

Thulium Diiodide

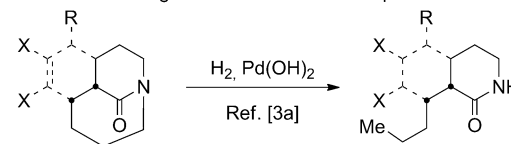
Uncovering the Importance of Proton Donors in TmI₂-Promoted Electron Transfer: Facile C–N Bond Cleavage in Unactivated Amides**

Michal Szostak,* Malcolm Spain, and David J. Procter*

The amide bond is one of the most ubiquitous functional groups in chemistry and biology.^[1] To date, the majority of strategies to functionalize amide bonds have focused on activation of the carbonyl group towards nucleophilic addition,^[2] however only few examples of the selective activation of σ C–N bonds in amides have been reported. In this regard, the cleavage of a σ C–N bond in amides was achieved in several highly innovative but very specialized bridged lactams, in which one of the C–N bonds was sufficiently distorted from planarity (Figure 1 a).^[3] Functionalization of the C–N bond in electronically activated phthalimides has also been described.^[4] However, a general method for the activation of σ C–N bonds in amides is unknown despite its considerable potential to advance the synthetic application of amide linkages in chemistry and biology.

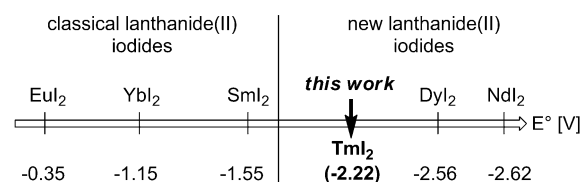
The discovery of new reactivity modes of underexplored elements underpins major advancements in synthesis. In this regard, the seminal discovery of Kagan and co-workers that SmI₂ acts as a strong electron donor^[5] has resulted in one of the most important single-electron transfer reagents in organic chemistry.^[6,7] However, the inherent limitation of SmI₂ is its relatively low redox potential (E° (Ln^{III/II}) = –1.5 V vs. NHE),^[8] especially when compared with the extremely powerful, albeit less chemoselective, alkali metals in liquid ammonia (i.e. Birch-type reductants).^[9] Recently, nonclassical lanthanide(II) iodides (TmI₂, thulium diiodide; DyI₂, dysprosium diiodide; NdI₂, neodymium diiodide) have emerged as an attractive solution to the problem of insufficient redox potential of SmI₂ (Figure 1 b).^[10] In analogy to SmI₂, these extremely reducing lanthanide iodides (E° (Ln^{III/II}) = –2.2, –2.5, –2.6 V vs. NHE,^[8] respectively) have been fully characterized in ethereal solvents^[11] and can be easily obtained in multigram quantities.^[12] Seminal work by Evans et al. provided the first evidence that TmI₂, DyI₂, and NdI₂ mediate challenging cross-coupling reactions beyond the scope of SmI₂.^[13] Evans et al. also reported DyI₂ as the first lanthanide(II) reagent capable of promoting Birch reductions under very mild conditions.^[11b] However, the direct use of

a) σ C–N bond cleavage in unactivated amides: previous work



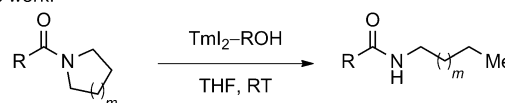
- highly-specialized "twisted amides"
- substrate control by ring distortion

b) Evolution of lanthanide(II) reagents (E° measured for Ln^{III}/Ln^{II}, NHE)

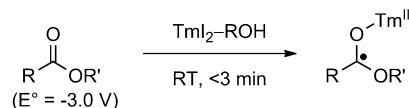


- valuable SET reagents
- key role of additives (proton donors, Lewis bases, metals)
- unexplored in organic synthesis
- stable in solid state and solution
- unknown influence of additives

c) This work:



- general σ C–N bond cleavage in planar amides
- reagent control by alcohol coordination to Ln(II)



- rapid generation of Tm(III) ketyl radicals
- first chemoselective reduction of acyclic esters with a lanthanide(II) reagent

Figure 1. a) Cleavage of unactivated σ C–N bonds in amides. b) Classical and nonclassical lanthanide(II) iodides. c) This study.

nonclassical lanthanides(II) to generate ketyl radicals has not been reported despite their significant potential to activate C=O groups that are typically resistant to open-shell reaction pathways.

