

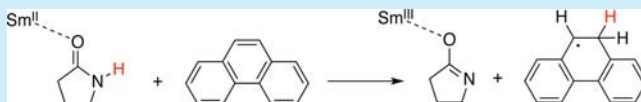
Secondary Amides as Hydrogen Atom Transfer Promoters for Reactions of Samarium Diiodide

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S Supporting Information

ABSTRACT: Two secondary amides (*N*-methylacetamide and 2-pyrrolidinone) were used as additives with SmI₂ in THF to estimate the extent of N–H bond weakening upon coordination. Mechanistic and synthetic studies demonstrate significant bond-weakening, providing a reagent system capable of reducing a range of substrates through formal hydrogen atom transfer.

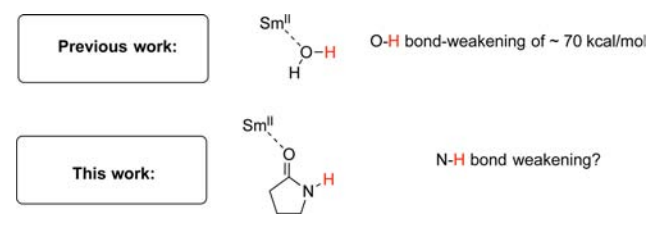


The use of additives in reactions of samarium diiodide (SmI₂) in THF and other solvents has a profound impact on the reactivity of the reagent.¹ Additives are generally divided into three subclasses: (1) Lewis bases, (2) inorganic salts, and (3) proton donors. Among Lewis bases, HMPA is the most useful and accelerates reactions by producing a more powerful Sm(II) single electron transfer reductant while oftentimes enhancing the stereochemical outcome of reactions and impacting post electron transfer steps.² Inorganic additives are typically utilized in two ways. They can be employed to provide a source of ligands that displace iodide from SmI₂ (LiBr, LiCl, etc.) to produce a different Sm(II) reductant *in situ*.³ They can also be used to promote reactions of low-valent transition metals. For example, the addition of Ni(II) salts to SmI₂ generates Ni(0) that is responsible for the cross-coupling of substrates.⁴ Proton donors are typically represented by alcohols, glycols, and water. In early synthetic work, alcohols and water were used with SmI₂ solely as proton donors. It was later discovered that some donors coordinate to Sm(II), while others do not, and that coordination has a significant impact on the reactivity of the SmI₂–proton donor complex.⁵

Among proton donors, water is unique since its addition to SmI₂ in THF enables the reduction and reductive coupling of functional groups well outside of the reducing power of SmI₂ alone.⁶ The elegant work of Procter has exploited this unusual reactivity of the SmI₂–water complex for the reduction of lactones and related functional groups to enable bond-forming reactions of great synthetic importance.^{7,8} Given the unusual reactivity of the Sm(II)–water complex, we became interested in the origin of the unique reactivity and recently proposed that substrate reductions proceed through proton-coupled electron-transfer (PCET).⁹ Additionally, we established that proton donors that strongly interact with Sm(II) through chelation promote reduction through a PCET process, demonstrating the potential of other Sm(II)–proton donor combinations to reduce substrates typically recalcitrant to reduction through single electron transfer (SET).¹⁰

Although water as a proton donor is the promoter of choice for many functional group reductions, we reasoned that a high affinity ligand for Sm(II) containing a strong X–H bond that is weakened upon coordination to the low-valent metal may produce an alternative approach for reductions and reductive coupling reactions. In considering potential choices, we were drawn to the work of Knowles and Gansauer who have demonstrated significant weakening of the N–H bonds of secondary amides bound to low-valent titanocenes.^{11,12} Knowles has shown that coordination of a secondary amide to Cp*₂Ti(III)Cl led to a 33 kcal/mol weakening of the N–H bond.¹¹ Gansauer and co-workers demonstrated that a low-valent titanocene containing a pendant amide on one of the Cp ligands led to a reversible coordination of the amide carbonyl that weakened the N–H bond by 39 cal/mol.¹² With this precedent established, we posited that coordination of a secondary amide to the highly reducing Sm(II) should lead to substantial bond-weakening as demonstrated in Scheme 1 below.

