J|A|C|S ARTICLES

Published on Web 07/06/2009

Catalytic Transamidation Reactions Compatible with Tertiary Amide Metathesis under Ambient Conditions

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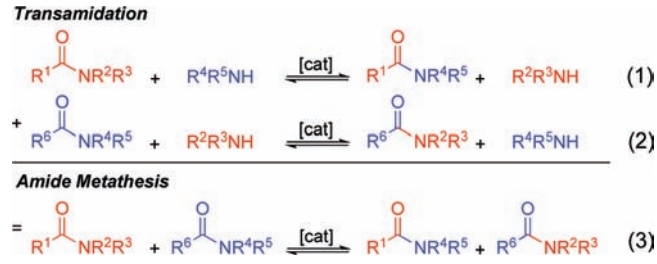
Abstract: The carbon−nitrogen bond of carboxamides is extremely stable under most conditions. The present study reveals that simple zirconium− and hafnium−amido complexes are highly efficient catalysts for equilibrium-controlled transamidation reactions between secondary amines and tertiary amides. In a number of cases, transamidation proceeds rapidly at room temperature. We find that these new catalysts are sufficiently active to promote the metathesis of tertiary amides, which arises from successive transamidation cycles. The catalytic activities we observe are unprecedented and represent a substantial step toward a long-range goal of conducting equilibrium-controlled reactions with carboxamides.

Introduction

Thermodynamically controlled chemical reactions can provide expeditious access to molecules that would be cumbersome to prepare by traditional, kinetically controlled bond-forming processes.[1] Most applications of the thermodynamic approach, or "dynamic covalent chemistry" (DCC), involve intrinsically facile reactions, such as thiol−disulfide, alcohol−ester, amine−imine, or thiol−thioester exchange.[1] This work has provided valuable insights into the capabilities of DCC, but the labile bonds present in these molecules limit the ultimate uses of the reaction products. The field of DCC would benefit from the development of new exchange reactions involving intrinsically robust bonds. In this regard, amine−carboxamide exchange reactions, transamidation (eqs 1 and 2) and amide metathesis (eq 3), represent highly appealing processes. However, the carboxamide group is notoriously stable under most conditions, and the development of catalysts that can promote carboxamide exchange reactions therefore represents a profound challenge in terms of reactivity. Known methods for amide exchange typically require very harsh conditions (>250 °C), long reaction times, or stoichiometric reagents that limit their potential application to DCC.[2−4]

Reported here is a significant advance in the catalysis of transamidation and amide metathesis reactions involving secondary amines and tertiary amides. These results have emerged from our ongoing fundamental exploration of carboxamide exchange reactivity.[5−8] The findings presented below represent an important step toward the long-range goal of implementing carboxamide-based DCC processes.



In previous work we showed that $Al_2(NMe_2)_6$ is an effective (pre)catalyst for transamidation reactions between primary amines and secondary amides.[5] These reactions face critical limitations, however: (1) they require elevated temperature to

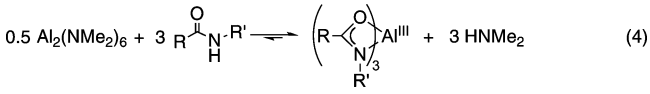
(1) For recent reviews of dynamic covalent chemistry: (a) Lehn, J.-M. *Chem. Eur. J.* **1999**, *5*, 2455–2463. (b) Rowan, S. J.; Cantrill, S. J.; Cousins, G. R. L.; Sanders, J. K. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 898–952. (c) Ramström, O.; Lehn, J.-M. *Nat. Rev. Drug Discovery* **2002**, *1*, 26–36. (d) Corbett, P. T.; Leclaire, J.; Vial, L.; West, R. K.; Wietor, J.-L.; Sanders, J. K. M.; Otto, S. *Chem. Rev.* **2006**, *106*, 3652–3711.

