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Mechanistic Study of SmI_2/H_2O and SmI_2/Amine/H_2O-Promoted Chemoselective Reduction of Aromatic Amides (Primary, Secondary, Tertiary) to Alcohols via Aminoketyl Radicals

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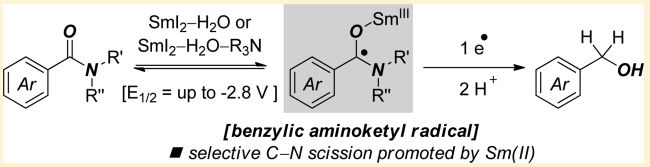
Supporting Information

ABSTRACT: Samarium(II) iodide–water and samarium(II) iodide–water–amine complexes have been recognized as valuable reagents for the selective generation of aminoketyl radicals from amides and derivatives. The resulting aminoketyl radicals can undergo reduction or reductive cyclization pathways, providing a powerful method for (i) direct synthesis of alcohols from amides by the challenging N–C bond scission and (ii) synthesis of nitrogen-containing heterocycles via polarity reversal of the amide bond. This report describes mechanistic investigation into samarium(II) iodide–water and samarium(II) iodide–water–amine-mediated generation of benzylic aminoketyl radicals from aromatic primary, secondary, and tertiary amides (benzamides). The mechanistic experiments suggest that the rate and selectivity of the reduction is closely dependent on the water concentration and the type of amide undergoing the reduction. The data also suggest that benzylic aminoketyl radicals generated in the reduction of benzamides are significantly more dependent on the electronic effects of α-substitution than the corresponding aminoketyl radicals generated by single-electron transfer to unactivated aliphatic amides; however, little variation in terms of steric influence of *N*-substituents is observed. These observations will have implications for the design of reductive processes involving Sm(II)-mediated reduction of amides and reductive umpolung cyclizations via aminoketyl radicals as a key step.



INTRODUCTION

The reduction of amides is among the most important and valuable processes in organic synthesis because of the versatility of the resultant amine and alcohol reduction products in industrial and academic settings.[1] Typically, amide reduction proceeds via C–O bond cleavage in the tetrahedral intermediate, resulting in the amine reduction products, and many reagents and conditions for this transformation have been reported.[2,3] In contrast, the analogous amide reduction to alcohols by selective C–N bond scission remains severely underdeveloped (Figure 1A).[4,5]

Recently, samarium(II) iodide–water and samarium(II) iodide–water–amine complexes[6,7] have emerged as valuable reagents for the selective generation of aminoketyl radicals from amides and derivatives.[8] The resulting aminoketyl radicals can undergo reduction[9] or reductive cyclization pathways,[10] providing a powerful method for (i) direct synthesis of alcohols from amides by the challenging N–C bond scission which is often not easily available by other methods and (ii) synthesis of nitrogen-containing heterocycles via polarity reversal of the amide bond to enable nucleophilic reactivity of the typically electrophilic amides (Figure 1B).[11,12] Coordination of the azaphilic Lewis acid Sm[13] to nitrogen[14] at the carbinolamine stage provides a driving force for the collapse of the carbinolamine intermediate with high N–C bond scission selectivity (Figure 1C). Note that Sm(III) might be able to act as a specific Lewis acid, leading to changes in the reaction selectivity.

In 2014, the first general process for the reduction of all types of aliphatic amides (primary, secondary, and tertiary) to alcohols with high C–N bond cleavage selectivity using SmI_2–amine–water reagent was reported (Figure 2A).[15] The success of this reaction relies on the high reduction potential of the SmI_2–amine–water reagent ($E_{1/2}$ = −2.8 V vs SCE) that permits direct electron transfer to unactivated aliphatic amides. In the same year, mechanistic investigation of the reduction of aliphatic amides to alcohols using SmI_2–amine–water was reported (Figure 2B).[16] These reactions exploit the synergistic effect of water and amines on increasing the reducing power of Sm(II)-based reagents[17] as elegantly demonstrated in several breakthrough studies by Hilmersson and co-workers;[18] however, the corollary of using highly powerful reductants involves the low stability of the formed aminoketyl radical intermediates. In contrast, the use of a milder ($E_{1/2}$ = −1.3 V vs SCE) and much more selective[19] SmI_2–water system[20,21] for the reduction of amides has received comparatively less attention. Limited studies on the reduction of primary aromatic amides have been reported by Kamochi and Kudo (Figure 2C);[22,23] however, the role of water ligand[20a] and selectivity of the amide reduction has not been investigated. Moreover, the reduction side products have often been observed in the course of umpolung reductive cyclization processes of amide derivatives using SmI_2–H_2O, such as cyclic imides introduced