Herein, we demonstrate that the TmI₂–ROH reagent (R = H, Me), formed from the first nonclassical lanthanide(II) iodide in the series, promotes a highly unusual cleavage of the σ C–N bond in planar amides. Moreover, we report that TmI₂–ROH is the first lanthanide(II) reagent to selectively generate ketyl radicals from aliphatic esters. Finally, we demonstrate that the presence of alcohols is critical for the formation of thermodynamically more powerful reductants from TmI₂ (TmI₂(ROH)_n, E° = –2.6 V vs. SCE).

[*] Dr. M. Szostak, M. Spain, Prof. Dr. D. J. Procter
School of Chemistry, University of Manchester
Oxford Road, Manchester M13 9PL (UK)
E-mail: michal.szostak@manchester.ac.uk
david.j.procter@manchester.ac.uk
Homepage: <http://people.man.ac.uk/~mbdssdp2/>

[**] We acknowledge the EPSRC and GSK for financial support.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201303178>.

We recently developed approaches for the chemoselective reduction of cyclic esters^[14a] and 1,3-diester^[14b] by using a $\text{SmI}_2\text{-H}_2\text{O}$ reagent. These reactions were the first examples of the activation of carbonyls that are traditionally unreactive towards SmI_2 . On the basis of these results, we initiated efforts to chemoselectively activate other types of carbonyl by using lanthanide(II) reagents. We hypothesized that the use of the more-reducing nonclassical lanthanide(II) iodides would result in a chemoselective generation of acyl-type radicals from carboxylic acid derivatives that lie beyond the scope of SmI_2 . In particular, we considered that highly reducing nonclassical lanthanide(II) iodides that are additionally activated by proton donors, could potentially permit productive electron transfer to amide carbonyls, a functional group that has been traditionally resistant to single-electron-transfer reductants, as a result of $n_{\text{N}} \rightarrow \pi_{\text{C=O}}$ conjugation.^[1] With these considerations in mind, we subjected *N,N*-dialkyl amide **1a** to several TmI_2 -mediated reaction conditions (Table 1). To our

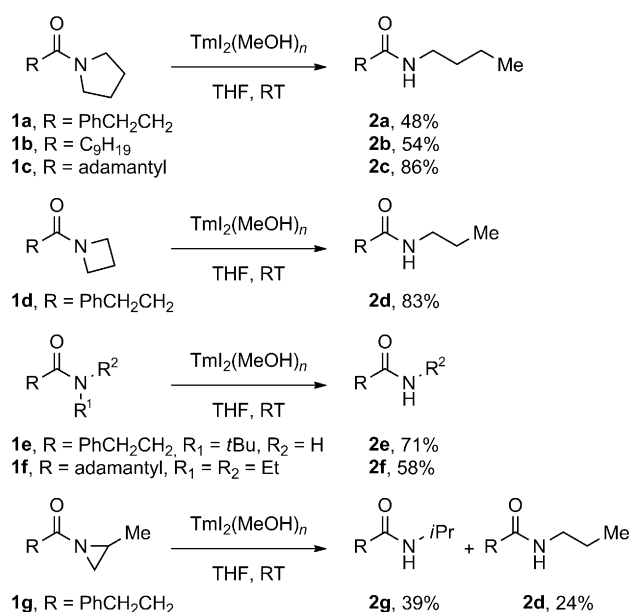
Table 1: Optimization of the C–N bond cleavage in unactivated amides in the presence of $\text{LnI}_2(\text{ROH})_n$.

