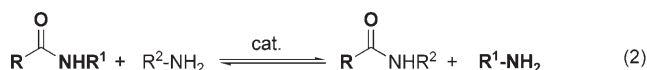
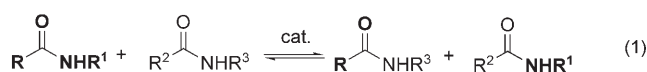


Catalytic Metathesis of Simple Secondary Amides**

Christen M. Bell, Denis A. Kissounko, Samuel H. Gellman,* and Shannon S. Stahl*

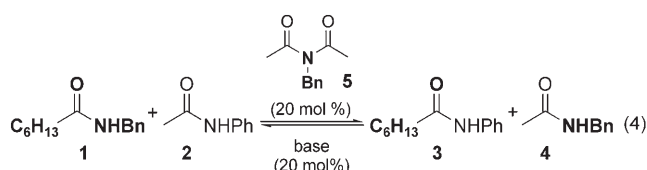
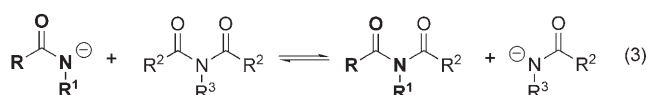
Reactions that interconvert strong covalent bonds, generally known as dynamic covalent chemistry (DCC), offer a powerful approach for the thermodynamically controlled synthesis of organic molecules with interesting structures and/or properties. DCC involving esters, thioesters, imines, and disulfides, among other functional groups, has provided access to interesting new molecules.^[1,2] Such efforts to date have focused on bonds that were previously known to be readily exchangeable. Extension of the DCC approach to other types of functional groups will require advances in organic reactivity and catalysis. It would be valuable, for example, to implement DCC with carboxamide-containing molecules,^[1c] but the low intrinsic reactivity of the carboxamide group has hampered efforts to achieve this goal. A fundamental challenge is the identification of catalysts that induce amide metathesis, that is, the interconversion of carboxamides based on cleavage and formation of the *N*-acyl bonds [Eq. (1)]. We recently described metal-catalyzed transamidation reactions [Eq. (2)],^[3] which in principle offer a pathway to amide metathesis. Subsequent studies in our lab, however, revealed that metathesis of secondary amides is not successful under the original transamidation conditions.^[4] Herein we describe an alternative and mechanistically novel strategy for catalytic amide metathesis that involves imide-mediated transacylation. The results provide a foundation for future efforts to implement amide-based DCC.

The only previous example of amide metathesis, to our knowledge, involved the use of proteases under conditions compatible with both peptide hydrolysis and synthesis.^[5] Drawbacks associated with these reactions include the limited substrate scope and long reaction times, and these prompted us to pursue the development of small-molecule catalysts for amide metathesis. As initial efforts using transamidation catalysts were unsuccessful, we sought an alternative strategy.



We postulated that substoichiometric quantities of an acyclic imide and a Brønsted base (the latter to generate amidate species) might promote acyl-group exchange between secondary amides [Eq. (3)]. Successive reactions of this type should enable equilibrium-controlled metathesis of secondary amides.^[6]

Initial efforts to promote the metathesis of *N*-benzylheptanamide and acetanilide [Eq. (4); Bn = benzyl] with the



imide *N*-benzylidiacetamide (**5**) established the feasibility of the proposed strategy.^[7] The effectiveness of several different bases was evaluated by comparing the ratio of the amides **3/1** obtained when the reaction was conducted in both the forward and reverse directions. Reactions that achieve equilibrium produce a **3/1** ratio that is independent of the reaction direction. The most effective bases were found to be $\text{NaN}(\text{SiMe}_3)_2$, $\text{KN}(\text{SiMe}_3)_2$, and KH (Figure 1); equilibrium was achieved in all three cases. Significant amide exchange was observed also for MeMgCl , KOtBu , and $\text{LiN}(\text{SiMe}_3)_2$. Metal complexes previously shown to promote transamidation,^[3a] $[\text{Al}_2(\text{NMe}_2)_6]$ and $[\text{Ti}(\text{NMe}_2)_4]$, were found not to promote amide metathesis. Based on previous observations,

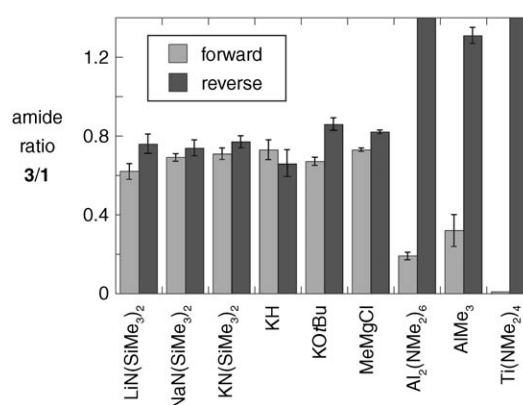


Figure 1. Results from the screening of bases for Equation (4). Reaction conditions: 1:1 mixture of amides (0.23 mmol; **1** and **2** for the forward reaction, or **3** and **4** for the reverse reaction), base (0.046 mmol), **5** (0.046 mmol), diglyme (0.8 mL), 120 °C, 18 h. Amide ratio was determined by GC analysis (Ph_3CH internal standard). Each bar represents the average of five runs.