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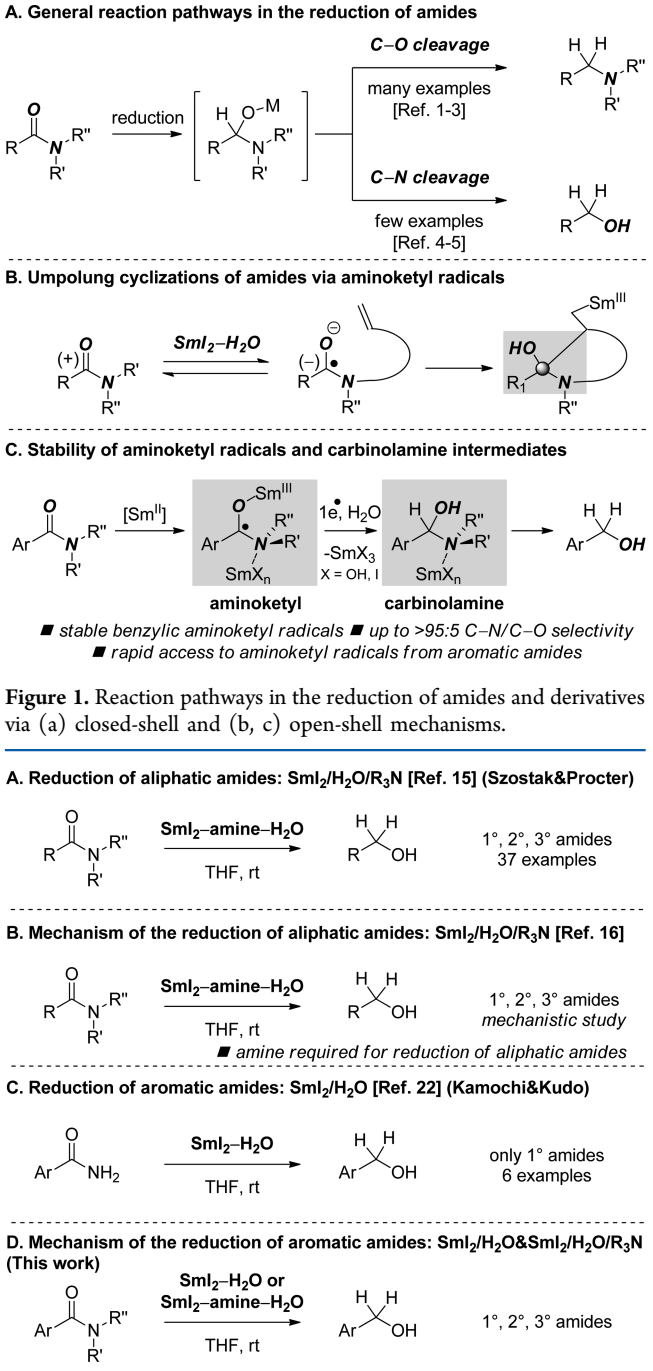

Figure 1. Reaction pathways in the reduction of amides and derivatives via (a) closed-shell and (b, c) open-shell mechanisms.

Figure 2. Previous studies (a–c) and this study (d) on the reduction of amides to alcohols using Sm(II)-based reagents.

by our laboratory[24] and barbituric acids as recently elegantly demonstrated by Procter and co-workers in several cascade processes.[25]

Our ongoing interest in umpolung cyclizations by aminoketyl radicals using Sm(II)-based reagents[24] and reactions of amides proceeding by selective N–C bond scission[26] prompted us to undertake a thorough mechanistic investigation of the reduction of aromatic amides to alcohols using SmI_2–H_2O and SmI_2–amine–H_2O reagents. While the use of SmI_2–amine–H_2O reagents for the reduction of aliphatic amides has been well studied,[15,16] the possibility of an analogous electron transfer to common amide substrates *that favor reductive transfer events by their electronic properties remains unexplored.* This gap is particularly significant when considering (1) the fundamental importance of the synthesis of alcohols from common, bench-stable amide precursors[1−3] where selected recent examples of SmI_2-mediated reduction of carboxylic acid derivatives and heterocycles demonstrate the utility of this reagent in complex synthesis;[6,19] (2) the potential to engage the formed aminoketyl radicals in reductive umpolung cyclization events to rapidly build up molecular complexity,[6−8] a process that, for example, has been elegantly demonstrated by Procter and co-workers in complex cyclization cascades of amide derivatives;[25] and (3) the potential to exploit these more easily reducible substrates in other processes involving ketyl-type radicals, including photoredox catalysis.[27,28] Note that the use of aliphatic carboxylic acid derivatives is currently beyond the scope of photoredox mechanisms.

Herein, we present a systematic mechanistic investigation into SmI_2–water and SmI_2–water–amine-mediated generation of benzylic aminoketyl radicals from aromatic primary, secondary, and tertiary amides (benzamides). The mechanistic experiments suggest that the rate and selectivity of the reduction is closely dependent on the water concentration and the type of amide undergoing the reduction. The data also suggest that benzylic aminoketyl radicals generated in the reduction of benzamides are significantly more dependent on the electronic effects of α-substitution than the corresponding aminoketyl radicals generated by single-electron transfer to unactivated aliphatic amides; however, little variation in terms of steric factors of *N*-substituents is observed. A significant difference in the reduction selectivity between the SmI_2–H_2O and SmI_2–H_2O–amine reagents in the reduction of secondary and tertiary benzamides has been identified. Selectivity studies demonstrate the relative reactivity order of carboxylic acid derivations with Sm(II)-based reagents. Overall, these observations will have important implications for the design and optimization of new reductive processes involving Sm(II)-mediated reduction of amides to alcohols and reductive umpolung cyclizations via aminoketyl radicals as a key step.

RESULTS AND DISCUSSION

SmI_2–H_2O: Effect of Water Stoichiometry. To gain preliminary insight into the role of water as an activating ligand for Sm(II) in the reduction of aromatic amides,[21,20a,23] a series of studies were conducted (Tables 1–3). 4-Methoxybenzamide (**1**), *N*-butyl-4-methoxybenzamide (**3**), and *N*,*N*-diethyl-4-methoxybenzamide (**4**) were selected as model substrates in the reduction of primary, secondary, and tertiary aromatic amides. No reaction was observed in the absence of water for all three amides for prolonged reaction times (18 h, Tables 1–3, entry 1).[17] Next, we carefully monitored the reduction of **1**, **3**, and **4** with increasing concentration of water and quenching the reactions with air after 5 min reaction time (Tables 1–3, entries 2–7). Remarkably, upon addition of water (50–1600 equiv, 8.3–267 with respect to SmI_2) excellent conversions were observed in the reduction of primary amide **1** irrespective of the amount of water used (>85%, Table 1, entries 2–7). The reduction of secondary amide **3** and tertiary amide **4** showed a nonlinear dependence on water concentration (Tables 2 and 3, entries 2–7, and Figure 3).[23a] At low concentrations of water, the rate was found to increase linearly with slope for both **3** and **4** (50–200 equiv), reaching a maximum at 100–200 equiv (**3**) and 200 equiv (**4**). Next, at higher concentrations of water (400–1600 equiv), the rate decreased dramatically, which may be indicative of substrate