(2) Transamidation at very high temperatures (>250 °C), typically with polyamides, has been reported: (a) Smith, M. E.; Adkins, H. *J. Am. Chem. Soc.* **1938**, *60*, 657–663. (b) Beste, L. F.; Houtz, R. C. *J. Polym. Sci.* **1952**, *8*, 395–407. (c) Ogata, N. *Makromol. Chem.* **1959**, *30*, 212–224. (d) Miller, I. K. *J. Polym. Sci., Part A: Polym. Chem.* **1976**, *14*, 1403–1417. (e) McKinney, R. J. *U.S. Patent* 5,302,756, 1994. (f) McKinney, R. J. U.S. Patent 5,395,974, 1995.

(3) For enzymatic approaches to secondary-amide exchange reactions, see: (a) Gotor, V.; Brieva, R.; González, C.; Rebolledo, F. *Tetrahedron* **1991**, *47*, 9207–9214. (b) Swann, P. G.; Casanova, R. A.; Desai, A.; Frauenhoff, M. M.; Urbancic, M.; Slomczynska, U.; Hopfinger, A. J.; LeBreton, G. C.; Venton, D. L. *Biopolymers* **1996**, *40*, 617–625. (c) Sergeeva, M. V.; Mozhaev, V. V.; Rich, J. O.; Khmelnitsky, Y. L. *Biotechnol. Lett.* **2000**, *22*, 1419–1422.

(4) Precedents for transamidation under synthetically practical conditions are typically limited to intramolecular reactions or require a stoichiometric reagent: (a) Galat, A.; Elion, G. *J. Am. Chem. Soc.* **1943**, *65*, 1566–1567. (b) Martin, R. B.; Parcell, A.; Hedrick, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 2406–2413. (c) Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* **1986**, *27*, 5151–5154. (d) Zaragoza-Dörwald, F.; von Kiedrowski, G. *Synthesis* **1988**, *11*, 917–918. (e) Gotor, V.; Brieva, R.; Gonzalez, C.; Rebolledo, F *Tetrahedron* **1991**, *47*, 9207–9214. (f) Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 4035–4036. (g) Suggs, J. W.; Pires, R. M. *Tetrahedron Lett.* **1997**, *38*, 2227–2230. (h) Langlois, N. *Tetrahedron Lett.* **2002**, *43*, 9531–9533. (i) Lasri, J.; González-Rosende, M. E.; Sepúlveda-Arques, J. *Org. Lett.* **2003**, *5*, 3851–3853. (j) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529–3533. (k) Alajarín, M.; Vidal, A.; Tovar, F. *Tetrahedron* **2005**, *61*, 1531–1537, P. (l) Çalimsiz, S.; Lipton, M. A. *J. Org. Chem.* **2005**, *70*, 6218–6221. (m) Dineen, T. A.; Zajac, M. A.; Myers, A. G. *J. Am. Chem. Soc.* **2006**, *128*, 16406–16409.

reach equilibrium (90 °C), and (2) the catalyst is insufficiently active to achieve amide metathesis via successive transamidation steps. Mechanistic studies revealed that a transamidation-based approach to secondary amide metathesis is intrinsically constrained by the catalytic mechanism.[6] Secondary carboxamides react rapidly with amidoaluminum species such as $Al_2(NMe_2)_6$ to form tris(κ^2-amidate)Al^{III} species (eq 4), which constitute the catalyst resting state under the reaction conditions. This reactivity is problematic with regard to catalysis of transamidation, because the metal-bound κ^2-amidate is a poorer electrophile than is a neutral metal-coordinated carboxamide, and a noncoordinated amine is a poorer nucleophile than is a metal-bound amido group. The rate law for primary amine−secondary amide transamidation catalyzed by a tris(κ^2-amidate)Al^{III} complex exhibits a first-order dependence on both [Al] and [amine]. This situation is not favorable for efficient promotion of secondary amide metathesis via multiple transamidation steps, since such a process should ideally require only a low concentration of the metal-based catalyst and little or no added amine.



