol %) but no added $AuClPPh_3$ gave **5d** in 11% yield and 75% ee.

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