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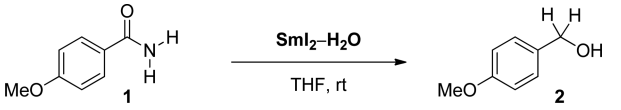
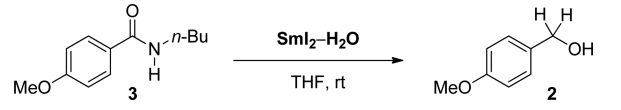
Table 1. Reduction of Primary Aromatic Amides to Alcohols Using SmI_2–H_2O: Effect of Water Stoichiometry



entry	SmI_2 (equiv)	H_2O (equiv)	time[a]	conv[b] (%)	selectivity[b] (%)	H_2O/SmI_2
1	6	0	18 h	<2		0
2	6	50	5 min	85	>98:2	8.3
3	6	100	5 min	>98	>98:2	16.7
4	6	200	5 min	>98	>98:2	33.3
5	6	400	5 min	>98	>98:2	66.7
6	6	800	5 min	>98	>98:2	133.3
7	6	1600	5 min	>98	>98:2	266.7

[a]Quenched with air after the indicated time. [b]Determined by ^1H NMR and/or GC–MS of crude reaction mixtures and comparison with authentic samples. [c]Selectivity refers to alcohol/amine ratio. Conversion = (100 − SM).

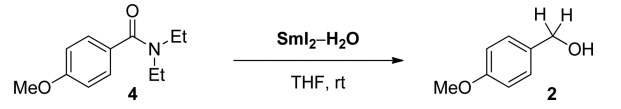
Table 2. Reduction of Secondary Aromatic Amides to Alcohols Using SmI_2–H_2O: Effect of Water Stoichiometry



entry	SmI_2 (equiv)	H_2O (equiv)	time[a]	conv[b] (%)	selectivity[c] (%)	H_2O/SmI_2
1	6	0	18 h	<2		0
2	6	50	5 min	21	>98:2	8.3
3	6	100	5 min	37	95:5	16.7
4	6	200	5 min	35	88:12	33.3
5	6	400	5 min	23	87:13	66.7
6	6	800	5 min	16	84:16	133.3
7	6	1600	5 min	15	82:18	266.7

[a]Quenched with air after the indicated time. [b]Determined by ^1H NMR and/or GC–MS of crude reaction mixtures and comparison with authentic samples. [c]Selectivity refers to alcohol/amine ratio. Conversion = (100 − SM).

Table 3. Reduction of Tertiary Aromatic Amides to Alcohols Using SmI_2–H_2O: Effect of Water Stoichiometry



entry	SmI_2 (equiv)	H_2O (equiv)	time[a]	conv[b] (%)	selectivity[c] (%)	H_2O/SmI_2
1	6	0	18 h	<2		0
2	6	50	5 min	15	87:13	8.3
3	6	100	5 min	57	73:27	16.7
4	6	200	5 min	71	71:29	33.3
5	6	400	5 min	62	67:33	66.7
6	6	800	5 min	38	72:28	133.3
7	6	1600	5 min	19	75:25	266.7

[a]Quenched with air after the indicated time. [b]Determined by ^1H NMR and/or GC–MS of crude reaction mixtures and comparison with authentic samples. [c]Selectivity refers to alcohol/amine ratio. Conversion = (100 − SM).

dissociation from the inner coordination sphere of Sm(II).[23a] It should be noted that contaminants in water or traces of oxygen

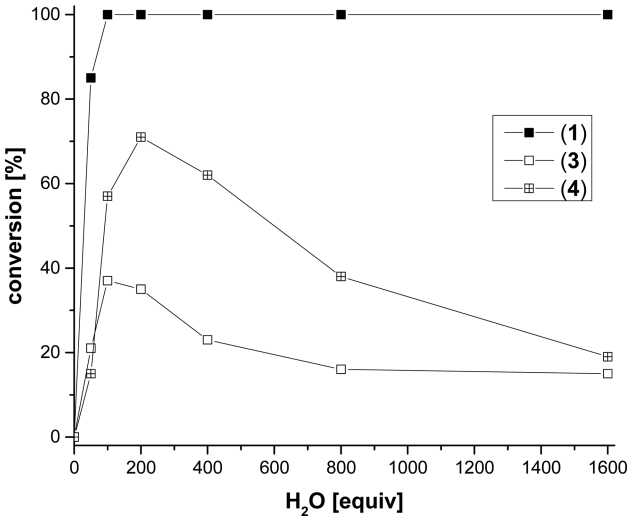


Figure 3. Plot of reduction of aromatic amides **1**, **3**, and **4** using SmI_2/H_2O as a function of concentration of water.

can lead to lower conversions. The addition of water resulted in a remarkable rate enhancement for all three amides examined reaching full (**1**, > 95%) and appreciable conversion (**3**, 35–37%; **4**, 71%) after only 5 min reaction time.

A plot of N–C/C–O cleavage selectivity vs water stoichiometry for amides **1**, **3**, and **4** is shown in Figure 4. In

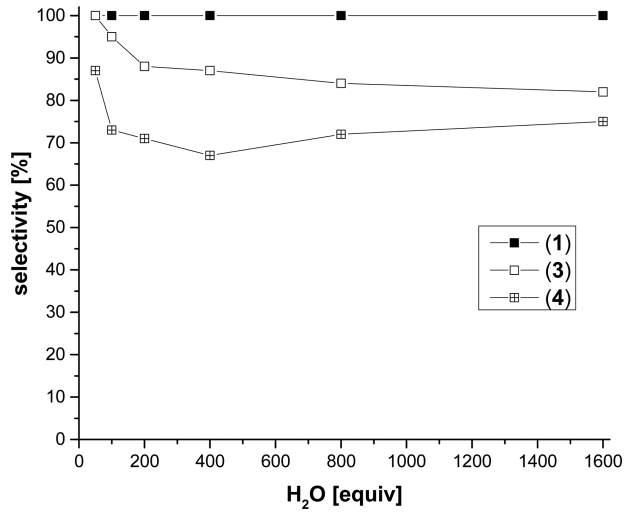


Figure 4. Plot of selectivity (alcohol/amine) in the reduction of aromatic amides **1**, **3**, and **4** using SmI_2/H_2O as a function of concentration of water.