The insights obtained from the study of secondary amide exchange reactions provided the basis for our subsequent investigation of exchange reactions between secondary amine−tertiary amide substrate pairs.[8] We reasoned that tertiary amides, which lack an acidic N−H group, would not form the kinetically problematic κ^2-amidate-Al species. This hypothesis proved to be correct, and $Al_2(NMe_2)_6$ was shown to be an effective (pre)catalyst for transamidation reactions between secondary amines and tertiary amides. Mechanistic studies revealed that the resting state of the catalyst in these reactions consists of an $Al(NR_2)_3$ species, and the catalytic rate law exhibits a zero-order dependence on [amine]. The latter observation suggested that a transamidation-based approach for the metathesis of tertiary amides might be possible; however, efforts to achieve this goal with Al-based catalysts were unsuccessful. Elevated temperatures (90 °C) were required to promote transamidation, and the Al catalyst did not exhibit sufficient activity and/or stability to achieve the multiple rounds of transamidation necessary to accomplish metathesis of tertiary amide substrate pairs (eqs 1−3).

More active amide exchange catalysts are clearly needed in order to achieve the long-term goal of carboxamide-based DCC. The present study reveals new, highly active catalysts for secondary amine−tertiary amide exchange reactions. With some simple substrates, the new catalysts promote *tertiary amide metathesis at room temperature*.

Results and Discussion

Transamidation. A variety of Lewis acids and metal−amido complexes were screened for their ability to catalyze the transamidation reaction between the tertiary amide **1** and benzylmethylamine (Figure 1). Under relatively vigorous conditions (16 h; 90 °C; 5 mol % catalyst, calculated on a metal atom basis), several metal−amido complexes in addition to the originally reported catalyst, $Al_2(NMe_2)_6$,[8] were able to achieve complete amine−amide equilibration, as indicated by their reaching the same ratio of amides **1** and **2** starting from either amine/amide pair. Successful new catalysts included $Li-N(SiMe_3)_2$, $LiNMe_2$, $Sc[N(SiMe_3)_2]_3$, $Sm[N(SiMe_3)_2]_3$, $Zr(NMe_2)_4$, and $Hf(NMe_2)_4$.

In order to identify the most active among these catalysts, we re-examined the reaction at 50 °C and determined the time required to reach equilibrium (Table 1). These results clearly revealed $Zr(NMe_2)_4$ and $Hf(NMe_2)_4$ to be the most effective catalysts; both achieved equilibrium in less than 1 h, whereas $Sm[N(SiMe_3)_2]_3$ required 5 h and $Sc[N(SiMe_3)_2]_3$ 10 h. Neither $LiN(SiMe_3)_2$ nor $Al_2(NMe_2)_6$ achieved equilibrium after 20 h. Further investigation revealed that $Zr(NMe_2)_4$-catalyzed transamidation of **1** and benzylmethylamine reached equilibrium within 10 h *at room temperature*. $Zr(NMe_2)_4$ and $Hf(NMe_2)_4$ displayed indistinguishable reactivity, and subsequent efforts focused on the former.

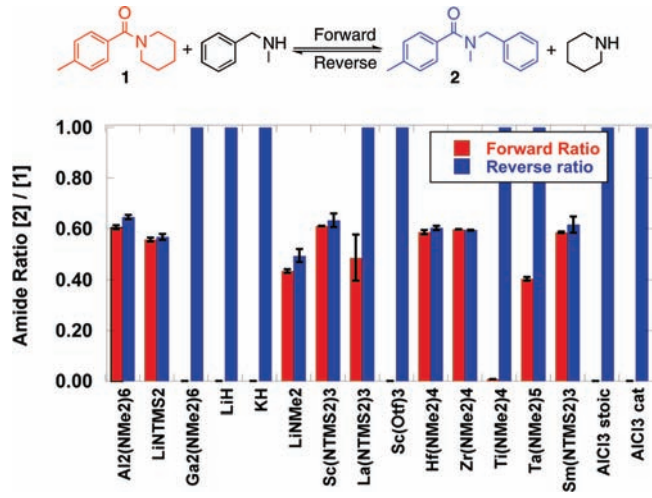
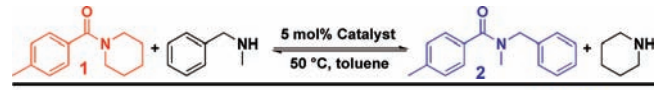


Figure 1. Representative catalyst screen. Standard conditions: equimolar amide and amine (0.33 mmol) with 5% catalyst (0.017 mmol) and triphenylmethane (0.875 M) (gas chromatography (GC) internal standard) in 2 mL of toluene. Reactions were carried out for 16 h at 90 °C. Amide ratios were determined by GC.