Entry	LnI_2	LnI_2 (equiv)	ROH	ROH (equiv) ^[a]	t ^[b]	Yield [%] ^[c]
1	TmI_2	3	–	–	2 h	< 2
2	TmI_2	3	MeOH	10	3 min	< 2
3	TmI_2	3	MeOH	100	3 min	48 (77) ^[d]
4 ^[e]	TmI_2	3	MeOH	100	3 min	< 2
5	TmI_2	3	H_2O	150	3 min	< 2
6 ^[f]	SmI_2	3	–	–	3 h	< 2
7 ^[f]	SmI_2	3	MeOH	100	3 h	< 2
8 ^[f]	SmI_2	3	H_2O	100	1 h	< 2

[a] With respect to LnI_2 . [b] Time elapsed until characteristic color change from Tm^{II} to Tm^{III} . [c] Determined by ^1H NMR spectroscopy and/or GC–MS. [d] In parentheses, yield based on the recovered starting material. TmI_2 (6 equiv) afforded **2a** in 45% yield. [e] The corresponding amine was used instead of the amide. [f] Azetidiny amide **1d** used instead of the pyrrolidiny amide. Reaction conditions: LnI_2 (3 equiv), ROH (H_2O , 150 equiv; MeOH, 100 equiv), THF, 23 °C. See the Supporting Information for details.

delight, with MeOH as the proton source, we observed efficient formation of *N*-monoalkyl amide **2a**, in which a highly unusual cleavage of the σ C–N bond took place (Table 1, entry 3; see the Supporting Information for reagent stability studies). Control reactions demonstrated that the reaction did not proceed in the absence of a proton source (Table 1, entry 1), at low concentration of MeOH (Table 1, entry 2), with H_2O as an alternative additive (Table 1, entry 5), and with a variety of SmI_2 systems (Table 1, entries 6–8; see also the Supporting Information). Furthermore, the corresponding aliphatic pyrrolidiny amine was inert to the reaction conditions (Table 1, entry 4), thus demonstrating high levels of chemoselectivity imparted by the TmI_2 reagent.^[15]

With the optimized conditions in hand, a series of amides was subjected to the reaction to provide an initial examina-



Scheme 1. Cleavage of unactivated σ C–N bonds in amides in the presence of $\text{TmI}_2(\text{ROH})_n$ at 23 °C.

tion of the scope of this transformation (Scheme 1). The C–N bond scission occurred for both unhindered and sterically encumbered pyrrolidiny amides (**1a–1c**). Moreover, the reaction of the azetidiny amide **1d** demonstrated that the reaction is applicable to other cyclic amides. In addition, two acyclic amides (**1e–1f**) were similarly cleaved, thus demonstrating that the cyclic structure of amides is not necessary for the scission. Importantly, secondary *n*-alkyl and *n*-aryl amides did not undergo the cleavage reaction (see the Supporting Information), thus indicating complete selectivity of the reducing system for these tertiary amides. To gain a preliminary mechanistic insight, we subjected a sterically biased aziridinyl amide **1g** to the reaction conditions. The reaction afforded an approximately 1.6:1.0 ratio of regioisomeric amides, with the predominant product resulting from cleavage at the less substituted carbon center. On the basis of this experiment and the known propensity of nonclassical LnI_2 to cleave C–O bonds in ethers,^[15] we propose that the mechanism of the TmI_2 -mediated cleavage involves a direct insertion of Tm^{II} into the C–N amide bond; however, a mechanism involving fragmentation of an initially-formed ketyl-type radical seems also to be operating in some cases as suggested by the correlation of the reaction efficiency with thermochemical stabilization energies (SE) of the fragmenting radical in the series: $t\text{Bu}$ (71 %, $\text{SE} = 4.35 \text{ kcal mol}^{-1}$) > $i\text{Pr}$ (29 %, $\text{SE} = 2.57 \text{ kcal mol}^{-1}$) > Me (< 2 %, $\text{SE} = -1.65 \text{ kcal mol}^{-1}$).^[16]

