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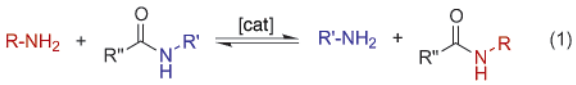
Catalytic Transamidation under Moderate Conditions

Sarah E. Eldred, David A. Stone, Samuel H. Gellman,* and Shannon S. Stahl*

Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, Wisconsin 53706

Received August 21, 2002; E-mail: gellman@chem.wisc.edu; stahl@chem.wisc.edu

The carboxamide group is chemically robust and generally requires harsh conditions or highly evolved enzymes to react. This stability underlies the prominence of amide-based molecules in living systems and the versatility of synthetic polyamides (e.g., nylons, Kevlar). The exciting recent developments in dynamic covalent chemistry[1] suggest that facile amide exchange reactions, which are presently unknown, would enable the synthesis of important new amide-based molecules and polyamide materials under equilibrium-controlled conditions. Here we describe the discovery of efficient metal-catalyzed transamidation reactions (eq 1) that represent an important step in this direction.



Few precedents or parallels exist for the metal-based catalysis of transamidation that we sought. High temperatures (>250 °C) can promote chemical exchange in amide polymers or polymer/amine mixtures,[2] and stoichiometric quantities of $AlCl_3$ mediate transamidation between amine-carboxamide pairs at 90 °C.[3,4] Enzyme-mediated transamidation has been achieved, although the reaction has limited substrate scope and requires long reaction times.[5]

The importance of secondary amides in synthetic and biological polymers led us to focus our attention on this class of substrates. We selected three classes of potential transamidation catalysts for evaluation. (1) Lewis acidic metal complexes were chosen on the basis of the precedents cited above.[2e,3] (2) Nucleophilic alkali-metal amides were examined because the corresponding alkoxides display high activity in ester metathesis reactions.[6] (3) Transition-metal and main-group amides were selected because they might display bifunctional reactivity involving the Lewis acidic metal center and the nucleophilic amide ligands.[7]

Potential catalysts from each group were tested for their ability to promote transamidation starting from benzylamine and *N*-phenyl heptanamide (Figure 1). This reaction is thermodynamically favored in the direction shown because of destabilizing cross-conjugation in the *N*-phenyl amide. In the absence of a catalyst, this reaction proceeds very slowly: only 39% conversion is observed after 1 month at 90 °C. In contrast, several metal complexes promote significant reaction within 16 h at this temperature (Figure 1). The reaction is quite sensitive to solvent. None of the catalysts is active (≤4 turnovers) in 1,2-dichloroethane, the solvent reported by Bertrand et al.,[3] whereas in toluene, several catalysts display activity. $Ti(NMe_2)_4$ and $Sc(OTf)_3$ (OTf = trifluoromethane sulfonate) promote nearly quantitative conversion to the *N*-benzyl heptanamide product. Other alkylamines display similar reactivity toward *N*-phenyl heptanamide in the presence of these two catalysts (Table 1), with the exception that methoxyethylamine inhibits the titanium catalyst, possibly through metal chelation.

Successful application of catalytic transamidation in dynamic covalent chemistry will require facile exchange in the absence of an intrinsic thermodynamic driving force. We therefore shifted our attention to approximately thermoneutral exchange reactions between alkylamines and *N*-alkyl secondary amides. Three alkylamine/*N*-alkyl amide pairs were selected, and their equilibration was studied at a 1:1 substrate ratio (Table 2). In contrast to the reaction in Figure 1, these substrates exhibit essentially no reaction in the absence of a catalyst, even after heating at 90 °C for 1 month. The dimeric aluminum complex, $Al_2(NMe_2)_6$, is an effective catalyst in each case. The experimentally indistinguishable yields obtained for reactions conducted in both forward and reverse directions demonstrate that equilibrium was achieved (Table 2, Figure 2). The

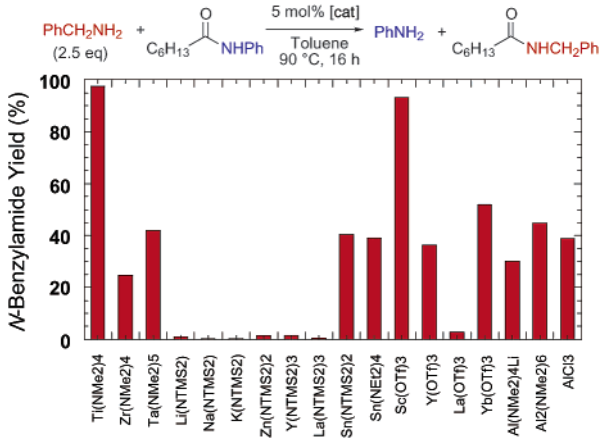
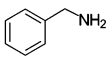
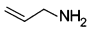
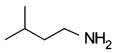
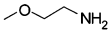


Figure 1. Catalyst screening results for the exchange of benzylamine and the *N*-phenyl heptanamide starting material. Yields are based on the average of duplicate runs. All catalysts are present at 5% loading with respect to the *N*-phenyl amide; $Al_2(NMe_2)_6$ loading is based on monomeric $Al(NMe_2)_3$.