the reduction of primary amide **1**, full N–C cleavage selectivity for was observed (**1**, > 95:5) irrespective of ligand stoichiometry (Figure 4). Interestingly, the reactions of secondary amide **3** and tertiary amide **4** showed strong dependence on the reduction selectivity vs concentration of water (Figure 4); however, in all examples, high N–C scission selectivity was observed (**3**, >80:20; **4**, >65:35). These results indicate that (1) water acts as a key additive to facilitate reduction of primary, secondary, and tertiary benzamides using SmI_2 (vide infra); (2) the rate of the reduction of primary benzamides is much faster than that of secondary and tertiary benzamides; and (3) chemoselective reduction of model primary, secondary, and tertiary amides by N–C scission is

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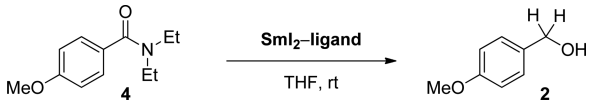
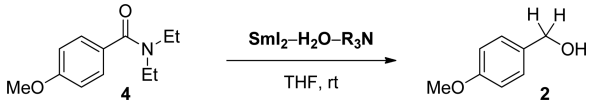
Table 4. Effect of Other Ligands on the Reduction of Tertiary Aromatic Amides to Alcohols Using SmI_2



entry	ligand	SmI_2 (equiv)	ligand (equiv)	time[a]	conv[b] (%)	yield[b] (%)	selectivity[b]
1	MeOH	6	4/1 v/v	3 h	<2	<2	
2	*t*-BuOH	6	36	3 h	<2	<2	
3	$(HOCH_2)_2$	6	36	3 h	12	<5	37:63
4	$MeOH/Et_3N$	6	72/72	3 h	>98	60	62:38
5	H_2O/Et_3N	6	72/72	5 min	>98	81	85:15[c]

[a]Quenched with air after the indicated time. [b]Determined by ^1H NMR analysis of crude reaction mixtures and comparison with authentic samples. Conversion = (100 − SM). Yield refers to the yield of alcohol. Selectivity refers to alcohol/amine ratio. [c]Other minor decomposition products were also detected. v/v = by volume. Note that control reactions using more easily reducible primary aromatic amide **1** with MeOH (4/1 v/vol) and *t*-BuOH (36 equiv) as ligands resulted in 19% and 16% conversion to the alcohol product, respectively.

Table 5. Effect of Reaction Conditions on the Reduction of Tertiary Aromatic Amides to Alcohols Using $SmI_2–H_2O–R_3N$[a]



entry	R_3N	SmI_2 (equiv)	H_2O (equiv)	R_3N (equiv)	conv[b] (%)	yield[b] (%)	selectivity[b]
1	Et_3N	6	200		71	50	71:29
2	Et_3N	6	200	72	>98	75	89:11
3	Et_3N	6	72	72	>98	81	90:10
4	Et_3N	6	36	36	>98	91	95:5
5	Et_3N	6	144	144	>98	82	91:9
6	Et_3N	3	72	72	67	59	93:7
7	Et_3N	12	72	72	>98	78	89:11
8	Et_3N	6	36	18	>98	70	81:19
9	Et_3N	6	36	72	>98	87	92:8
10	Et_3N	6	72	36	>98	79	87:13
11	Et_3N	6	18	36	>98	80	87:13
12	Et_3N	6	18	18	>98	74	83:17
13	NMM	6	72	72	>98	80	85:15
14	*n*-Bu_3N	6	72	72	>98	80	85:15
15	pyrrolidine	6	72	72	>98	68	87:13
16	*n*-$BuNH_2$	6	72	72	>98	74	82:18
17	TMEDA	6	72	36	>98	81	89:12

[a]Quenched with air after 5 min reaction time. [b]Determined by ^1H NMR analysis of crude reaction mixtures and comparison with authentic samples. Conversion = (100 − SM). Yield refers to the yield of alcohol. Selectivity refers to alcohol/amine ratio. For studies on the effect of amines on the selectivity of $SmI_2–H_2O–R_3N$ reagents, see ref 18. NMM = *N*-methylmorpholine. TMEDA = *N,N,N,N*-tetramethylethylenediamine.

feasible. The effect of water concentration on the reduction of esters using $SmI_2–H_2O$ has been studied.[23a] While in some cases similar dependence was observed, it should be noted that the maximum reduction rate is different for various functional groups under synthetically relevant reaction conditions.

SmI_2–ROH: Effect of Other Ligands. To gain additional insight into the electron transfer steps, we evaluated the reduction of tertiary amide **4** using various Sm(II)–ROH systems (Table 4).[20b,23a] Interestingly, the use of alcohols that form complexes with SmI_2 such as MeOH (entry 1) and ethylene glycol (entry 3)[23] as well as noncoordinating alcohols such as *t*-BuOH (entry 2)[23] resulted in no (entries 1–2) or negligible (entry 3) reduction of **4**. Moreover, control reactions conducted with the more easily reducible primary amide **1** using MeOH and *t*-BuOH (not shown) resulted in 19% and 16% conversion to the alcohol, respectively. By contrast, the use of tricomponent-amine-based Sm(II) systems[18] resulted in high conversion of **4** to the alcohol (entries 4–5). Overall, these results demonstrate that water acts as a unique proton donor in activating Sm(II) for the reduction of aromatic amides; however, the addition of amines can significantly increase the reduction rate, in agreement with previous studies.[18,19,15,16]