Scheme 1. Bond-Weakening upon Coordination to Sm(II)



If bond-weakening occurs as proposed above producing a reagent that reduces substrates through hydrogen atom transfer (HAT), it may be possible to develop alternative approaches for substrates resistant to reduction through SET. Because amides are relatively hard ligands, they may further enhance the

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reactivity of Sm(II) by stabilizing the +3 oxidation state of Sm in a manner analogous to that proposed for HMPA.¹³

The suppositions described above suggest that two preconditions should be met for an amide to act as an effective HAT agent in concert with Sm(II): (1) the amide should have a high affinity for Sm(II) and (2) the reductant formed upon coordination of the amide to Sm(II) should oxidize more readily, producing a stronger reductant upon coordination. To test the assertions above, we chose two secondary amides to study, *N*-methylacetamide (NMA) and 2-pyrrolidinone (2-P). These amides were chosen since they are readily available from commercial sources and highly soluble in THF. The UV–vis spectrum of SmI₂ was examined with increasing amounts of NMA and 2-P. Unfortunately, the addition of NMA led to gradual precipitation, but addition of 2-P provided a soluble complex. Figure 1 contains UV–vis spectra of SmI₂ and the

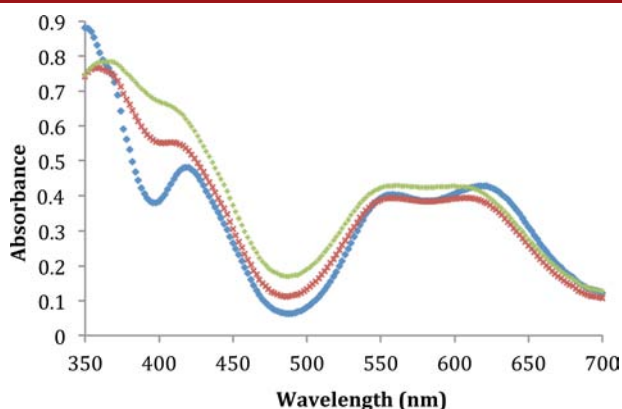


Figure 1. UV–vis spectrum of 2.5 mM SmI₂ in THF (blue ◆) containing 8 equiv of 2-P (red ×) and 15 equiv of 2-P (green +).

impact of addition of 2-P. The data are fully consistent with coordination of 2-P to Sm(II) in THF. Next, the influence of amide addition to the redox potential of SmI₂ was examined using cyclic voltammetry (CV). The CV data demonstrates that the addition of 10 equiv of 2-P to SmI₂ shifts the redox potential by −0.3 V, producing a more powerful reductant (see [Supporting Information](#)). To further assess the impact of 2-P concentration on the reducing power of SmI₂, we employed 1-bromododecane as a substrate. This substrate was chosen since it is resistant to reduction by SmI₂ alone, does not coordinate to the metal, and is reduced through a rate-limiting dissociative electron transfer.¹⁵ As a consequence, it provides a useful measure of the impact of additive concentration on the reactivity of Sm(II) in the absence of competing mechanistic pathways. Complete conversion to dodecane was obtained with at least 13 equiv of the additive in relation to [SmI₂]. Lower concentration of the reductant led to incomplete conversion (see [Supporting Information](#)). Taken together, the UV–vis, CV, and substrate reduction experiments demonstrate that 2-P coordinates to Sm(II) while simultaneously providing a more powerful reductant.

With data in hand supporting the hypothesis that amides can potentially be used as hydrogen atom donors in reductions, we next examined the reduction of a series of arenes. Both NMA and 2-P were employed as additives in the reduction of anthracene, *trans*-stilbene, and phenanthrene ([Table 1](#)). Previous work by Procter established that the addition of water to SmI₂ promoted the reduction of anthracene and partial reduction of stilbene, but phenanthrene was found to be unreactive.¹⁴ In the present case, only 5 equiv of NMA or 2-P (based on [SmI₂]) are required to