[*] C. M. Bell, D. A. Kissounko, Prof. S. H. Gellman, Prof. S. S. Stahl
Department of Chemistry
University of Wisconsin-Madison
1101 University Avenue, Madison WI 53706 (USA)
Fax: (+1) 608-262-6143
E-mail: gellman@chem.wisc.edu
stahl@chem.wisc.edu

[**] We gratefully acknowledge financial support from the NSF Collaborative Research in Chemistry Program (CHE-0404704).

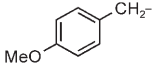
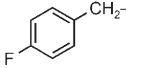
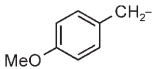
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we suspect that these complexes form stable Al–amidate or Ti–amidate adducts,^[8] which are insufficiently nucleophilic to react with the imide.

Several different pairs of secondary amides were evaluated under the metathesis conditions (Table 1). We examined three classes of amide reactant pairs (*N*-aryl/*N*-aryl, *N*-aryl/*N*-alkyl, and *N*-alkyl/*N*-alkyl). The reactions were performed in both forward and reverse directions to determine whether equilibrium was achieved. The metathesis of the pairs of *N*-aryl/*N*-aryl (Table 1, entries 1–3) and *N*-aryl/*N*-alkyl amides (Table 1, entries 4–9) generally reached completion within the error limits of the product analysis. The presence of a bulky branched alkyl substituent on the amide nitrogen does not appear to hinder the exchange (Table 1, entry 7).

The metathesis of the *N*-alkyl/*N*-alkyl amide pairs proved to be more challenging. Partial exchange was observed, but these reactions did not achieve equilibrium after 18 h under the standard conditions (Table 1, entries 10 and 11). No further exchange was observed with longer reaction times (36 h). We speculated that imide decomposition, which perhaps involved deprotonation at the α position, could have prematurely terminated the metathesis process. To test this hypothesis, we examined the exchange between non-enolizable amide substrates (Table 2). Since the imide initiator incorporates the acyl fragments of the amide substrates during the reaction, the use of nonenolizable amide substrates

Table 1: Metathesis of pairs of secondary amides.^[a]

		$\text{C}_6\text{H}_{13}\text{C(=O)NHR} + \text{CH}_3\text{C(=O)NHR}^1 \xrightleftharpoons[\text{reverse}]{\text{forward}} \text{C}_6\text{H}_{13}\text{C(=O)NHR}^1 + \text{CH}_3\text{C(=O)NHR}$			
Entry	R	R ¹	Forward	Reverse	Amide ratio B/A ^[b]
	R = aryl	R ¹ = aryl			
1	Ph	<i>p</i> -MeOC ₆ H ₄	0.91 (0.07)	1.04 (0.08)	
2	Ph	<i>p</i> -tolyl	1.02 (0.03)	1.09 (0.04)	
3	<i>p</i> -tolyl	<i>p</i> -FC ₆ H ₄	0.77 (0.01)	0.83 (0.03)	
	R = alkyl	R ¹ = aryl			
4	Bn	Ph	0.73 (0.05)	0.66 (0.07)	
5	Bn	<i>p</i> -MeOC ₆ H ₄	0.64 (0.05)	0.72 (0.07)	
6	Bn	<i>p</i> -FC ₆ H ₄	0.66 (0.04)	0.69 (0.02)	
7		Ph	0.69 (0.06)	0.61 (0.06)	
8		Ph	0.95 (0.06)	0.88 (0.05)	
9		Ph	0.87 (0.07)	0.81 (0.01)	
	R = alkyl	R ¹ = alkyl			
10		Bn	0.98 (0.06)	0.69 (0.02)	
11		Bn	0.73 (0.02)	0.87 (0.02)	

[a] Reaction conditions: 1:1 mixture of amides (0.23 mmol each); KH (0.046 mmol); imide **5** (0.046 mmol), 0.8 mL of diglyme, 120 °C, 18 h. [b] Amide ratio determined by GC (internal standard = Ph₃CH). Data represents the average of five runs; standard deviation in parentheses.

Table 2: Metathesis of pairs of nonenolizable amides.^[a]

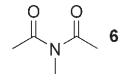
		$\text{R-C(=O)NHR}^1 + \text{Ph-C(=O)NHR}^2 \xrightleftharpoons[\text{reverse}]{\text{forward}} \text{R-C(=O)NHR}^2 + \text{Ph-C(=O)NHR}^1$			
Entry	R	R ¹	R ²	Forward	Reverse
1	<i>p</i> -tolyl	Bn		0.82 (0.02)	0.83 (0.04)
2	C ₆ H ₁₃	Bn		0.58 (0.11)	0.92 (0.05)

[a] See footnote from Table 1 for reaction conditions and analytical methods.

should minimize imide deprotonation, even if **5** is initially the imide component. This strategy proved to be successful: equilibrium was achieved with an *N*-alkyl/*N*-alkyl substrate pair (Table 2, entry 1). When only one of the starting amides was nonenolizable, however, equilibrium was not achieved (Table 2, entry 2).

