A peptide-catalyzed asymmetric Stetter reaction†

Steven M. Mennen, Jarred T. Blank, Michelle B. Tran-Dubé, Jason E. Imbriglio and Scott J. Miller*

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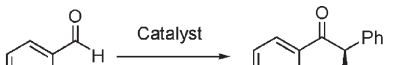
Thiazolylalanine, in appropriately functionalized form, has been found to function as an enantioselective catalyst for an intramolecular Stetter reaction. Incorporation of the residue in a number of environments has resulted in a family of catalysts that promote the cyclization of a test substrate with up to 81% enantiomeric excess.

The range of reactions that may be catalyzed by simple organic molecules, including peptides, is undergoing an expansion.[1] Historically, among the early examples of this strategy in asymmetric catalysis are those that stem from acyl anion catalysis in the context of the biomimetic study of thiamine-dependent enzymes. Following the pioneering studies of Breslow[2] and Sheehan,[3] highly selective catalysts based on triazolium-derived catalysts have been documented in the context of both the benzoin (eqn. 1) and Stetter reactions (eqn. 2) by Enders[4] and Rovis.[5] Our interest in this area stems from the study of families of peptides that might be suitable catalysts for a range of organic reactions.[6] In this context, we have initiated a study of thiazolylalanine (Taz)[7] derivatives as catalysts for reactions in the benzoin and Stetter classes.



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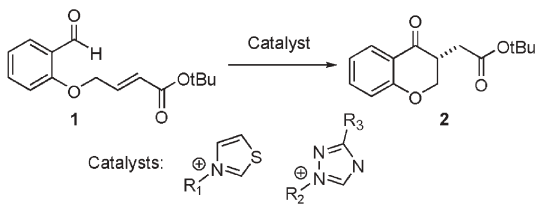
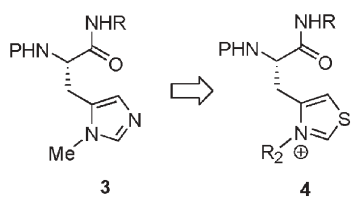


(2)

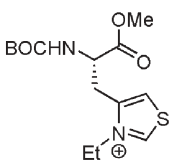
We have previously documented that histidine-derived peptides (**3**) may function as catalysts for a range of enantioselective reactions including acylation,[8] phosphorylation,[9] azide conjugate addition,[10] the Morita–Baylis–Hillman process[11] and sulfinyl transfer.[12] We speculated that the scope of these catalysts might be extended by the exchange of imidazole for thiazolium as in catalyst family **4**.

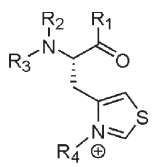


† Electronic supplementary information (ESI) available: experimental section and analytical data. See http://www.rsc.org/suppdata/cc/b4/b414574g/

*scott.miller.1@bc.edu

Our studies began with an examination of the intramolecular Stetter cyclization depicted in eqn. 2 (Table 1). In terms of a catalyst scaffold, we examined simple derivatives of Taz in order to establish whether or not the single residue would provide a catalytically active substructure. To our surprise, simple derivatives of the single amino acid (**4a–f**) proved to afford appreciable selectivity in the cyclization. When catalyst **4a** was employed under optimized conditions (20 mol%, see Table 1), a modest selectivity of 42% ee was observed in the product, which was isolated in low yield. Of note, when the urethane nitrogen was alkylated as in catalyst **4b**, the enantioselectivity was completely eroded (<5% ee). The nature of the nitrogen protecting group was also found to have a considerable effect on selectivity. For example, exchange of BOC for acetyl resulted in an increase in both yield and selectivity (catalyst **4c**, 63% ee, 38% isolated yield). Examination of tosyl amides also provided an improvement with catalyst **4d** delivering 70% ee at low conversion. The quaternizing agent was also found to play a significant role in the performance of the catalyst. For example, the methyl thiazolium salt **4f** delivered similar results (73% ee, 10% yield). On the other hand, quaternization with benzyl (**4e**) affords a catalyst that delivers the product with 80% ee, and an improved level of efficiency such that the product may be isolated in 40% yield.





We next sought to improve upon the efficiency of the reaction in terms of both yield and overall selectivity. In order to do so, we sought to embed Taz in an appropriate scaffold such that selectivity and conversion would improve. We suspected, based on

Table 1 Results of Stetter cyclization (eqn. 2) with catalysts **4a–4f**[a]

Entry	R_1	R_2	R_3	R_4/X^-	Ee (%)	Yield
1, **4a**	MeO	H	Boc	Et/I^-	42	<10
2, **4b**	MeO	Me	Boc	Et/I^-	0	11
3, **4c**	MeO	H	Ac	Et/I^-	63	38
4, **4d**	MeO	H	Ts	Et/I^-	70	10
5, **4e**	MeO	H	Ts	Bn/Br^-	80	40
6, **4f**	MeO	H	Ts	Me/I^-	73	<10