Table 1. Evaluation of Transamidation Catalysts at 50 °C[a]

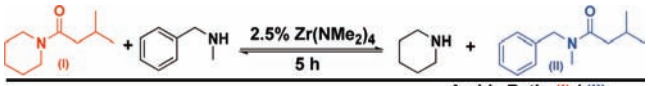


Entry	Catalyst	Time (min)	Amide Ratio (1) / (2) Forward	Amide Ratio (1) / (2) Reverse
1	$Hf(NMe_2)_4$	60	0.63/0.37	0.62/0.38
2	$Zr(NMe_2)_4$	60	0.63/0.37	0.63/0.37
3	$Sm(NTMS_2)_3$	335	0.63/0.37	0.64/0.36
4	$Sc(NTMS_2)_3$	640	0.65/0.35	0.63/0.37
5	$LiNTMS_2$	1169	0.64/0.36	0.57/0.43
6	$Al_2(NMe_2)_6$	1169	0.76/0.24	0.34/0.66

[a] See Figure 1 for standard reaction conditions.

(5) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422–3423.
(6) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 5177–5183.
(7) Secondary amide metathesis can achieved by imide-catalyzed transacylation (i.e., without the involvment of amine−amide exchange steps), but this process requires high temperatures: Bell, C. M.; Kissounko, D. A.; Gellman, S. H.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 761–763.
(8) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 647–654.

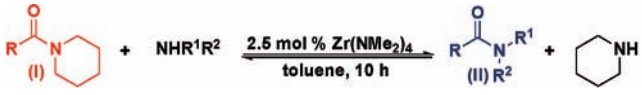
Table 2. Evaluation of Solvents in Transamidation Reactions[a]

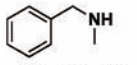
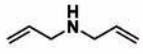
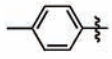
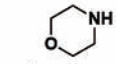
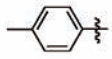
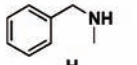
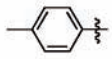
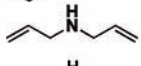
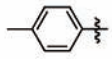
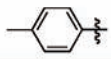
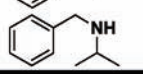


Entry	Solvent	Temp (°C)	Amide Ratio (I) / (II) Forward	Reverse
1	toluene	25	0.55 / 0.45	0.55 / 0.45
2	dichloromethane	25	0.60 / 0.40	0.40 / 0.60
3	chlorobenzene	25	0.56 / 0.44	0.56 / 0.44
4	THF	25	0.62 / 0.38	0.55 / 0.45
5		50	0.55 / 0.45	0.54 / 0.46
6	pyridine	25	0.75 / 0.25	0.41 / 0.59
7		50	0.57 / 0.43	0.57 / 0.43
8	diglyme	90	1.00 / 0.00	0.00 / 1.00
9	DMSO	50	1.00 / 0.00	0.00 / 1.00
10	acetonitrile	50	1.00 / 0.00	0.00 / 1.00

[a] See Figure 1 for standard reaction conditions.

Table 3. Amine Variation in Transamidation Reactions[a,b]

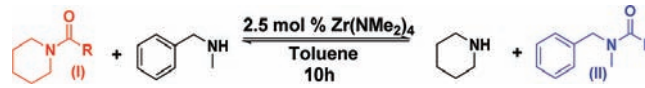


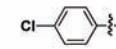
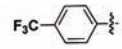
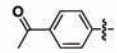
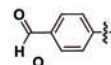
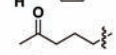
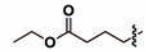
Entry #	R	NHR¹R²	Temp/ °C	Amide Ratio (I) / (II)[b] Forward	Reverse
1	$H_{13}C_6$		25	0.56/ 0.44	0.55/ 0.45
2	$H_{13}C_6$		25	0.71/ 0.29	0.70/ 0.30
3	$H_{13}C_6$		25	0.73/ 0.27	0.73/ 0.27
4			25	0.78/ 0.22	0.80/ 0.20
5			25	0.59/ 0.41	0.57/ 0.43
6			50	0.79/ 0.21	0.79/ 0.21
7			50	1.00/ 0.00	1.00/ 0.00
8			90	1.00/ 0.00	0.00/ 1.00

[a] See Figure 1 for standard reaction conditions. [b] In addition to amide products **I** and **II**, small quantities of *N*,*N*-dimethylcarboxamide (≤5% yield) are observed in these reactions.

