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$Sc(OTf)_3$-catalyzed synthesis of anhydrides from twisted amides†

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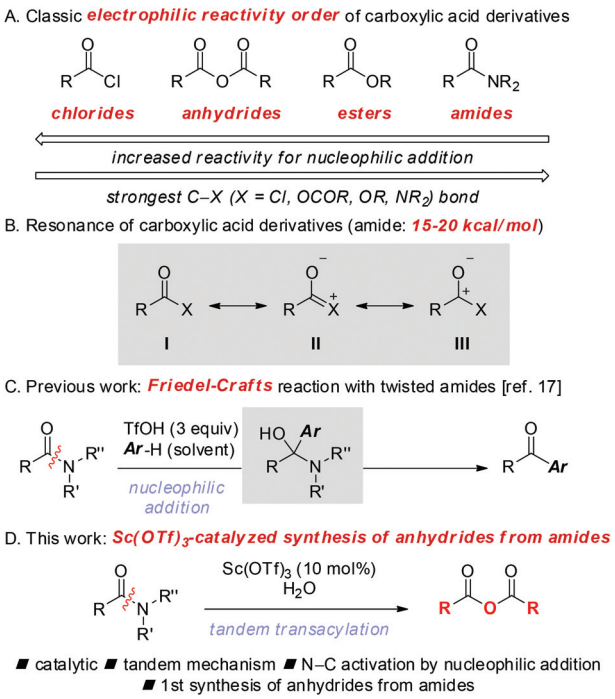
A novel synthesis of anhydrides from twisted amides is reported. $Sc(OTf)_3$ catalysis in the presence of water is used to synthesize anhydrides in one step from amides without external nucleophiles. Mechanistic studies indicate that the coordination of the catalyst is critical to induce the challenging N–C activation step. This process further highlights the utility of twisted amides in organic synthesis. Notably, the reaction indicates that twisted amides based on the glutarimide scaffold are more reactive than carboxylic acid anhydrides under the developed conditions, which opens the door to controlled sequential catalysis through amide N–C bond cleavage.

The reactivity trend in nucleophilic addition to carboxylic acid derivatives represents a classic effect in organic synthesis that is taught to undergraduates in all introductory organic chemistry courses worldwide (Scheme 1A).[1,2] The observed reactivity correlates with the extent of delocalization of the lone pair on the heteroatom (X = Cl, OCOR, OR, NR_2) onto the $\pi^*_{C=O}$ orbital of the carbonyl group (Scheme 1B).[3] The resonance stabilization in acyl chlorides is the weakest, followed by anhydrides and esters, while amides show the highest degree of resonance stabilization. Amidic resonance ($n_N \rightarrow \pi^*_{C=O}$ conjugation, in planar amides 15–20 kcal mol^{-1}) entails that amides are among the least reactive electrophiles in nucleophilic addition to the carbonyl group.[4] As a consequence, amides are rarely utilized as acyl-transfer reagents (*cf.* products) in organic synthesis.[5] Enhanced resonance leads to unusual stability; for example, hydrolysis of carboxylic acid anhydrides has been estimated to be 9 orders of magnitude more facile than that of planar amides.[6]

Our laboratory has developed new methods for activation of amide bonds by resonance destabilization (Schemes 1C and 2).[7] The amide bond destabilization concept is particularly relevant in the context of N–C bond cross-coupling reactions[8,9] as recently reported by us[10] and others[11–14] (Scheme 2). It should be emphasized that all of these recently reported methods utilize bench stable, readily tuneable amides,[15] thus enabling a new disconnection mode of the amide bond in organic synthesis. These amides are characterized by decreased amidic resonance (*e.g.* by additional N conjugation) to enable selective metal insertion. However, despite the successful realization of acyl and aryl cross-coupling manifolds by selective metal insertion into the N–C amide bond,[7] the nucleophilic addition platform to the amide bond remains severely underdeveloped. Herein, we report an unprecedented synthesis of anhydrides from twisted amides. $Sc(OTf)_3$ cataly-



Scheme 1 (a) Classic reactivity of carboxylic acid derivatives. (b) Resonance stabilization. (c) Previous and (d) this work.