$SmI_2–H_2O–R_3N$: Effect of Reaction Conditions. Since our studies on the effect of water stoichiometry indicated that (1) the reduction of secondary and tertiary aromatic amides is slower than that of primary amides and (2) N–C scission selectivity in the reduction of secondary and tertiary amides is lower than in the case of primary amides, we next investigated in detail the effect of reaction conditions on the reduction of amides to alcohols withthe $SmI_2–H_2O–R_3N$ system using tertiary amide **4** as our model substrate. The results are presented in Table 5. It is well-established that tricomponent Sm(II)–H_2O–R_3N reagents lead to significant rate enhancement in reductions due to base-assisted deprotonation of water, which facilitates the electron-transfer step.[18,19,15,16] This effect is evident from comparing the reduction of **4** using $SmI_2–H_2O$ (6–200 equiv, 5 min, 71% conversion) (entry 1) with the reduction under identical conditions with the addition of amine

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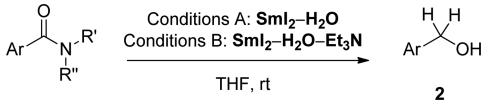
Table 6. Effect of Amide *N*-Substituents on the Reduction of Aromatic Amides to Alcohols Using SmI_2–H_2O and SmI_2–H_2O–Et_3N



entry	amide	NR'R''	yield (%)	selectivity	conditions[a,b]
1	**1**	NH_2	98	>98:2	A
2	**1**	NH_2	93	>98:2	B
3	**5**	NHMe	63	>98:2	A
4	**5**	NHMe	81	95:5	B
5	**3**	NH*n*-Bu	48	85:15	A
6	**3**	NH*n*-Bu	89	93:7	B
7	**6**	NH*t*-Bu	17	52:48	A
8	**6**	NH*t*-Bu	84	90:10	B
9	**7**	NHPh	49	51:49	A
10	**7**	NHPh	80	82:18	B
11	**8**	NHallyl	33	>98:2	A
12	**8**	NHallyl	74	>98:2	B
13	**9**	NMe_2	82	92:8	A
14	**9**	NMe_2	86	93:7	B
15	**4**	NEt_2	79	79:21	A
16	**4**	NEt_2	81	90:10	B
17	**10**		51	83:17	A
18	**10**		89	94:6	B
19	**11**		44	68:32	A
20	**11**		83	91:9	B
21	**12**		39	49:51	A
22	**12**		55	73:27	B
23	**13**	N(*i*-Pr)$_2$	<5	-	A
24	**13**	N(*i*-Pr)$_2$	57	63:37	B

[a]Conditions A: SmI_2 (6 equiv), THF, H_2O (200 equiv), 30 min, 23 °C. [b]Conditions B: SmI_2 (6 equiv), Et_3N (72 equiv), H_2O (72 equiv), 5 min, 23 °C. Ar = 4-MeO-C_6H_4. Quenched with air after the indicated time. Yields determined by ^1H NMR analysis of crude reaction mixtures and comparison with authentic samples. Yields refer to the yield of alcohol. Selectivity refers to alcohol/amine ratio. Note that incomplete conversions were observed with SmI_2–H_2O reagent under these conditions. For a discussion of SmI_2–H_2O decay, see ref 23a.

(SmI_2–H_2O–Et_3N, 6–200–72 equiv, 5 min, > 98% conversion) (entry 2). Interestingly, the addition of amine also leads to higher N–C bond scission selectivity in the reduction (71:29 vs 89:11) (entry 1 vs entry 2). Careful evaluation of the reagent stoichiometry (entries 3–12) revealed that optimum results in terms of conversion, product purity, and N–C scission selectivity are obtained using 1:12:12 or 1:6:6 SmI_2/H_2O/amine ratio (entries 3 and 4). Note that a stoichiometric amount of SmI_2 is required for the reduction (entry 6) and that the reaction selectivity does not significantly change at the lower conversion (entry 6). Additionally, 1:6:12 reagent stoichiometry gives good selectivity (entry 9). The effect of other amine ligands on the reduction selectivity was also investigated (Table 5, entries 13–17). Importantly, high reduction selectivity of **4** to the alcohol is observed with tertiary (entries 13–14), secondary (entry 15), primary (entry 16), and bidentate (entry 17) amine ligands.[18d] Note that more reducing SmI_2/amine/H_2O reagents lead to lower selectivity due to decomposition (entries 15 and 16). Overall, these results demonstrate the beneficial effect of SmI_2–H_2O–amine system on the reduction of tertiary benzamides to alcohols.

Effect of Amide *N*-Substitution. We next performed experiments to gain insight into the role of amide *N*-substitution on the reduction efficiency and N–C/C–O cleavage selectivity using SmI_2–H_2O (conditions A: 6–200 equiv, 30 min) and SmI_2–H_2O–Et_3N (conditions B: 6–72–72 equiv, 5 min) reagents (Table 6). *N*-Amide substitution is well-known to impact the amide reduction selectivity by impeding ligand coordination and changing the collapse pathway at the carbinolamine intermediate stage.[3,4] Notably, we determined that while both SmI_2–H_2O and SmI_2–H_2O–Et_3N reagents can be used for the reduction of primary benzamide **1** with similar efficiency and selectivity (entries 1 and 2), the use of SmI_2–H_2O–Et_3N provided generally better results than SmI_2–H_2O

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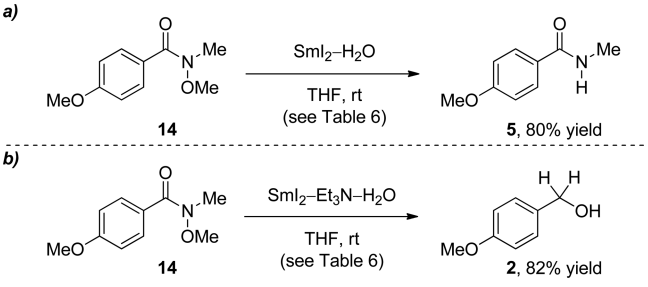
in the reduction of secondary (entries 3−12) and tertiary (entries 13−24) amides. Moreover, a significant substituent effect on the reduction selectivity has been observed. Specifically, the reduction of unhindered secondary amides such as NHMe (entries 3 and 4) proceeds with good efficiency with both reagent systems; however, a drop of N−C cleavage selectivity using SmI_2−H_2O with increasing steric demand of the substituent should be noted (entries 3−8). This effect is also accompanied by much lower conversions with increasing *N*-steric demand of the substituents. By contrast, the use of SmI_2−H_2O−Et_3N permits high levels of N−C cleavage selectivity and high reaction rates irrespective of steric demand of the *N*-substituent (entries 3−8). Moreover, electronically biased substituents which are often problematic in the reduction of amides to alcohols,[3g,4f] such as *N*-allyl and *N*-phenyl, do not interfere with the reduction selectivity using SmI_2−H_2O−Et_3N (entries 9−12). Interestingly, in the reduction of simple tertiary amides, such as *N*,*N*-dimethyl and *N*,*N*-diethyl (entries 13−16), both systems perform with good efficiency and selectivity; however, the SmI_2−H_2O−Et_3N reagent outperforms SmI_2−H_2O in the reduction of cyclic (entries 17−22) and sterically hindered (entries 23−24) amides.