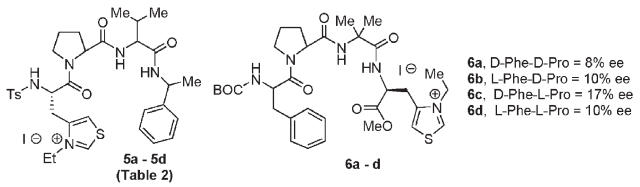
[a] Each reaction was performed in CH_2Cl_2 with 20 mol% catalyst and 100 mol% DIPEA. Reactions were run for 48 h at 4 °C. Enantioselectivities were determined by chiral HPLC and yields refer to the mass of isolated, pure compound after silica gel chromatography.

Table 2 Results of Stetter cyclizations with catalysts **5a–5d**

Entry[a]	Pro	AA	α-(Me)Bn	R_2/X^-	Ee (%)	Yield
1, **5a**	L	D-Val	(*R*)	Et/I^-	14	15
2, **5b**	L	D-Val	(*S*)	Et/I^-	15	17
3, **5c**	D	L-Val	(*R*)	Et/I^-	21	14
4, **5d**	D	L-Val	(*S*)	Et/I^-	18	11

[a] Each reaction was performed in CH_2Cl_2 with 20 mol% catalyst and 100 mol% DIPEA. Reactions were run for 48 h at 25 °C. Enantioselectivities were determined by chiral HPLC and yields refer to the mass of isolated, pure compound after silica gel chromatography. See ESI.

literature precedent, that one of the problems with the single amino acid catalysts was that catalyst decomposition occurs when the thiazolium-derived carbene is not sufficiently protected from dimerization.[13] We then chose incorporation of Taz into peptide sequences that might (a) provide steric hindrance to inhibit decomposition, and (b) provide conformational control over enantioselectivity. In order to explore these questions, several Taz-derived peptide catalysts were examined. Catalysts wherein Taz was located at the *N*-terminal position (**5a–5d**) were compared to those where Taz was inserted at the *C*-terminal end (**6a–6d**).



The results for the two families of catalysts suggested that embedding Taz in a peptide could provide enhancements in catalyst stability, but that improvements in % ee were less readily observed. As indicated in Table 2, a representative set of catalysts that had variations in residue stereochemical configuration, side-chain identity, and *N*-terminal protecting group was synthesized and screened. Notably, the stereochemical identity of the *C*-terminal amide substituent plays a minimal role in dictating enantioselectivity. In each case, enantioselectivity was reduced in comparison to the modified single Taz-residue (ee: 11% to 17%). A similar result was obtained upon screening catalysts **6a–6d**. With this group, enantioselectivities still remained unacceptably low.

On the other hand, incorporation of Taz in an internal position within a small peptide did allow us to observe significant enantioselectivity, while retaining some improvement in the isolated yield of **2**. For example, catalysts in family **7** have allowed isolation of **2** with up to 73% ee and 67% isolated yield (Table 3).

Table 3 Results of Stetter cyclizations with catalysts **7a–7e**

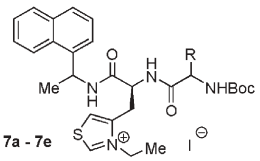
Entry[a]	α-Nap	R	Ee (%)	Isolated yield
1, **7a**	*R*	L-Phe	55	20
2, **7b**	*S*	D-Phe	81	20
3, **7c**	*S*	L-Phe	80	28
4, **7d**	*S*	L-Val	65	22
5, **7e**	*S*	L-Thr(Bn)	73	67

[a] See legend for Table 2.

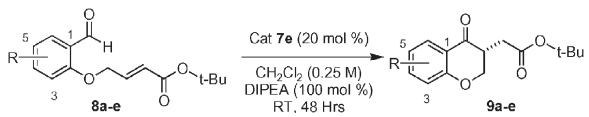
Table 4 Results of Stetter cyclizations (eqn. 3) with substrates **8a–8e**

Entry[a]	R	Ee (%) (0.25 M)	Yield (0.25 M)	Ee (%) (0.4 M)	Yield (0.4 M)
1, **8a**	5-Me	72	32	75	45
2, **8b**	3-Me	73	45	69	43
3, **8c**	5-MeO	69	13	64	47
4, **8d**	4-MeO	73	17	76	39
5, **8e**	5-NO_2	0	78	0	88

[a] See legend for Table 2.