Table 1. Transamidation of *N*-Phenyl Heptanamide, $C_6H_{13}C(O)NHPh$, with Primary Alkyl Amines[a]

	Amine	Catalyst	% Yield[b]
1		$Sc(OTf)_3$	97
		$Ti(NMe_2)_4$	99 (80)
2		$Sc(OTf)_3$	98 (79)
		$Ti(NMe_2)_4$	88
3		$Sc(OTf)_3$	68
		$Ti(NMe_2)_4$	98 (84[c])
4		$Sc(OTf)_3$	99 (98)
		$Ti(NMe_2)_4$	2

[a] Reaction conditions: amine (0.83 mmol), *N*-phenyl heptanamide (0.33 mmol), catalyst (0.017 mmol), 2 mL of toluene, 90 °C, 16 h. [b] GC yields (internal standard = triphenylmethane); isolated yield in parentheses from scaled-up reactions (2−5 mmol). [c] Yield based on ^{1}H NMR integration of the isolated amide mixture.

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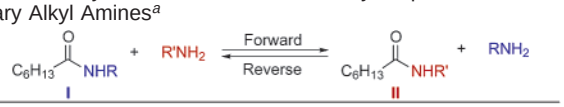
Table 2. Catalytic Transamidation of *N*-Alkyl Heptanamide with Primary Alkyl Amines[a]



	R	R'	Catalyst	Amide Ratio (I/II)[b] Forward	Reverse
1			$Sc(OTf)_3$	89/11	6/94
			$Ti(NMe_2)_4$	92/8	5/95
			$Al_2(NMe_2)_6$	**50/50**	**49/51**
2			**$Al_2(NMe_2)_6$**	**46/54**	**44/56**
3			**$Al_2(NMe_2)_6$**	**57/43**	**55/45**

[a] Reaction conditions: amine (0.33 mmol), amide (0.33 mmol), catalyst (0.017 mmol), 2 mL of toluene, 90 °C, 20 h. [b] Determined by GC (internal standard = triphenylmethane) and ^{1}H NMR. The starting materials and products shown are the only species observed by these methods.

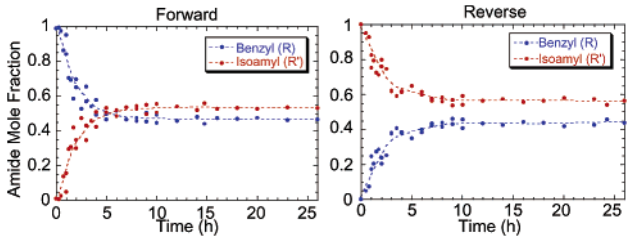


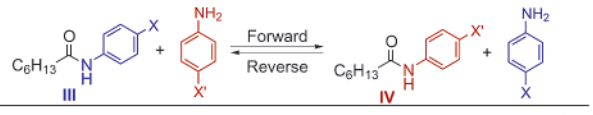
Figure 2. Representative time-course data (GC) for the $Al_2(NMe_2)_6$-catalyzed equilibrium exchange between *N*-benzyl heptanamide/isoamylamine, forward, and *N*-isoamyl heptanamide/benzylamine, reverse (see entry 2, Table 2).

previously successful scandium and titanium complexes (Figure 1) are not effective catalysts for the *N*-alkyl amide exchange reactions (Table 2).

Equilibrium transamidation can be achieved between anilines and *N*-aryl amides as well, although somewhat more forcing conditions are required (Table 3). Both metal amide complexes (Ti and Al) display activity; however, in this case, the titanium catalyst is more effective. $Sc(OTf)_3$ fails to promote these nearly thermoneutral reactions, as seen previously with the alkylamine/*N*-alkyl amide reactions.

To our knowledge, these results provide the first demonstration of metal-catalyzed transamidation under moderate conditions. The data provide several insights regarding the identity of successful catalysts. Lewis-acid catalysts, such as $Sc(OTf)_3$, can promote thermodynamically favored transamidation; however, they proved to be ineffective for the more difficult and interesting thermoneutral equilibrations. Alkali-metal amides are even more limited, being unable to promote transamidation with any of the substrate classes. This result highlights an important distinction between the reactivity of carboxylic esters and amides. Secondary amides possess a relatively acidic N−H group. Therefore, the basicity of the metal amide must be attenuated to prevent carboxamide deprotonation, which would destroy the catalytic species. The promotion of transamidation by titanium and aluminum amides appears to reflect their reduced basicity. In these cases, catalysis might proceed by a bifunctional mechanism involving both substrate activation by a Lewis acidic metal center and nucleophilic attack by a coordinated amide ligand.[7] The limited transamidation activity displayed by simple Lewis acids and the nonreactivity of highly basic amide anions suggest that a bifunctional pathway may be crucial for effective catalysis.

Table 3. Catalytic Transamidation of *N*-Aryl Amides with Aryl Amines[a]



	X	X'	Catalyst	Amide Ratio (III/IV)[b] Forward	Reverse
1	H	CH_3	$Sc(OTf)_3$	98/2	1/99
			$Ti(NMe_2)_4$	**42/58**	**42/58**
			$Al_2(NMe_2)_6$	65/35	43/57
2	H	CH_3O	**$Ti(NMe_2)_4$**	**34/66**	**32/68**
3	CH_3	CH_3O	**$Ti(NMe_2)_4$**	**40/60**	**41/59**

[a] Reaction conditions: amine (0.33 mmol), amide (0.33 mmol), catalyst (0.033 mmol), 2 mL of *p*-xylene, 120 °C, 20 h. [b] Determined by GC (internal standard = triphenylmethane). The starting materials and products shown are the only species observed.

The substrate-dependent variations in catalytic activity that emerge from our results (cf. alkyl vs arylamide substrates) are intriguing because they suggest that it might be possible to develop catalysts with functional group selectivity. Elucidation of the mechanistic principles underlying these novel transamidation reactions is a focus of our ongoing work and should enable the development of new equilibration catalysts with even greater activity and selectivity. Catalysts spawned by these studies will be applied to equilibrium-controlled syntheses of new amide-based molecules and materials.

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