Our initial studies were performed in toluene because this solvent was most effective in some of our previous studies. Evaluation of other solvents revealed that the reactivity was not limited to toluene (Table 2). Complete equilibration was observed within 5 h at room temperature when chlorobenzene was used as solvent (entry 3), and partial exchange was achieved within 5 h with dichloromethane. In the coordinating solvents THF and pyridine, significant transamidation was observed at room temperature, but it was necessary to increase the temperature to 50 °C to achieve equilibrium within 5 h (entries 4 and 5). In previous work, we found diglyme [bis(2-methoxy)ethyl ether] to support imide-mediated amide metathesis reactions that proceed via a transacylation mechanism;[7] however, diglyme is incompatible with Zr-catalyzed transamidation reactivity, even

Table 4. Acyl Group Variation in Transamidation Reactions[a]



Entry	R	Temperature/ °C	Amide Ratio (I) / (II) Forward	Reverse
1		25	0.64/0.36	0.64/0.36
2		25	0.55/0.45	0.55/0.45
3		25	0.63/0.37	0.62/0.38
4		25	0.49/0.51	0.47/0.53
5		25	0.67/0.33	0.66/0.34
6		25	0.65/0.35	0.67/0.33
7		25	0.61/0.39	0.59/0.41
8		50	0.60/0.40	0.60/0.40
9		50	0.60/0.40	0.52/0.48
10		50	0.65/0.35	0.65/0.35
11		50	0.65/0.35	0.60/0.40
12		50	1.00/0.00	0.00/1.00
13		50	1.00/0.00	0.00/1.00
14		50	1.00/0.00	0.00/1.00
15		50	1.00/0.00	0.00/1.00
16		90	0.78/0.22	0.04/0.96

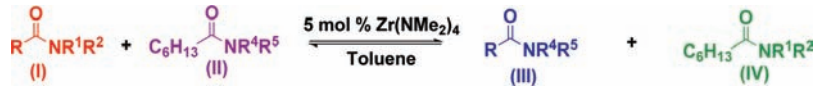
[a] See Figure 1 for standard reaction conditions.

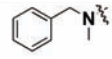
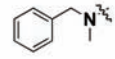
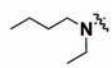
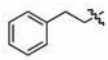
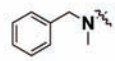
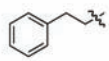
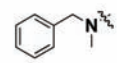
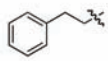
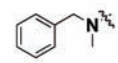
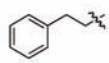
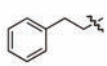
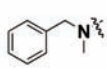
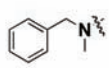
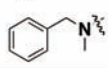
at 90 °C (entry 8). Chelation of the Zr atom by the ether oxygen atoms in this solvent probably hinders coordination of the substrates, thereby inhibiting the transamidation. No reaction is observed in DMSO or acetonitrile (entries 9 and 10), solvents that are coordinating and have relatively acidic C−H bonds. Both of these properties could lead to catalyst inhibition or deactivation. Protic solvents such as methanol react rapidly with Zr−amido ligands to form Zr−alkoxides[9] and, therefore, are incompatible with the reactions.

Analysis of a variety of substrate pairs under a standard set of conditions illuminated the scope and limitations of the transamidation reactions (Tables 3 and 4). A number of reactions were successful under ambient conditions (Table 3, entries 1−5), while others required heating to 50 °C (entries 6 and 7). Comparison of entries 3 and 6 suggests that heptanamides are more reactive toward transamidation than are toluamides; with diallyl amine, the toluamide substrate required 50 °C to achieve full equilibration within 10 h, while the heptanamide version of this reaction reached equilibrium at room temperature during the same time period. Entry 7 is the only example expected to display a substantial intrinsic thermodynamic bias, favoring the aniline−amide pair over the amine−anilide pair, and only the aniline−amide products are observed from the equilibration

(9) Bradley, D. C.; Thomas, I. M. *J. Chem. Soc.* **1960**, 3857–3861.