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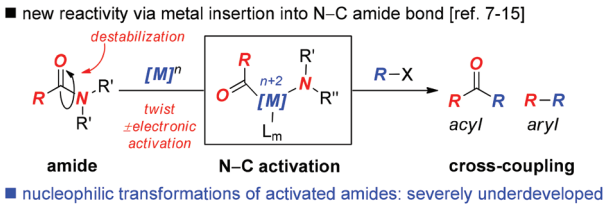
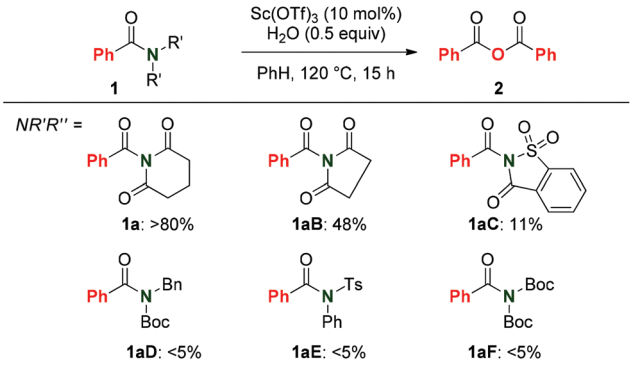


Scheme 2 Activation concept for amide N–C bond cross-coupling.



Scheme 3 $Sc(OTf)_3$-catalyzed synthesis of anhydrides from amides: the effect of amide *N*-substituents.

sis in the presence of water is employed to synthesize anhydrides in one step from amides without added external nucleophiles by a tandem catalysis mechanism. Notably, the reaction constitutes the first example of a synthesis of anhydrides from amides.[16] The bench-stability of these amides as well as high reactivity enabled by both the twist and the nitrogen conjugation with imide carbonyls should be noted. Given the classically much higher reactivity of anhydrides than amides due to $n_X \rightarrow \pi^*_{C=O}$ resonance stabilization,[1–4] the ability to develop new previously elusive catalytic amide bond reactivity modes through N–C cleavage by judicious choice of amide precursors and reaction conditions presents enabling tactics for organic synthesis.

It is well established that while amides are the least reactive carboxylic acid derivatives (Scheme 1A), some twisted amides break this rule due to decreased N_{lp} to $\pi^*_{C=O}$ conjugation; steric effects in the nucleophilic addition to sterically-distorted amides dominate the selectivity of these reactions.[16g–j] Twisted amides have been used to acylate alcohols to form esters as elegantly demonstrated by Yamada;[16g,h] however, in general, these acylation reactions using 1,3-thiazolidine-2-thiones proceed after alcohol deprotonation or require bulky 3-pivaloyl-1,3-thiazolidine-2-thiones. Thus far nucleophilic addition reactions to twisted amides have been limited to alcohols. Transacylation reactions with other nucleophiles, including carboxylic acids, or synthetically-useful tandem processes have not been developed.

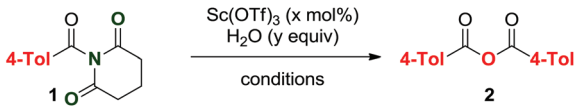
We have recently reported the first Friedel–Crafts reaction with twisted amides as acylating reagents.[17,18] The method utilized stoichiometric TfOH, and required an excess of arene nucleophile (ArH as solvent) (Scheme 1C). Therefore we became interested in developing a catalytic variant of the Friedel–Crafts[19] reaction using bench-stable twisted acyclic amides as the acyl source to enhance the synthetic utility of the process. However, in contrast to our reaction design, we serendipitously discovered that when using $Sc(OTf)_3$ as a catalyst in the presence of water,[19] a tandem nucleophilic addition process[20] affords anhydrides in preference to ketones (Scheme 1D) (*cf.* direct Friedel–Crafts acylation).

Initial experiments focused on evaluating the effect of amide bond *N*-substitution (destabilization) under $Sc(OTf)_3$-catalyzed conditions (Scheme 3). Unsurprisingly, the facility of nucleophilic addition could be correlated with the amide bond distortion (**1a–1aC**: **1a**: τ = 91.4°; **1aB**: τ = 46.1°; **1aC**: τ = 23.0°).[15b,10i] Additional products were not detected using moderately distorted twisted *N*-acyl-Boc-carbamates (**1aD**), *N*-acyl-sulfonamides (**1aE**) and electronically-activated *N*,*N*-Boc_2-amides (**1aF**), recently introduced by our laboratory in metal catalyzed N–C cleavage.[10g,h] Unexpectedly, we discovered that twisted amides **1a–1aC** featuring the ground-state steric distortion generated the anhydride product. Importantly, the reaction occurred with exclusive chemo- (anhydride *vs.* ketone) and site-selectivity (N–CO *vs.* adjacent σ N–C bond).

