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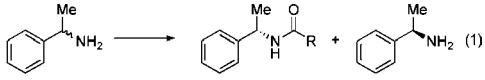
Peptide-Catalyzed Kinetic Resolution of Formamides and Thioformamides as an Entry to Nonracemic Amines

Brandon S. Fowler, Peter J. Mikochik, and Scott J. Miller*

Department of Chemistry, Yale University, P.O. Box 208107, New Haven, Connecticut 06520-8107

Received December 22, 2009; E-mail: scott.miller@yale.edu

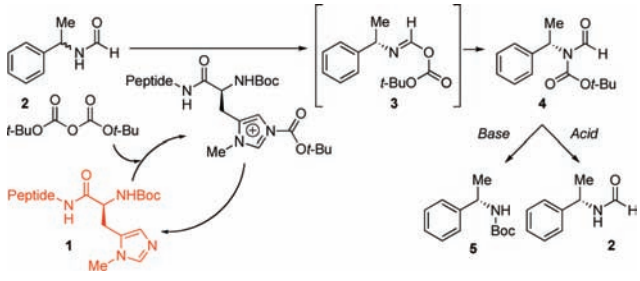
The kinetic resolution (KR) of amines is a long-standing problem in the field of asymmetric synthesis (eq 1). Approaches to this problem have included the application of enzymes[1] as well as chiral acylating agents employed in stoichiometric quantities.[2] Small-molecule catalytic approaches have also been advanced.[3] An elegant strategy based on the use of chiral hydrogen-bond donors in combination with achiral nucleophiles as cocatalysts has also appeared recently.[4] In each case, important advances have resulted, but significant challenges remain, including substrate scope, simplicity of catalysts, and use of straightforward, room-temperature reaction conditions.



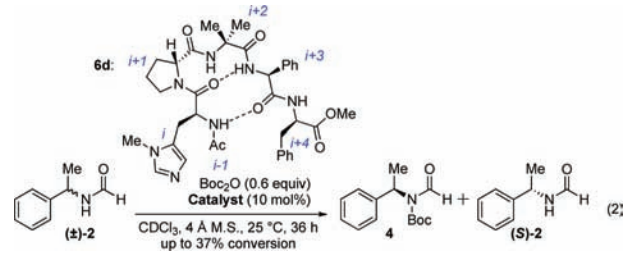
It is perhaps fair to say that progress in amine KR has trailed the parallel challenge of alcohol KR, wherein a wide variety of catalysts that collectively address a broad range of substrate types, conceptual strategies, and mild reaction conditions have been introduced.[5] Among the challenges associated with amines as substrates is their higher level of reactivity: oftentimes, the background rate of reactions of amines with simple derivatization agents (e.g., anhydrides) is competitive with catalytic rates, leading to low levels of selectivity. Approaches to this problem have included the use of low-reactivity amines (e.g., indolines)[3a,c] or reduced-activity electrophiles (e.g., *O*-acyloxazolines), each leading to processes amenable to enantioselective catalysis.[3b]

Our approach to the KR of amines and their derivatives has centered on the application of a common catalyst scaffold based on simple π-methylated histidine derivatives (Pmh-peptides, **1**; Scheme 1). The approach has been applied to the selective functionalization of a broad range of alcohols with a variety of electrophiles.[6] For amine functionalization, we sought a simple substrate that might exhibit enhanced rates of catalytic acylation with reduced background rates relative to the reactivity of a free amine. Our hypothesis was that simple formamides (**2**) would react through a kinetically favorable O-acylation of the formamide oxygen followed by a rearrangement of the unstable O-acylated intermediate **3** to give the stable imide **4**. Our goal was to capitalize on chiral frameworks previously derived from **1** for enantioselectivity. Furthermore, if the amine derivatization reagent were established as the ubiquitous di-*tert*-butyldicarbonate (Boc_2O), products such as **4** could then be converted to practical building blocks such as *N*-Boc-amines (**5**) or back into the corresponding formamides (**2**) under straightforward conditions.

Scheme 1



In initial experiments, we were pleased to find that formamides were inert to reactions with Boc_2O alone but subject to catalytic functionalization with Pmh-containing peptides (eq 2). Moreover, catalysts in a β-turn series (**6a**−**e**) were found to exhibit enantioselectivity (Table 1). For example, catalyst **6a** led to **4** with a 79.5:20.5 er at 22% conversion (k_{rel} = s-factor[7] = 4.6; entry 1).