Table 5. Zr-Catalyzed Metathesis of Tertiary Carboxamides[a]



Entry #	R	NR^1R^2	NR^4R^5	Temperature	Time	Amide Ratio [(I)/ (II)/ (III)/ (IV)] Forward	Reverse
1				25°C	5h	.26/ .20/ .28/ .26	.26/ .20/ .28/ .26
2				25°C	5h	.22/ .23/ .34/ .21	.22/ .24/ .33/ .21
3				50°C	5h	.29/ .26/ .23/ .22	.29/ .25/ .23/ .22
4				25°C	5h	.24/ .29/ .28/ .18	.24/ .30/ .28/ .18
5				25°C	5h	.23/ .33/ .21/ .22	.23/ .34/ .22/ .21
6				25°C	5h	.25/ .28/ .19/ .27	.25/ .29/ .20/ .26
7				25°C	10h	.20/ .27/ .29/ .24	.17/ .29/ .30/ .24
8				25°C	10h	.27/ .23/ .31/ .19	.25/ .21/ .33/ .20
9				50°C	5h	.24/ .34/ .21/ .22	.21/ .36/ .23/ .20
10				90°C	12h	.19/ .24/ .31/ .27	.19/ .24/ .31/ .27
11				90°C	12h	.23/ .20/ .33/ .25	.23/ .20/ .32/ .25
12				90°C	12h	.28/ .29/ .25/ .18	.22/ .23/ .30/ .25

[a] See Figure 1 for standard reaction conditions.

reaction performed in either direction. When the amine bears an α-branched alkyl group (entry 8), no reaction was observed even at 90 °C, suggesting that this catalytic process is very sensitive to steric factors.

The examples in Table 4 probe the effect of variations in the acyl group on the Zr-catalyzed transamidation reactions and provide some insight into the functional group compatibility of the reaction. Several examples achieved equilibrium at room temperature (entries 1−7), while others were more sluggish (entries 8−11 and 16). In general, substituents with a methylene group adjacent to the amide carbonyl undergo facile transamidation at room temperature (Table 3, entries 1−3; Table 4, entries 2−4). A wide variety of functional groups can be tolerated in Zr-catalyzed transamidation. Examples include terminal alkyne (entry 4) and aryl chloride (entry 5) as well as furanyl (entry 7) and pyridinyl (entries 10 and 11) groups. The terminal alkyne (entry 4) is potentially susceptible to hydroamination in the presence of group 4 metal−amido complexes;[10] however, such reactivity is not observed under the mild transamidation reaction conditions. The incomplete reactivity of the acetamide substrate was unexpected (entry 9); we speculate that this unhindered amide might undergo deprotonation of the acetyl methyl group, with an amido ligand serving as base, to yield a Zr−enolate species. The amide with a 4-pyridinyl substituent (entry 10) undergoes significant transamidation at room temperature after 10 h but requires 50 °C to achieve full equilibration during this time period. No exchange reaction is observed at room temperature with the amide bearing the 2-pyridinyl substituent, probably reflecting kinetic inhibition arising from substrate chelation; however, this substrate achieves nearly complete equilibration within 10 h upon heating to 50 °C (entry 11). No transamidation activity was observed with amides bearing more reactive carbonyl groups, including those derived from an aldehyde, ketones, or an ester (entries 12−15). ^{1}H NMR spectroscopy indicated that these substrates undergo some alternative form of reaction in the presence of the Zr catalyst. This reactivity was not explored in detail, but it is probably related to the known irreversible stoichiometric reactivity of group 4 metal−amido complexes with organic compounds containing carbonyl groups.[11] The limited reactivity observed with an α-branched amide (entry 16) strengthens the

(10) (a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708–1719. (b) Odom, A. L. *Dalton Trans.* **2005**, 225–233. (c) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420. (d) Lee, A. V.; Schafer, L. L. *Eur. J. Inorg. Chem.* **2007**, 2243–2255.