Table 1. Impact of Additive on Arene Reduction^a

entry	substrate	additive (equiv)	yield (%)
1	anthracene	NMA (5)	99 ^b
2	anthracene	2-P (5)	94 ^b
3	<i>trans</i> -stilbene	NMA (15)	90 ^b
4	<i>trans</i> -stilbene	2-P (10)	90 ^b
5	phenanthrene	NMA (20)	NR
6	phenanthrene	2-P (20)	26 ^c
7	phenanthrene	2-P (20)	39 ^d
8	phenanthrene	NMP (20)	NR
9	phenanthrene	NMP (20) TFE (20)	NR

^aConditions: 2.5 equiv of SmI₂, rt, overnight. ^bIsolated yield. ^c% conversion of starting material by ¹H NMR. ^d3 equiv of SmI₂.

reduce anthracene (entries 1 and 2). Both amide promoters also fully reduce *trans*-stilbene in concert with SmI₂ (entries 3 and 4). Interestingly, addition of up to 20 equiv of NMA to SmI₂ lead to only recovered starting material, whereas the same amount of 2-P provides some reduction of phenanthrene (entries 5 and 6). Increasing the concentration of SmI₂ leads to further conversion (entry 7).

The reactions described above demonstrate that 2-P facilitates the reduction of phenanthrene, but does not provide a basis for the effect of the promoter. Since CV and spectroscopic studies show that coordination of 2-P to SmI₂ enhances the ease of metal oxidation, it is possible that the effect of the additive is a consequence of the reagent combination providing a more powerful reductant. To investigate further the basis of the effect, *N*-methyl-2-pyrrolidinone (NMP) was employed as an additive. The addition of NMP to SmI₂ is known to produce a more powerful reductant,¹⁶ but the reagent lacks an N–H necessary for proton transfer. Addition of 20 equiv of NMP to a solution of SmI₂ and phenanthrene led to the complete recovery of starting material ([Table 1](#), entry 8) after 24 h of reaction. Next we employed NMP in concert with trifluoroethanol, a non-coordinating proton donor.¹⁷ No reduction of phenanthrene was observed after an extended time ([Table 1](#), entry 9). In addition, when *N*-deuterated 2-P was employed in the reduction of *trans*-stilbene, deuterium incorporation in the product was observed (see [Supporting Information](#)). The experiments described above are consistent with our hypothesis that secondary amides coordinated to Sm(II) can act as HAT promoters.

To assess the degree of N–H bond-weakening upon amide coordination to SmI₂, the bond dissociation free energies (BDFEs) in THF for the N–H bond of 2-P and the initial radical formed upon HAT to *trans*-stilbene and phenanthrene were calculated using density functional calculations employing standard methods.¹⁸ Subtraction of the N–H BDFE from the arene radical provides an estimate of bond-weakening as demonstrated in [Scheme 2](#) for the reduction of phenanthrene by the combination of SmI₂ and 2-P. Using this approach, the bond-weakening required for reduction of *trans*-stilbene is 63.1 kcal/mol, while the limit of N–H bond-weakening for reduction of phenanthrene is 70.8 kcal/mol. The range of N–H bond-weakening of 63–71 kcal/mol is greater than that displayed for amide-Ti(III) complexes^{11,12} but consistent with O–H weakening in Sm(II)–water and glycol complexes.^{9,10}

With this data in hand, we employed both HAT promoters for the reduction of a range of carbonyl compounds ([Table 2](#)).

Both NMA and 2-P promote pinacol coupling of the two aldehydes examined. This could be a consequence of a sequential

Scheme 2. Estimate of Degree of N–H Bond Weakening upon Coordination of 2-Pyrrolidinone to Sm(II) in THF