The mechanistic implications of the C–N cleavage merit further discussion. The present reaction with TmI_2 represents the first case of a general scission of unactivated σ C–N bonds in planar amides, and compares favorably with the previous examples of the cleavage of a σ C–N bond in distorted lactams^[3] (reagent vs. substrate control). Moreover, it strongly suggests that the reactivity of nonclassical lanthanides(II) extends beyond being the reagents that simply close the energy gap between SmI_2 and the Birch-type reductants.^[11,13a]

Having established that $\text{TmI}_2\text{-ROH}$ is capable of an efficient electron transfer to the amide carbonyl group but not their reduction, the reagent system was applied to the generation of ketyl radicals from esters (Table 2). In previous

Table 2: Reduction of aliphatic esters in the presence of $\text{TmI}_2(\text{ROH})_n$ at 23 °C.^[a]

Entry	Ester/Acid	ROH	<i>t</i> [min] ^[a]	Yield [%] ^[b]
1		H ₂ O	2–3	88
2		MeOH	2–3	99
3		MeOH	2–3	96
4		MeOH	2–3	85
5		MeOH	2–3	94
6		MeOH	2–3	63
7		MeOH	2–3	58
8		MeOH	2–3	< 5 ^[c]

[a] Time elapsed until characteristic color change from Tm^{II} to Tm^{III} .

[b] Determined by ^1H NMR spectroscopy. [c] Decanoic acid recovered in > 95 %. Reaction conditions: TmI_2 (6–8 equiv), ROH (H₂O, 150 equiv; MeOH, 100 equiv), THF, 23 °C. See the Supporting Information for details.

work, we reported the reduction of lactones in the presence of $\text{SmI}_2\text{-H}_2\text{O}$,^[14a] however, this reaction suffered from long reaction times, was limited to unhindered substrates, and could be applied only to six-membered lactones; other ring systems and acyclic esters were unreactive under the reaction conditions. In sharp contrast, $\text{TmI}_2\text{-ROH}$ reacted with a wide range of substrates, including lactones (Table 2, entry 1), aliphatic (Table 2, entries 2 and 3), aromatic (Table 2, entries 3 and 4), alpha-substituted (Table 2, entries 4–6), and sterically demanding (Table 2, entry 7) esters. In all cases rapid (within 2–3 min) reduction to the corresponding alcohols took place, clearly demonstrating the higher reactivity of $\text{TmI}_2\text{-ROH}$. Control reactions established that, in the absence of proton donors, TmI_2 does not reduce aliphatic esters. Acids are not reduced under the reaction conditions (Table 2, entry 8), thus opening the door for highly chemoselective reductions of carboxylic acid derivatives through single-electron reaction pathways that are not possible with the traditional alkali or transition metal hydrides.^[9] Overall, this study outlines the reactivity scale for the generation of ketyl-type radicals with $\text{TmI}_2\text{-ROH}$ (see the Supporting Information for comparison tables between TmI_2 and SmI_2), demonstrates that useful levels of chemoselectivity are possible with $\text{TmI}_2\text{-ROH}$, and opens the door for the use of TmI_2 -generated ketyls in radical bond-forming reactions.

To gain a preliminary mechanistic insight into the key effect of protic additives on the properties of the TmI_2 reagent

(note that in both cases no reaction was observed with TmI_2 alone, see the Supporting Information), we examined the reactivity of TmI_2 with a set of aromatic hydrocarbons with gradually increasing redox potentials in the presence of MeOH (Table 3).^[17] In this study, the $\text{TmI}_2\text{-MeOH}$ complex was found to reduce aromatic hydrocarbons with redox

Table 3: Determination of the redox potential of $\text{TmI}_2(\text{ROH})_n$ by reduction of aromatic hydrocarbons.