Optimization of the catalyst structure led to the identification of critical sectors. Catalyst **6b**, with alteration of the $i + 3$ residue (L-valine to L-phenylglycine), is incrementally more selective than **6a** (s-factor = 7.8; entry 2). Catalyst **6c**, with D-pipecolinic acid in place of D-proline, is less selective (s-factor = 5.3; entry 3), implying that secondary structure is important.[8] Moreover, modification at the N- and C-termini (**6d** and **6e**, respectively) proved important, revealing that when the N-terminal substituent is changed from Boc to acetyl, the selectivity is enhanced (s-factor = 9.6; entry 4). This change may be due to the heightened integrity of the β-hairpin structure associated with a stronger amide-to-amide hydrogen bond.[9] In addition, when the catalyst is truncated at the C-terminal side (**6e**, with the $i + 4$ residue replaced by NMe_2; entry 5), the s-factor drops to 3.2. Thus, we established catalyst **6d** as our lead catalyst.

Table 1. Catalyst Screen and Optimization Results with Formamide Substrate **2**

Entry	Catalyst	$i-1$	$i+1$	$i+2$	$i+3$	$i+4$	s-factor[a]
1	**6a**	Boc	D-Pro	Sp6[b]	L-Val	D-Phe-OMe	4.6
2	**6b**	Boc	D-Pro	Aib[c]	L-Phg[d]	D-Phe-OMe	7.8
3	**6c**	Boc	D-Pip[e]	Aib[c]	L-Phg[d]	D-Phe-OMe	5.3
4	**6d**	Ac	D-Pro	Aib[c]	L-Phg[d]	D-Phe-OMe	9.6
5	**6e**	Boc	D-Pro	Aib[c]	L-Phg[d]	NMe_2	3.2

[a] Calculated using the method of Kagan.[7a] [b] 1-Aminocyclohexanecarboxylic acid. [c] 1-Aminoisobutyric acid. [d] Phenylglycine. [e] Pipecolinic acid.

While the data in Table 1 revealed an ability to modulate the selectivity, the reactivity of formamides was modest. Reactions typically proceeded to only ~37% conversion after 36 h at 25 °C. Furthermore, to reach the ideal extent of conversion (50%), 20 mol % catalyst and an excess of Boc_2O (1.2 equiv) were needed. Inspired by classical literature regarding the reactivity of thiocarbonyl compounds,[10] we hypothesized that *thio*formamides would be more reactive. Furthermore, it had been shown that thioformamides react with acyl chlorides via S-acylation followed by intramolecular S-to-N

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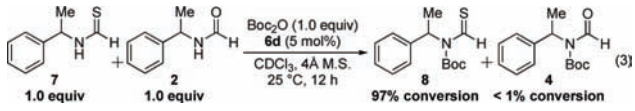
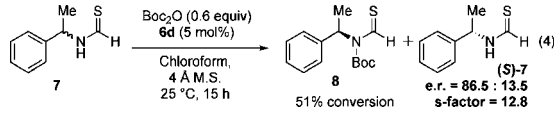
acyl transfer.[11] Indeed, a competition experiment involving formamide **2** and the corresponding thioformamide **7** (eq 3) confirmed our hypothesis. Upon exposure to 1 equiv of Boc_2O, a 1:1 mixture of **2** and **7** was converted almost exclusively to **8**. Moreover, near total conversion was observed within 12 h with only 5 mol % catalyst at 25 °C.



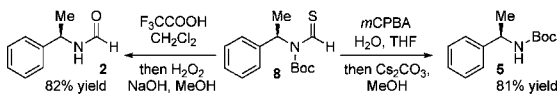
Under conditions of KR, **7** reaches the 50% conversion point within 15 h with only 5 mol % **6d** and only 0.6 equiv of Boc_2O (eq 4). Importantly, substrate **7** undergoes reaction with a nominal s-factor of 12.8 under these conditions.[12−14] Moreover, thioformamides exhibit the same selectivity trends as their formamide analogues when evaluated with other catalysts.[15] In addition, substrates in both the formamide and thioformamide series undergo KR with excellent reproducibility on scales of up to 0.5 mmol.