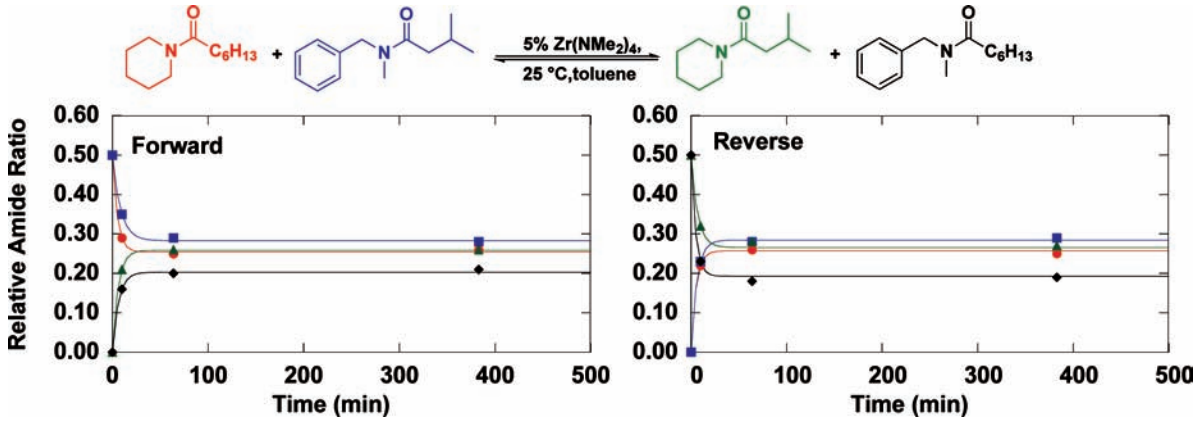


Figure 2. Amide metathesis time course at 24 °C. Individual reaction vials were used for each time point. Reaction conditions: equal amounts of amides (0.33 mmol) in 2 mL of toluene in the presence of $Zr(NMe_2)_4$. Color of amides corresponds to color of markers in time course plot.

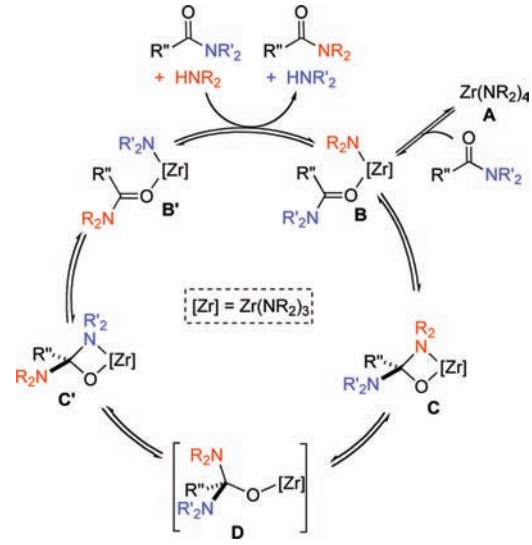
conclusion that steric bulk near the amide moiety hinders exchange (see also entry 8 of Table 3).

Amide Metathesis. The unprecedented activity of $Zr(NMe_2)_4$ as a transamidation catalyst suggested that amide metathesis might be possible; indeed, we found that a number of tertiary amide substrate pairs undergo full equilibration in the presence of 5 mol % $Zr(NMe_2)_4$ in toluene (Table 5, entries 1−7). Some of the amide exchange processes occurred extremely rapidly. For example, the metathesis equilibration corresponding to entry 1 of Table 5 was complete *within minutes at room temperature*.

A time-course plot reflecting this rapid equilibration is shown in Figure 2. The origins of substrate reactivity differences evident in Table 5 are not yet clear, but the data once again reveal that amides with a methylene unit bonded to the carbonyl carbon are intrinsically more reactive than amides in which an aromatic ring is bonded to the carbonyl carbon (entries 1 and 4 vs 10; 2 and 5 vs 11; and 6 vs 12).

