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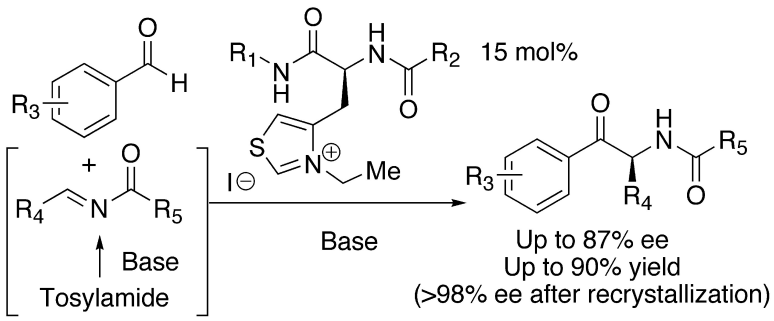

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Thiazolylalanine-Derived Catalysts for Enantioselective Intermolecular Aldehyde−Imine Cross-Couplings

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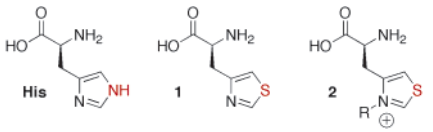
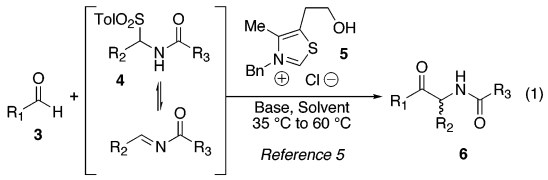
Amino acids have evolved with side chains that often play important roles in catalysis. In recent years, several amino acids have also been co-opted as catalysts for various reactions outside of their known biological context.[1] They have also been inserted into small peptides such that their catalytic prowess may be tuned by the structure of a peptide sequence. An intriguing question at the interface of chemistry and biology is the following: Are there "unnatural" amino acids that may not have been encountered yet, or which have been deselected by evolution, that can be induced to catalyze useful bond-forming reactions? The proteinogenic amino acid histidine, of course, is a work-horse of biological catalysis, and we had observed that histidine-containing oligomers can be used as enantioselective catalysts for a range of reactions.[2] Could thiazolyl alanine (Taz, **1**)[3] and its thiazolium derivatives (**2**) be found



that catalyze synthetically useful reactions that proceed through formal acyl anion intermediates?[4] Taz derivatives are, in some ways, sulfur analogues of histidine. We report herein a Taz-containing peptide that indeed catalyzes enantioselective additions of aldehydes to in situ-generated acylimines, affording optically enriched α-amido ketone derivatives as products.

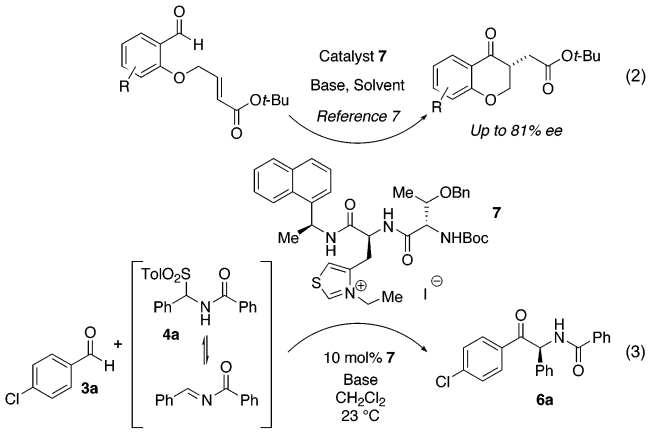
In 2001, the Merck group reported a cross-coupling reaction between aldehydes (**3**) and tosylamides (**4**) to deliver α-amido ketones (**6**, eq 1).[5,6] The catalyst for the addition was reported as



the thiazolium salt **5**. Subsequently, in a pilot study, we found that peptide **7** is a moderately selective catalyst for the enantioselective Stetter cyclization (eq 2).[7] We now document a new application of catalyst **7**: the enantioselective intermolecular aldehyde−imine cross-coupling.

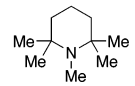
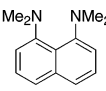
Our studies began with an initial examination of catalyst **7** in the cross-coupling of *p*-chlorobenzaldehyde (**3a**) with benzaldehyde-derived tosylamide **4a** (eq 3). We were pleased to see that this catalyst does indeed exhibit some versatility: when Hünig's base (2 equiv) was employed along with 10 mol % of **7** in a room-temperature reaction, product **6a** could be isolated as a 93:7 ratio of enantiomers (86% ee).