Overall, these studies establish the ease of reduction of aromatic amides to alcohols using SmI_2−H_2O and SmI_2−H_2O−Et_3N reagents. Given the well established reversibility of the first electron-transfer events in reductions of carbonyl derivatives with Sm(II),[23a] these results strongly suggest that amide *N*-substitution can be employed to tune the stability of aminoketyl radicals from the reduction of aromatic secondary and tertiary amides using SmI_2−H_2O. Importantly, in several examples (entries 9, 13), a promising selectivity for the synthetically useful switch of the reaction pathway for the C−O scission has been observed, providing an entry point for future studies.

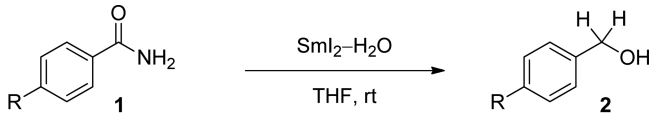
Divergent Reduction of Weinreb Amides. Weinreb amides are excellent substrates for the reduction (Scheme 1).[29]

Scheme 1. Divergent Reactivity of Aromatic Weinreb Amides Using SmI_2−H_2O and SmI_2−Et_3N−H_2O: (a) Deoxygenation; (b) Reduction to Alcohol



Interestingly, the presence of oxygen atom is not required for Sm(II) coordination. In contrast, divergent selective deoxygenation using SmI_2−H_2O (3−100 equiv) to give the secondary benzamide (Scheme 1A) and selective reduction to the alcohol using SmI_2−H_2O−Et_3N (8−72−72) (Scheme 1B) is observed. The latter reaction proceeds via stepwise deoxygenation/secondary amide reduction.[19] Thus, aromatic Weinreb amides follow the same reduction pathway as aliphatic amides using SmI_2 reagents.[15] Note that selective N−O cleavage with SmI_2 has been exploited in complex synthesis.[19]

SmI_2−H_2O: Hammett Studies. We next sought to gain insight into the electronic stabilization of the aminoketyl radical intermediate in the reduction of primary, secondary and tertiary aromatic amides using SmI_2−H_2O (Figures 5-7). Hammett



(R = MeO, H, F, Cl, CF_3) ρ = +3.90 (vs. σ)

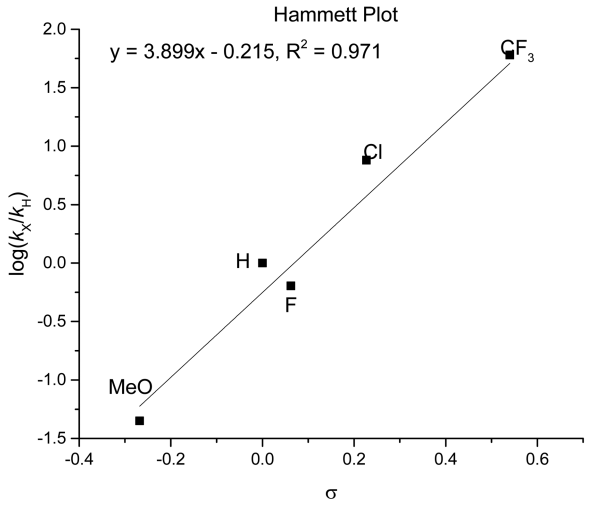
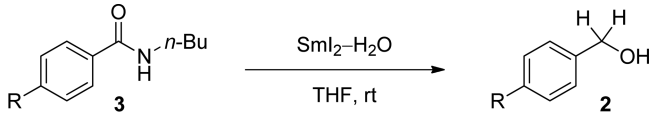


Figure 5. Plot of log *k* vs σ for the reduction of benzamides with SmI_2−H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [H_2O] = 1.25 M. *T* = 23 °C.



(R = MeO, H, F, Cl, CF_3) ρ = +4.37 (vs. σ)

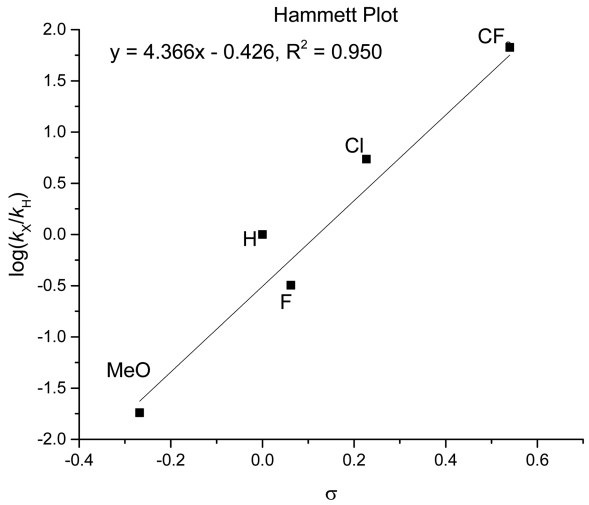


Figure 6. Plot of log *k* vs σ for the reduction of *N*-butylbenzamides with SmI_2−H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [H_2O] = 1.25 M. *T* = 23 °C.