We then wished to establish the role of substrate structure on reaction selectivity (Table 4, eqn. 3, **8a–e**). While enantioselectivities using catalyst **7e** were similar with a range of electron donating substituents in various positions (**8a–8d**: 69–73% ee), yields were modest under standard conditions (17–45%). However, increasing the concentration from 0.25 M in the substrate to 0.4 M produced higher yields, albeit with the sacrifice of selectivity. Finally, we have noted that electron withdrawing substituents lead to products with low ee, in part due to product racemization under the reaction conditions.[14]



(3)

It is interesting to note that in terms of enantioselectivity, we have not yet found a catalytic Taz-peptide that is significantly better than those related to **4d–4f**. X-Ray structural analysis of **4f** reveals that there may be a compact structure for the catalyst that contributes to a stereo defined environment (Fig. 1).[15]

In summary, we have demonstrated that appropriately functionalized Taz derivatives may be used to catalyze an enantioselective Stetter reaction. Future studies will endeavor to optimize the catalysts and the scope of their functions.[16]

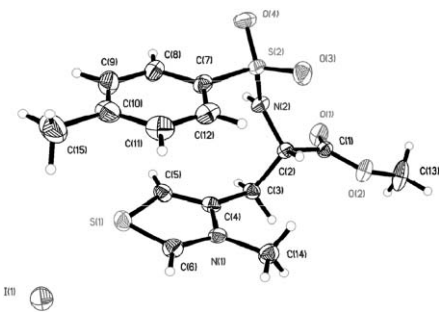


Fig. 1 X-Ray structure for catalyst **4f**.

Steven M. Mennen, Jarred T. Blank, Michelle B. Tran-Dubé, Jason E. Imbriglio and Scott J. Miller*
Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA, 02467, USA. E-mail: scott.miller.1@bc.edu; Fax: +1 617-552-2473; Tel: +1 617-552-3620

Notes and references

1 (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138–5175; (*b*) E. R. Jarvo and S. J. Miller, *Tetrahedron*, 2002, **58**, 2481–2495; (*c*) *Acc. Chem. Res.*, 2004, **37**, Special Issue.
2 (*a*) R. Breslow, *J. Am. Chem. Soc.*, 1958, **80**, 3719–3726; (*b*) R. Breslow and R. Kim, *Tetrahedron Lett.*, 1994, **35**, 699–702; (*c*) R. Breslow and C. Schmuck, *Tetrahedron Lett.*, 1996, **37**, 8241–8242.
3 (*a*) J. C. Sheehan and D. H. Hunneman, *J. Am. Chem. Soc.*, 1966, **88**, 3666–3667; (*b*) J. C. Sheehan and T. Hara, *J. Org. Chem.*, 1974, **39**, 1196–1199.
4 D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534–541.
5 (*a*) M. S. Kerr, J. R. de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 10298–10299; (*b*) M. S. Kerr and T. Rovis, *Synlett*, 2003, **12**, 1934–1936.
6 S. J. Miller, *Acc. Chem. Res.*, 2004, **37**, 601–610.
7 B. Imperiali, K. A. McDonnell and M. Shogren-Knaak, *Top. Curr. Chem.*, 1999, **202**, 1–38.
8 G. T. Copeland and S. J. Miller, *J. Am. Chem. Soc.*, 2001, **123**, 6496–6502.
9 (*a*) B. R. Sculimbrene and S. J. Miller, *J. Am. Chem. Soc.*, 2001, **123**, 10125–10126; (*b*) B. R. Sculimbrene, A. J. Morgan and S. J. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 11653–11656; (*c*) B. R. Sculimbrene, A. J. Morgan and S. J. Miller, *Chem. Commun.*, 2003, 1781–1785.
10 D. J. Guerin and S. J. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 2134–2136.
11 J. E. Imbriglio, M. M. Vasbinder and S. J. Miller, *Org. Lett.*, 2003, **5**, 3741–3743.
12 J. W. Evans, M. B. Fierman, S. J. Miller and J. A. Ellman, *J. Am. Chem. Soc.*, 2004, **126**, 8134–8135.
13 Y.-T. Chen and F. Jordan, *J. Org. Chem.*, 1991, **56**, 5029–5038.
14 We have shown that resubmission of optically enriched **3** (R=NO_2) to the reaction conditions leads to a reduction in ee of the product over time.
15 Crystal data for **4f**: $C_{15}H_{19}IN_2O_4S_2$, M = 482.34, triclinic, a = 7.2693(6) Å, α = 80.624(2)°, b = 7.7618(7) Å, β = 72.296(2)°, c = 8.7263(7) Å, γ = 85.313(2)°, U = 462.51(7) Å^3, T = 193(2) K, space group $P1$, Z = 1, μ = 1.978 mm^{-1}, 3450 reflections collected ($R1$ = 0.0190, $wR2$ = 0.0477), 2761 independent reflections (R(int) = 0.0300, $R1$ = 0.0190, $wR2$ = 0.0477)‡.
16 This work was supported by the U.S. National Science Foundation (CHE-0236591). We are grateful to Merck and Pfizer for additional support, and to Synthetech (Albany, OR) for a generous donation of Taz.

‡ CCDC 251033. See http://www.rsc.org/suppdata/cc/b4/b414574g/ for crystallographic data in .cif or other electronic format.