Optimization studies revealed that a number of parameters influence reaction efficiency. Most notably, the structure and stoichiometry of the base used has a significant impact on enantioselectivity. This is particularly significant since the most obvious roles for the base are (a) conversion of the tosylamide to the acylimine, and (b) deprotonation of the thiazolium moiety to the catalytically active species. Our observations indicate that a hindered base is optimal for enantioselectivity (Table 1). Hünig's base (entry 1, 2 equiv) and pentamethylpiperidine (entry 3, 2 equiv) allow for formation of **6a** with 86% ee. On the other hand, less hindered bases such as TMEDA (entry 2, 2 equiv) and proton sponge (entry 4, 2 equiv) result in slightly (78% ee), and substantially lower ee (5% ee), respectively. Perhaps more importantly, in all cases additional equivalents of amine base result in erosion of product ee. *This observation led us to speculate that the product of the reaction was subject to racemization under the reaction conditions, and that the reactions could be improved if racemization could be suppressed (or rendered substantially slower than cross-coupling).*



Our hypothesis that product racemization was a potential pitfall in reaction development was supported by the observation of an isotope effect related to product ee. In particular, we observed that the degree of product racemization was lower when deuterated

Table 1. Effect of Amine Base for Aldehyde−Imine Cross-Coupling[a]

entry	base	equiv (base)	ee[b]	entry	base	equiv (base)	ee[b]
1	*i*-Pr$_2$NEt	2	86	3		2	86
		5	83			5	81
		10	66			10	76
		15	62			15	71
2		2	78	4		2	5
		5	61			5	5
		10	42			10	5
		15	29			15	5

[a] All reactions were run at 23 °C under identical conditions and uniformly quenched after 1 h (see Supporting Information for reaction details). [b] All enantiomeric excesses were measured by Chiral HPLC, and yields refer to the mass isolated after silica gel chromatography.

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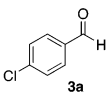
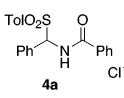
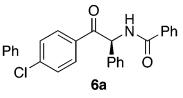
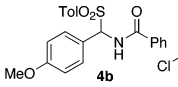
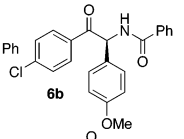
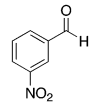
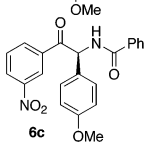
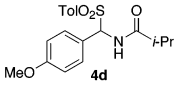
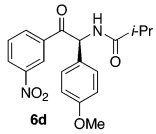
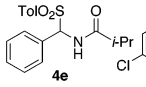
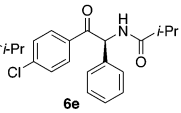
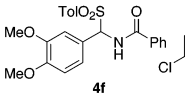
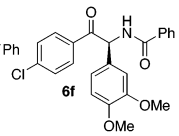
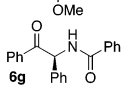
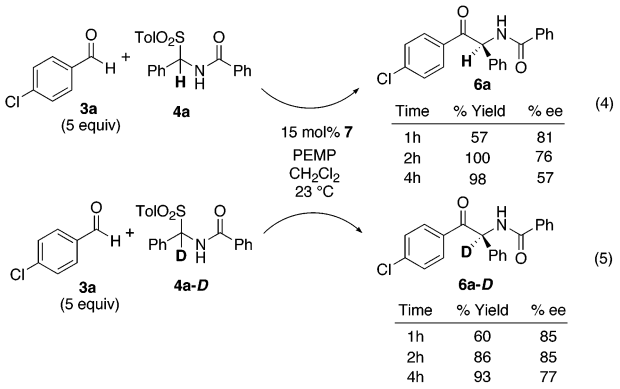
Table 2. Examples of Aldehyde−Imine Cross-Coupling[a]

Entry	Aldehyde	Tosylamide Precursor	Product	Reaction Time	Isolated Yield[b]	ee[c]
1	 **3a**	 **4a**	 **6a**	1 h 2 h	57 100 (60)[d]	81 76 (>98)[d]
2a[f] 2b[f]	**3a**	 **4b**	 **6b**	2 h 2 h	90 91 (72)[d]	87 85 (>98)[d]
3	 **3b**	**4b**	 **6c**	15 min	77	82
4	**3b**	 **4d**	 **6d**	15 min	63 (23)[e]	79 (>98)[e]
5	**3a**	 **4e**	 **6e**	2 h	97 (48)[e]	75 (>98)[e]
6	**3a**	 **4f**	 **6f**	1 h	80	81
7		**4a**	 **6g**	2 h	15	83