Entry	Hydrocarbon	$-E_{1/2}$ [V] ^[a]	Reaction with TmI_2 observed ^[c]
1	cyclooctatetraene ^[b]	1.83	+
2	anthracene	1.98	+
3	stilbene	2.21	+
4	1,4-diphenylbenzene	2.40	+
5	1,3,5-triphenylbenzene	2.51	+
6	naphthalene	2.61	+
7	styrene	2.65	+
8	benzene	3.42	–

[a] In volts vs. SCE; $E_{1/2}$ describes half-reduction potential; see Ref. [17].

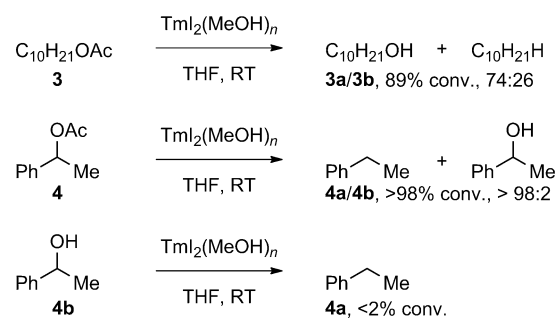
[b] Ref. [13d]. [c] Determined by GC and/or ^1H NMR spectroscopy.

potentials up to -2.6 V (vs. SCE); however, benzene was inert under the reaction conditions. These results suggest that the addition of MeOH to TmI_2 results in an increase of the reduction potential of TmI_2 by approximately 0.6 V.^[13d]

Furthermore, deuterium incorporation and kinetic isotope effect studies in the reduction of stilbene, a reaction that is known to proceed through an outer-sphere electron-transfer mechanism,^[18] using $\text{TmI}_2\text{-ROH}$ ($[\text{D}_4]$ methanol, 96.5 % D_2 incorporation, $k_{\text{H}}/k_{\text{D}} = 1.13 \pm 0.1$; D_2O , 98.0 % D_2 incorporation, $k_{\text{H}}/k_{\text{D}} = 1.27 \pm 0.1$), suggest that the increase in reduction potential of the reagent results from complexation between the proton donor and TmI_2 .

A detailed examination of different proton donors in the model system (see the Supporting Information) revealed that a much lower concentration of alcohols (10 equiv) is required to enhance the redox potential of TmI_2 in comparison with SmI_2 (100 equiv).^[19] This result is consistent with the smaller radial size of Tm^{II} and bodes well for the development of catalytic cycles based on regeneration of the TmI_2 reagent.^[20]

Finally, to test whether in analogy to amides a bond cleavage mechanism also contributes to the reduction of esters with TmI_2 , we subjected decyl and 1-phenylethyl acetate to the reaction conditions (Scheme 2). C–O bond



Scheme 2. Investigating the mechanism of ester reduction with $\text{TmI}_2\text{-(ROH)}_n$.

scission was the minor pathway in the case of **3** and the predominant one in the case of **4**; these results indicate that the cleavage is also operating in the ester reduction and provides a unifying reactivity model for the TmI_2 -mediated electron transfer.^[13a]

In summary, the highly unusual cleavage of unactivated σ C–N bonds in amides in the presence of TmI_2 , the first nonclassical lanthanide(II) iodide in the series (TmI_2 , DyI_2 , NdI_2), has been achieved. This method was also applied to the first chemoselective reduction of esters with any lanthanide(II) reagent.^[21] Initial mechanistic studies suggest that proton donors play a key role in activating the reagent^[22] and that Tm^{III} -bound ketyl radicals are more stable than the corresponding Sm^{III} ketyls.^[23] We fully expect that this work will serve as a platform to enable discovery of novel electron-transfer processes based on nonclassical lanthanide(II) iodides.

Received: April 16, 2013

Published online: June 12, 2013

Keywords: amides · C–N cleavage · electron transfer · lanthanides · thulium diiodide

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