Mechanistic Considerations. Scheme 1 shows the catalytic cycle we envision to explain the Zr-based transamidation reactivity documented above. This mechanistic hypothesis closely resembles the catalytic cycle we proposed for $Al_2(NMe_2)_6$-catalyzed trasamidation of secondary amine/tertiary amide pairs, on the basis of experimental and computational mechanistic studies.[8] A key feature of this hypothesis is the simultaneous activation of the electrophile (carboxamide) and the nucleophile (amido) via coordination to a Zr atom (intermediate **B**). Intramolecular attack of the amido on the coordinated amide gives rise to a Zr-stabilized tetrahedral intermediate (**C**), which can interconvert with an isomeric intermediate (**C′**), ultimately leading to formation of a new amide/amido pair coordinated to the Zr atom (**B′**). If the transamidation processes catalyzed by homoleptic dimethylamido complexes of Al^{III}, Zr^{IV}, and Hf^{IV} all proceed via this type of mechanism, then it will be intriguing to determine why the Zr- and Hf-based processes are so much more facile than that based on Al. The attenuated reactivity of the Al−amido species might reflect their less hindered coordination environment, which often results in the formation of dimeric, possibly less reactive structures. Alternatively, the participation of d-orbitals in the Zr- and Hf-based catalysts might

Scheme 1. Proposed Catalytic Cycle for Zr-Catalyzed Transamidation Reactions



enhance the rates of ligand association, dissociation, or substitution or the rates of reactions within the metal coordination sphere, thereby contributing to more rapid catalytic turnover. Further studies will be needed to explore these possibilities.

Conclusions

This study demonstrates that secondary amine−tertiary amide transamidations can be catalyzed efficiently by a commercially available complex, $Zr(NMe_2)_4$. The catalytic activity is sufficiently high to enable rapid tertiary amide metathesis, which presumably involves successive transamidation steps (eqs 1−3). These results represent a substantial advance in carboxamide exchange reactivity relative to the precedents in this challenging reaction manifold, and they strongly suggest that carboxamide-based DCC will be feasible. Such a process might provide interesting, perhaps even useful, oligoamides that are extremely stable under most conditions.

Experimental Section

General Considerations. The handling of air-sensitive materials was carried out in a nitrogen atmosphere glovebox. Toluene was dried with an activated alumina purification column. Gas chromatography was performed with a Shimadzu GC-17A gas chromatograph equipped with a Restek, 15 m RTX-5 capillary column. Metal

(11) For leading references, see: (a) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *Organometallics* **1993**, *12*, 3705–3723. (b) Lee, S. Y.; Bergman, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 6396–6406. (c) Kissounko, D. A.; Guzei, I. A.; Gellman, S. H.; Stahl, S. S. *Organometallics* **2005**, *24*, 5208–5210. (d) Kissounko, D. A.; Hoerter, J. M.; Guzei, I. A.; Cui, Q.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 1776–1783.

complexes were purchased from Aldrich and Strem and used as received. Amines were purchased from Aldrich and distilled from CaH_2 prior to use. Amides were synthesized following standard procedures, and liquid amides were further purified by vacuum distillation from CaH_2.

Representative Procedure for Transamidation Studies. Under a nitrogen atmosphere, a toluene solution of amide (0.33 M), amine (0.33 M), and triphenylmethane (0.09 M) was prepared. A toluene solution of catalyst (0.017 M for 5 mol % loading and 0.0083 M for 2.5% catalyst loading) was also prepared. The amide solution (1 mL) was dispensed into a 4 mL glass vial, and transamidation was initiated by the addition of 1 mL of catalyst solution. The glass vials were sealed with a Teflon-lined cap, removed from the glovebox, placed on a heated 48-well metal block, and agitated for the allotted reaction time. The reaction was quenched by the addition of 0.5 mL of methanol to the reaction solutions. The reaction mixture was then analyzed by gas chromatography using triphenylmethane as an internal standard.

Representative Procedure for Amide Metathesis Studies. The transamidation protocol was followed using 5 mol % catalyst (0.017 mmol) and equivalent amounts of two different amides (0.33 mmol) in 2 mL of toluene. The reaction was quenched with methanol and analyzed by gas chromatography using triphenylmethane as internal standard.

Acknowledgment. We thank Dr. J. M. Hoerter for many useful discussions. This work was supported by the NSF Collaborative Research in Chemistry program (CHE-0404704).

JA8094262