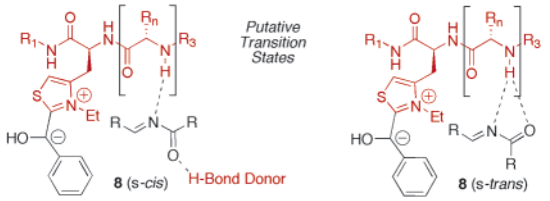
[a] All reactions were run at 23 °C in the presence of pentamethylpiperidine (PEMP, 10 equiv) and 15 mol % of catalyst **7** (see Supporting Information for details). [b] Yields refer to the mass isolated after silica gel chromatography. [c] All enantiomeric excesses were measured using Chiral HPLC. The major enantiomer was shown to be (*S*) for entry 7. [d] % ee of material collected from mother liquor after racemate crystallizes out. [e] % ee of isolated crystals after one recrystallization; unoptimized. [f] Entry 2a was conducted on a 0.065 mmol scale with respect to limiting tosylamide; entry 2b was scaled up by a factor of 13 (0.86 mmol) with very similar results.

tosylamide precursor **4a-*D*** (eq 5) was compared to the protonated substrate **4a** (eq 4), consistent with the possibility that enolization is at the heart of product racemization.[8] This observation also led to the elucidation of a time-dependence on product ee that led to execution of the asymmetric reaction in a time window that allowed only minimal product racemization to occur.



Having identified a useful set of reaction conditions, we carried out an initial study of substrate scope (Table 2). *p*-Chlorobenzaldehyde can be coupled to tosylamide **4a** to deliver product **6a** in 57% isolated yield with 81% ee (entry 1). In this case (and in several others), we also found that after one recrystallization **6a** is isolated from the mother liquor with >98% ee (60% isolated yield). Use of *p*-methoxy-substituted tosylamide **4b** results in an improved reaction, yielding product **6b** in 90% yield with 87% ee (entry 2a). It is possible that the electron donating groups reduce the propensity of the product to enolization. Notably, results are quite similar whether reactions are conducted on dozens or hundreds of milligrams (entry 2b). *m*-Nitrobenzaldehyde (**3b**) participates in a rapid reaction with **4b**, delivering coupled product **6c** in 77% yield and 82% ee within 15 min (entry 3). Substitution on the sulfinamide nitrogen is also tolerated. Coupling of **3b** to the *iso*-butyryl tosylamide **4d** affords compound **6d** in 63% yield and 79% ee (>98% ee after recrystallization; entry 4). *iso*-Butyryl tosylamide **4e** also couples to **3a** to deliver **6e** in 97% yield and 75% ee (>98% ee after recrystallization; entry 5). Electron-rich tosylamide **4f** couples to **3a** yielding **6f** in 80% yield and 81% ee (entry 6). Finally, benzaldehyde itself is representative of sluggish reactions that occur with unactivated aldehydes. Nevertheless, benzaldehyde may be coupled to **4a** to deliver **6g** with 83% ee, albeit in only 15% yield after a 2 h reaction (entry 7).

The mechanism of the asymmetric catalysis is now under study. Our current hypothesis is exploring the possibility of a bifunctional mechanism. Perhaps covalent catalysis occurs in a chiral pocket that benefits from simultaneous activation of the acyl anion equivalent derived from the aldehyde, with H-bond activation of the *N*-acylimine component derived from the sulfinamide precursor. Among the issues that remain to be defined include the cis−trans configuration of the electrophilic component (e.g, stuctures such as **8**). It is our hope that insights from these studies, in combination with expanded data derived from other catalysts, will lead to further understanding and optimization of this process.



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Supporting Information Available: Experimental procedures and product characterization for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (b) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481−2495.
(2) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601−610.
(3) Imperiali, B.; McDonnell, K. A.; Shogren-Knaak, M. *Top. Curr. Chem.* **1999**, *202*, 1−38.
(4) For some of the pioneering work in asymmetric catalysis that involves formal acyl anion equivalents, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534−541. (b) Sheehan, J. C.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666−3667. (c) Kerr, M. S.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298−10299. For pioneering work related to mechanism, see: (d) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719−3726.
(5) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696−9697.
(6) For an alternative synthesis of α-amido ketones such as **6** using catalytic asymmetric synthesis (Neber rearrangement), see: Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640−7641.
(7) Mennen, S. M.; Blank, J. T.; Tran-Dubé, M. B.; Imbriglio, J. E.; Miller, S. J. *Chem. Commun.* **2005**, 195−197.
(8) Emmons, W. D.; Hawthorne, M. F. *J. Am. Chem. Soc.* **1956**, *78*, 5593−5596.

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