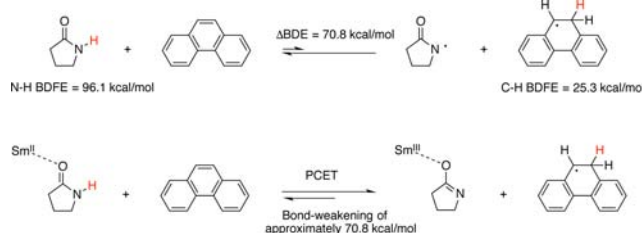


Table 2. Reduction of Substrates by SmI₂ and NMA or 2-P

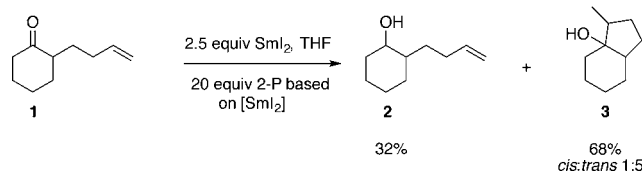
substrate	additive	product	yield (%)
benzaldehyde	NMA ^a	hydrobenzoin	90 ^d
	2-P ^a		81 ^d
heptanal	NMA ^a	7,8-tetra decanediol	73 ^d
	2-P ^a		77 ^d
2-octanone	NMA ^b	2-octanol	63 ^e
	2-P ^b		72 ^d
5-decanolide	NMA ^c	1,5-decanediol	52 ^f
	2-P ^c		85 ^d
methyl anisate	NMA ^c	4-methoxy benzyl alcohol	73 ^f
	2-P ^c		99 ^d
2,4-dimethoxy-1-nitrobenzene	NMA ^c	2,4-dimethoxy aniline	91 ^d
	2-P ^c		93 ^d

Conditions. ^a2.5 equiv of SmI₂, 5 equiv of additive (based on [SmI₂]). ^b2.5 equiv of SmI₂, 10 equiv of additive (based on [SmI₂]). ^c6 equiv of SmI₂, 10 equiv of additive (based on [SmI₂]). ^dIsolated yield. ^eGC yield. ^f% conversion of starting material by ¹H NMR.

electron–proton transfer^{9a} or possibly reduced steric constraints that promote homocoupling after formal HAT. For the reaction of 2-octanone with SmI₂, 2-P led to reduced product exclusively, whereas NMA provided the reduced product with the pinacol product (see [Supporting Information](#)). In the reduction of 5-decanolide, 2-P provided a very good yield of 1,5-decanediol, whereas the use of NMA provided only about 50% conversion. Conversely, both additives were equally effective for the reduction of methyl anisate and 2,4-dimethoxy-1-nitrobenzene. It is important to note that the substrates in [Table 2](#) can be reduced with SmI₂ containing water,¹ but there are some minor differences in reaction outcomes. For instance, reduction of heptanal by SmI₂–water provides 1-heptanol,^{9a} whereas the use of NMA or 2-P leads to pinacol coupling.

In addition to the substrates contained in [Table 2](#), we also examined a ketone alkene cyclization using 2-but-3-enyl-cyclohexan-1-one (**1**). The use of 20 equiv of 2-P provided complete conversion to the reduced product (**2**) and cyclized product (**3**) as shown in [Scheme 3](#). The use of lower amounts of 2-P led to complete conversion, but provided a greater amount of reduced product. This finding demonstrates that a secondary

Scheme 3. Reaction of 1 with SmI₂ and 2-P



amide can be used to carry out a reductive coupling successfully providing comparable yields to SmI₂–water.^{5a}

Overall, these studies demonstrate that secondary amides can be employed as additives to promote formal HAT to substrates when coordinated to SmI₂. The critical feature for successful implementation of this approach is the high affinity of the carbonyl oxygen for Sm(II) for bond-weakening of the N–H bond. While it is premature to state unequivocally that strong coordination leading to bond-weakening is a general phenomenon, we posit that water, glycols, amides, and related additives capable of coordinating to Sm(II) can be considered HAT promoters in the cases that we have examined to date.^{9,10} Furthermore, there is substantial literature evidence demonstrating that interaction of ligands with low-valent metals can also lead to significant weakening of N–H and C–H bonds proximal to the site of coordination,⁹ suggesting that this approach can be used for the activation of other strong bonds, providing potential alternative avenues to reduction and bond-forming reactions. We are currently examining this supposition in the study of other Sm(II)-functional group interactions, and the results of this work will be presented in due course.

■ ASSOCIATED CONTENT

§ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03664.

Experimental procedures and spectral and computational data ([PDF](#))

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Notes

The authors declare no competing financial interest.

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