The effect of key reaction parameters on this unusual tandem nucleophilic addition reaction is presented in Table 1. As is shown, careful screening of water loading verified that the control of water stoichiometry is critical to achieve the best results (entries 1–4). The loading of $Sc(OTf)_3$ moderately affects the reaction (entries 5–7). Exploration of the solvent concentration (entries 8 and 9) and other solvents (entries 10 and 11) showed the modest effect on the reaction efficiency. Control experiments revealed that a lower temperature completely suppresses the reaction (entry 12). It should be noted that in all productive reactions, the remaining mass balance corresponded to the acid hydrolysis product. Since this pointed at the transacylation step as the key part of the mechanism, we examined the direct transacylation of twisted amide **1** using carboxylic acid as a nucleophile (entries 13–21, Table 1). Note that comparable results were obtained using carboxylic acid as a transacylating reagent. Careful examination of the $Sc(OTf)_3$ loading (entries 13 and 14), temperature (entries 15–17), stoichiometry (entries 18 and 19), and solvents (entry 20) reveals that although the reaction with acid proceeds at a lower temperature (*vide infra*), the product is formed in similar yields as with water as the only additive (entries 1–12). Control experiments demonstrated that the reaction does not take place in the absence of $Sc(OTf)_3$ (entry 21). Taken together, this suggests that $Sc(OTf)_3$ is necessary to catalyze both steps in the reaction mechanism.[20]

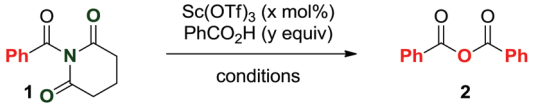
With these optimized conditions in hand, the scope of the reaction was briefly evaluated (Table 2). Amides **1** bearing neutral (entry 1), and electron-donating substituents at the 4-position (entries 2 and 3) were well-tolerated. Moreover, polyaromatics such as naphthalene (entry 4) and substitution with

Table 1 Optimization of $Sc(OTf)_3$-catalyzed synthesis of anhydrides from twisted amides[a]



Entry	$Sc(OTf)_3$ (mol%)	H_2O (equiv.)	Solvent	T (°C)	Yield (%)
Water loading					
1	5	—	PhH	120	<5
2	5	0.25	PhH	120	25
3	5	0.5	PhH	120	61
4	5	1	PhH	120	21
$Sc(OTf)_3$ loading					
5	5	0.5	PhH	120	61
6	10	0.5	PhH	120	70
7	20	0.5	PhH	120	53
Concentration, solvent, temperature					
8[b]	5	0.5	PhH	120	65
9[c]	5	0.5	PhH	120	52
10	10	0.5	DCE	120	61
11	10	0.5	PhMe	120	65
12	10	0.5	PhH	80	<5

Transacylation with $PhCO_2H$



Entry	$Sc(OTf)_3$ (mol%)	$PhCO_2H$ (equiv.)	Solvent	T (°C)	Yield (%)
13	10	1.0	PhH	120	58
14	20	1.0	PhH	120	60
15	10	1.0	PhH	110	67
16	10	1.0	PhH	100	47
17	10	1.0	PhH	80	38
18	10	2.0	PhH	120	71
19	10	3.0	PhH	120	67
20	10	1.0	PhMe	140	60
21[d]	10	1.0	PhH	120	<5

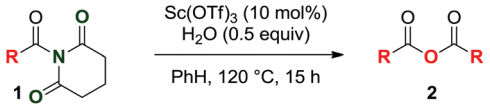
[a] Conditions: amide (1.0 equiv.), $Sc(OTf)_3$ (x mol%), H_2O, solvent (0.2 M), T, 15 h. [b] 1.0 M. [c] 4.0 M. [d] Without $Sc(OTf)_3$. See the ESI for full experimental details.

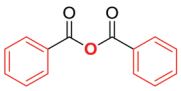
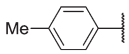
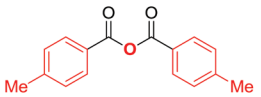
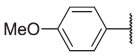
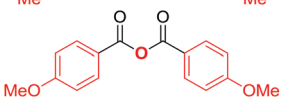
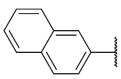
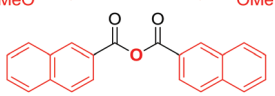
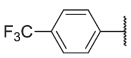
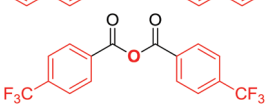
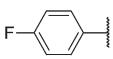
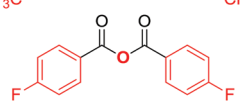
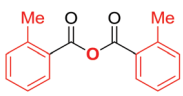
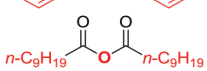
electron-withdrawing substituents at the 4-position, such as trifluoromethyl (entry 5) and fluoro (entry 6), were well-accommodated. However, substitution at the 2-position of the arene (entry 7) and the use of aliphatic amides (entry 8) resulted in low conversion to the desired product. Further extension of the substrate scope is currently underway and will be reported in due course.