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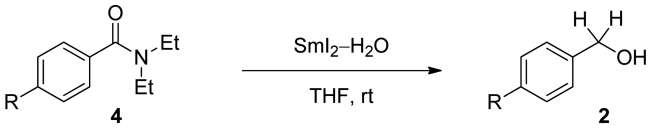


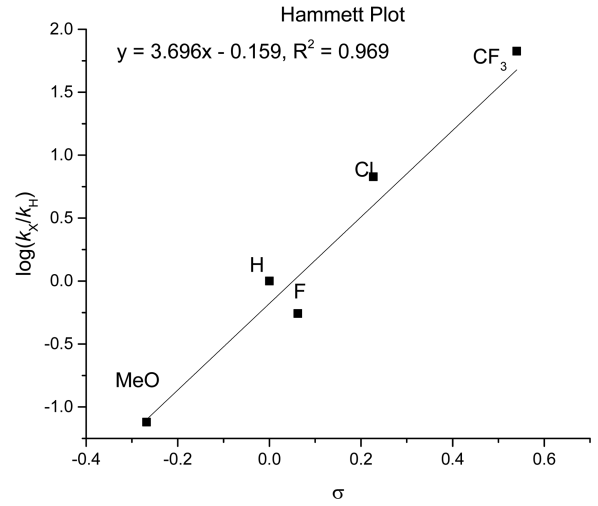
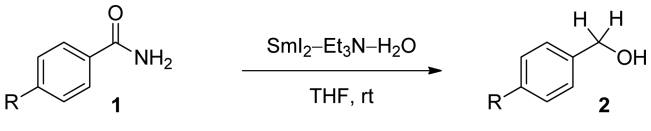


Figure 7. Plot of log k vs σ for the reduction of *N,N*-diethylbenzamides with SmI_2–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [H_2O] = 1.25 M. T = 23 °C.



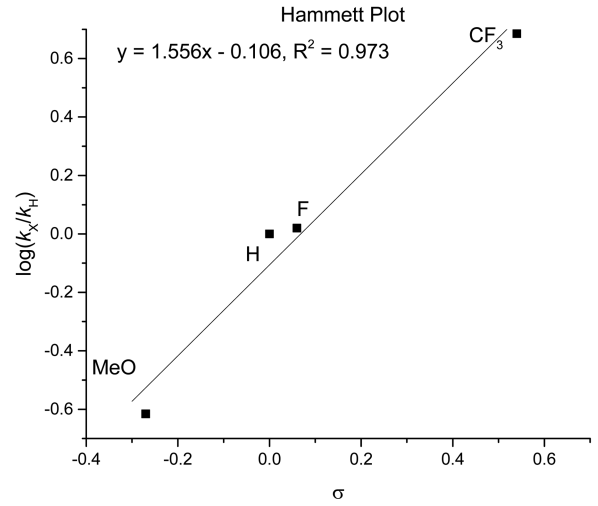
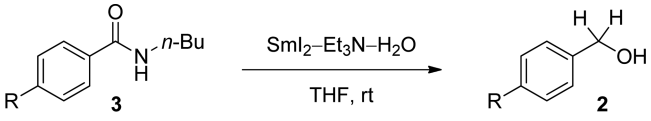


Figure 8. Plot of log k vs σ for the reduction of benzamides with SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.

correlations studies[30−32] were conducted for various para-substituted benzamides (Figure 5), *N*-butylbenzamides (Figure 6), and *N,N*-diethylbenzamides (Figure 7) as representative primary, secondary, and tertiary amides. Relative reaction rates were obtained by intermolecular competition experiments using concentrations of starting materials. Intercept was considered in the analysis of the Hammett equation. Hammett correlation studies showed large positive ρ values of +3.90 (R^2 = 0.97), +4.37 (R^2 = 0.95), and +3.70 (R^2 = 0.97) for the reduction of primary, secondary, and tertiary amides, respectively, which can be compared with ρ values of +0.52, +0.13, and +0.60 for the reduction of analogous (i.e., NH_2, NH-*n*-Bu, NEt_2) para-substituted 2-phenylacetamides using SmI_2–H_2O–Et_3N. Note that the reduction of aliphatic amides using SmI_2–H_2O is not feasible (vide infra). The very large positive ρ values suggest that (1) an anionic intermediate is formed in the transition state of the reduction of all three types of amides and (2) the formed radical anion intermediate is stabilized to a much larger extent than the related intermediate formed in the Sm(II)-mediated reduction of aliphatic amides.[16] This may have significant implications for the design of reductive cyclization processes of aromatic amides via stable benzylic aminoketyl radical intermediates.[12,8]

SmI_2–H_2O–Et_3N: Hammett Studies. The extent of electronic stabilization of the aminoketyl radical in the reduction of representative primary, secondary, and tertiary aromatic amides using the SmI_2–H_2O–Et_3N reagent was also evaluated (Figures 8–10).[30−32] Hammett correlation studies for para-substituted benzamides (Figure 8), *N*-butylbenzamides (Figure 9), and *N,N*-diethylbenzamides (Figure 10) using SmI_2–H_2O–Et_3N showed large positive ρ values of +1.56 (R^2 = 0.97), +3.49 (R^2 = 0.97), and +2.97 (R^2 = 0.97) for the reduction of primary, secondary, and tertiary amides, respectively. Note that in the reduction of primary amides



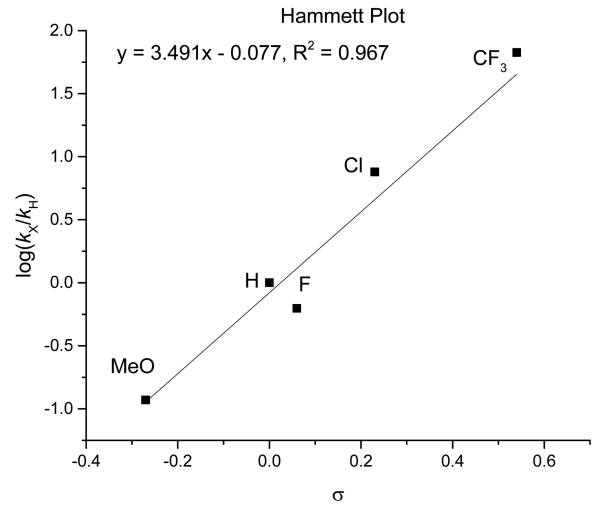


Figure 9. Plot of log k vs σ for the reduction of *N*-butylbenzamides with SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.