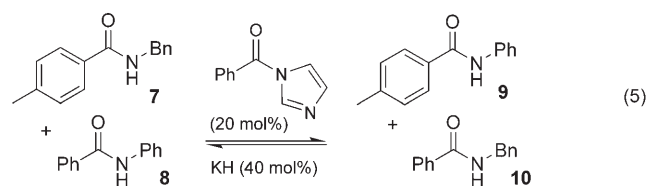
Imide initiator **5**, which was employed in each of the reactions presented in Table 1 and Table 2, is not commercially available.^[9] We were therefore encouraged to find that the commercially available imide *N*-methyldiacetamide (**6**) is equally effective as an initiator of amide metathesis (Table 3, entry 1). Even more significant is that simple acylating agents, such as acetyl chloride and acetylimidazole, promote amide metathesis (Table 3, entries 2 and 3). The latter reagents, which presumably form imides in situ, are attractive because they minimize the quantity of initiator-derived acyl and amine fragments present in the reaction mixture. For example, *N*-methylamide side products were observed when **6** was used as the initiator, but no analogous side products are possible when either acetyl chloride or acetylimidazole is used. Furthermore, acid chlorides bearing an acyl fragment that matches one (or both) of the amide substrates can be readily obtained from the corresponding carboxylic acids.

Table 3: Alternative initiators for amide metathesis [Eq. (4)].^[a]

Entry	Initiator	Forward	Reverse
1		0.83 (0.02)	0.88 (0.03)
2 ^[c]		0.73 (0.08)	0.82 (0.05)
3 ^[c]		0.73 (0.05)	0.81 (0.05)

[a] Reaction conditions: 1:1 mixture of amides (0.23 mmol; **1** and **2** for the forward reaction, **3** and **4** for the reverse reaction), KH (0.046 mmol), initiator (0.046 mmol), diglyme (0.8 mL), 120 °C, 18 h. [b] Amide ratio determined by GC analysis (internal standard = Ph₃CH). Data represents the average of five runs; standard deviation in parentheses. [c] KH (0.092 mmol) The requirement for a two-fold excess of base relative to the acylating agent presumably reflects the formation of the imide in situ, that is, one equivalent of base is consumed in the formation of the imide.

The reaction shown in Equation (5) features nonenolizable substrates together with *N*-benzoylimidazole as the initiator. As the plots of the forward and reverse reactions



against time reveal (Figure 2), equilibrium is reached within approximately one hour at 90°C. The exchange reaction in Equation (6), which features an *N*-butylamide, proceeds to equilibrium with acetyl chloride as the initiator. This result complements the data in Table 1 and Table 2, which feature *N*-benzylic substrates and an *N*-benzylimide initiator.

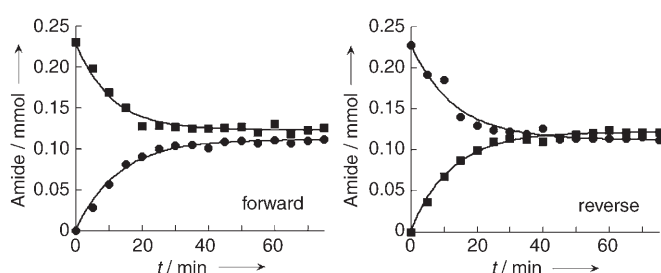
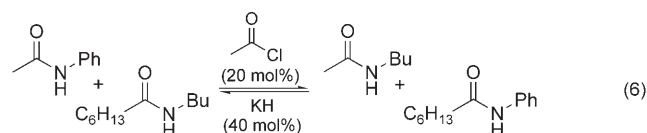


Figure 2. Plots of the approach to equilibrium for Equation (5) both in forward and reverse directions (based on GC analysis of carboxamides **7** ■ and **9** ●). Reaction conditions: **7** and **9** (0.23 mmol), KH (0.092 mmol), **11** (0.046 mmol), diglyme (0.8 mL), 90°C.



In summary, we have shown that the metathesis of simple secondary amides can be achieved through the combined action of simple acylating agents and Brønsted bases. These findings establish a conceptually novel strategy for inducing carboxamide exchange reactivity. Significant challenges remain to be overcome in this class of reactions, such as the avoidance of competing decomposition reactions for amide substrates bearing protons adjacent to the carbonyl, and the enhancement of catalytic efficiency. We anticipate that mechanistic studies will facilitate further advances.^[10] The results presented above provide a basis for implementing carboxamide-based dynamic covalent chemistry, a prospect that we are actively exploring.

Received: September 2, 2006

Published online: December 13, 2006

Keywords: amides · dynamic covalent chemistry · homogeneous catalysis · metathesis · synthetic methods

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