Next, studies were conducted to probe the mechanism of this intriguing process (Table 3 and Scheme 4). The role of $Sc(OTf)_3$ in the reaction was studied in a series of stability studies (Table 3). Interestingly, no reaction was observed in the presence of water (10 equiv.), in the absence (entry 1) and in the presence of $Sc(OTf)_3$ (entry 2) at room temperature. Moreover, incubation of amide **1** with water at 120 °C resulted in the recovery of **1** (entry 3). The high stability of acyclic twisted amides such as **1** to protic conditions stands in contrast to hydrolytically unstable classic bridged lactams, representing a unique synthetic advantage.[7b] Incubation of **1** with water and $Sc(OTf)_3$ at 120 °C resulted in slow hydrolysis of **1** to benzoic acid (entry 4). Studies were conducted to shed light on the feasibility of thermal dehydration of acid under the developed reaction conditions (Scheme 4). Subjecting benzoic acid in the absence and presence of glutarimide to the standard reaction conditions at 120 °C did not result in the formation of **2**. These results rule out the formation of anhydride **2** directly from the corresponding carboxylic acid. Preliminary cross-over experiments showed the lack of cross-over products (not shown). The lack of cross-over products may indicate that the reaction sequence takes place within the coordination sphere of the catalyst.[21] Further studies to elucidate the mechanism are ongoing.

Based on the above mechanistic observations, we tentatively propose a $Sc(OTf)_3$-mediated activation of the amide bond toward nucleophilic addition. The catalyst coordination to the

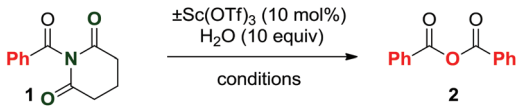
Table 2 $Sc(OTf)_3$-catalyzed synthesis of anhydrides from twisted amides[a]



Entry	Amide (R)	1	Product	2	Yield (%)
1		**1a**		**2a**	87
2		**1b**		**2b**	77
3		**1c**		**2c**	69
4		**1d**		**2d**	58
5		**1e**		**2e**	58
6		**1f**		**2f**	60
7		**1g**		**2g**	<5
8		**1h**		**2h**	<5

[a] Amide (1.0 equiv.), $Sc(OTf)_3$ (10 mol%), H_2O (0.5 equiv.), PhH, 120 °C, 15 h. See ESI for full details.

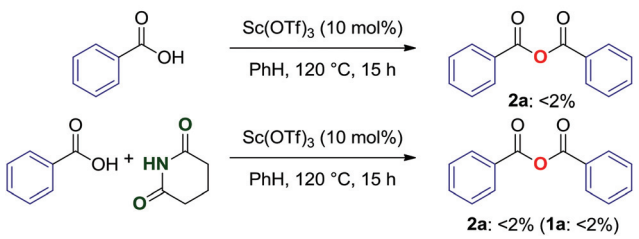
Table 3 Stability studies on $Sc(OTf)_3$-catalyzed synthesis of anhydrides from twisted amides[a]



Entry	Conditions	Results: 1[b] (%)	Results: 2 (%)
1	H_2O (10 equiv.), RT	>80	<5
2	$Sc(OTf)_3$, H_2O (10 equiv.), RT	>80	<5
3	H_2O (10 equiv.), 120 °C	>80	<5
4	$Sc(OTf)_3$, H_2O (10 equiv.), 120 °C	18	48[c]

[a] Amide (1.0 equiv.), $Sc(OTf)_3$, H_2O (10 equiv.), PhH, T, 15 h. [b] Recovery yield of **1**. [c] Yield of benzoic acid.

Condensation Experiments



Scheme 4 Mechanistic studies.

glutarimide oxygen atom activates the amide N–C bond for nucleophilic addition.[15b,19,21] Optimization studies showed that amide hydrolysis requires more forcing conditions than direct transacylation. The success of the reaction arises from the ability to fine-tune the relative rate of catalytic steps in an engineered sequence using amide bond properties and reaction conditions. Future work will be focussed on elucidating the mechanism.

In conclusion, the synthesis of anhydrides from twisted amides has been demonstrated for the first time. This unusual reaction proceeds in a single step using a $Sc(OTf)_3$ catalyst in the presence of water. Initial mechanistic studies suggest that tandem transacylation with coordination of the catalyst is critical to induce the challenging N–C activation step. Transition metal catalyzed activation of C–O bonds in anhydrides has

gained substantial maturity compared to that of direct metal insertion into the amide N–C bond.[16e,f] We envision that enlisting controlled sequential catalysis will enable the discovery of new reactivity of amides by N–C bond cleavage. Investigations directed at broadening the scope of the process and further application of the nucleophilic reactivity platform of destabilized amides are currently underway. However, within the context of the classic electrophilic reactivity of carboxylic acid derivatives, amide destabilization is sufficiently powerful to overturn the reactivity preference of carbonyl functional groups.

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