Having established a catalyst that operates at 5 mol % loading and a substrate that exhibits enhanced reactivity and appreciable selectivity at 25 °C, we sought to assess the substrate scope (Table 2). In addition to the parent *sec*-phenethylamine derivative (entry 1), a variety of arylethylamines are excellent substrates for catalyst **6d**. In fact, the data presented below represent, in most of the cases, the highest s-factors observed for nonenzymatic KRs of the corresponding amines or their simple amine derivatives, particularly when these reactions are carried out at 25 °C. *m*-Methoxy-substituted formamide **9** underwent the KR with a nominal s-factor of 32.5 (entry 2). The corresponding *m*-phenoxy-substituted compound **10** was also an excellent substrate (s-factor = 25.2; entry 3), while the analogous *m*-bromo-substituted compound **11** was somewhat less selective (s-factor = 12.5; entry 4). 3′,5′-Dimethoxy-substituted derivative **12** yielded the highest s-factor we have observed to date (43.7; entry 5). Para substitution is also tolerated: *p*-methoxy- and *p*-phenyl-substituted compounds **13** and **14** exhibited s-factors of 12.2 and 10.2, respectively (entries 6 and 7). 2′-Naphthyl-substituted compound **15** had an s-factor of 13.8 (entry 8), and arylpropylamine **16** exhibited an s-factor of 9.4 (entry 9). Even **17**, presenting heteroaryl and phenyl rings within the substrate, gave an s-factor of 5.6 (entry 10), suggesting the potential for KR of amine derivatives having unusual functionality.

The protocol we have established also allows access to amine derivatives of practical utility. For example, the conversion of **8** to carbamate **5** by oxidative hydrolysis is possible (Scheme 2). Conversely, **8** can be converted to formamide **2** by acidic cleavage of the Boc group and S-to-O exchange.

Scheme 2



In summary, we have developed a new strategy for the KR of formamides and thioformamides based on catalyst **6d**. This work expands the generality of Pmh-based catalysts to include a novel class of amine-based substrates.

Acknowledgment. We are grateful to the Foundation for the National Institutes of Health (GM-068649) for financial support.

Table 2. Substrate Scope for the KR of Thioformamides with Peptide **6d**[a]

Entry	Substrate	% Conversion[b]	e.r.[c]	Nominal s-factor[d]
1	**7**, X=H	51	86.5 : 13.5	12.8
2	**9**, X = OMe	52	95.5 : 4.5	32.5
3	**10**, X = OPh	58	97.5 : 2.5	25.2
4	**11**, X = Br	52	88 : 12	12.5
5	**12**	52	96.5 : 3.5	43.7
6	**13**, X = OMe	52	88.2 : 11.8	12.2
7	**14**, X = Ph	53	86.5 : 13.5	10.2
8	**15**	54	90.8 : 9.2	13.8
9	**16**	52	85 : 15	9.4
10	**17**	53	79 : 21	5.6

[a] Reactions were carried out at 25 °C for 24 h in $CHCl_3$ (0.30 M) with 0.6 equiv of Boc_2O and 5 mol % **6d** in the presence of $(TMS)_2O$ as an internal standard and 4 Å molecular sieves (entries 3 and 10 employed 0.65 equiv of Boc_2O). [b] Based on substrate relative to the internal standard. [c] Reported for recovered starting material after conversion to the formamide and determined by chiral HPLC analysis. In the case of entry 1, the fast-reacting enantiomer was found to be (*R*)-**7**, providing (*S*)-**7** as the recovered starting material. The other cases were not explicitly established. [d] See note 12.

Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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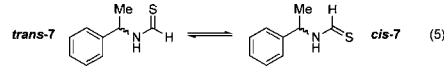
(12) Thioformamides exhibit high cis−trans rotational barriers (eq 5), leading to the possibility of independent reactivity of the cis and trans isomers. Thus, the two isomers may exhibit different enantioselectivities (i.e., distinct s-factors). It is unclear which rotational isomer is more reactive at this time. This issue could have a significant effect on the calculation of the s-factor. Nonetheless, our reported data are "nominal" s-factors calculated by treating the rotational isomers of the starting material and product in a collective fashion.



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(14) The inclusion of 4 Å molecular sieves led to a modest rate acceleration.
(15) See the Supporting Information for details.

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