with SmI_2–H_2O–Et_3N the 4-Cl substrate undergoes dearomatization. These results demonstrate (1) greater electronic stabilization of the aminoketyl radical intermediate in the reduction of aromatic vs aliphatic amides[16] (ρ values of +0.52,

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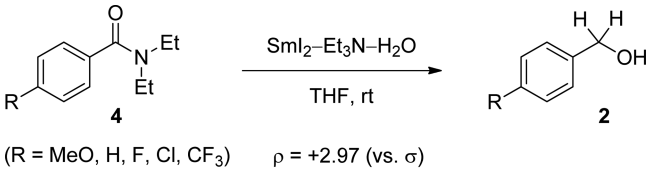


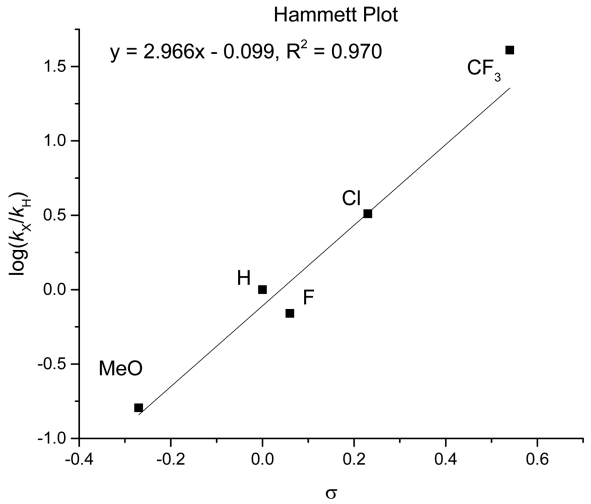
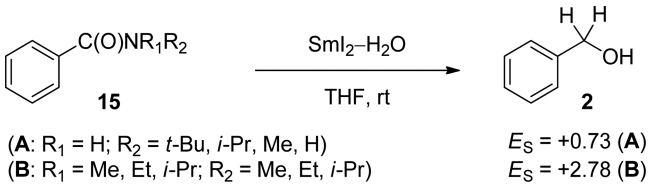


Figure 10. Plot of log k vs σ for the reduction of *N,N*-diethylbenzamides with SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.

+ 0.13 and +0.60) using the same SmI_2–H_2O–Et_3N system (note that both sets of experiments were conducted under the same experimental conditions) as a result of radical generation at the benzylic position; (2) comparable, albeit slightly lower, stabilization of the radical from secondary and tertiary amides using SmI_2–H_2O–Et_3N than SmI_2–H_2O (ρ values of +4.37 and +3.70); and (3) much lower stabilization of the radical intermediate from primary amides using SmI_2–H_2O–Et_3N than SmI_2–H_2O (ρ value of +3.90). Table 7 summarizes the electronic and steric effect (see section below) observed in the reduction of aromatic amides using SmI_2–H_2O and SmI_2–H_2O–Et_3N reagents. While Hammett correlations for an aryl directly connected to the reactive center should show more conjugation than for aliphatic amides, this study gives insight into the extent of the conjugation and the effect of the reagent system (SmI_2–H_2O and SmI_2–H_2O–Et_3N). In addition, note that Hammett correlations using SmI_2–H_2O for the reduction of aliphatic amides are not possible due to low reactivity of the reagent system. The lower stabilization of the aminoketyl radical from primary amides under the SmI_2–H_2O–Et_3N conditions suggests that an additional charge is present in the transition state of the reaction (e.g., N–H deprotonation may be taking place prior to the rate-determining step of the reaction).

SmI_2–H_2O: Taft Studies. To gain further insight into the steric stabilization the aminoketyl radical intermediate in the reduction of aromatic amides, Taft correlation studies using SmI_2–H_2O were carried out (Figure 11).[33] Taft correlation was



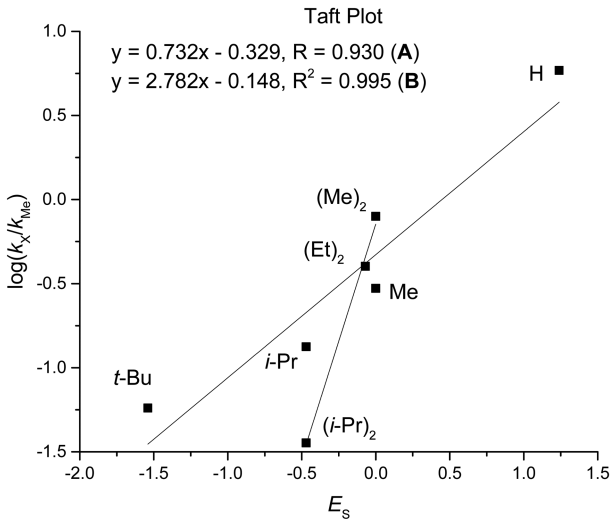


Figure 11. Plot of log k vs E_S for the reduction of *N*-mono and *N,N*-disubstituted benzamides with SmI_2–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [H_2O] = 1.25 M. T = 23 °C.

obtained by plotting log(k_{obs}) vs E_S in a series of *N*-mono- and *N,N*-disubstituted benzamides and showed positive slopes of +0.73 (R^2 = 0.93) and +2.78 (R^2 = 0.99) for the reduction of secondary and tertiary amides, respectively. These values can be compared with a positive slope of +0.92 and +3.25 determined for the reduction of *N*-mono- and *N,N*-disubstituted 3-

Table 7. Summary of Hammett and Taft Studies in the Reduction of Aromatic Amides to Alcohols Using SmI_2–H_2O and SmI_2–Et_3N–H_2O[a,b]

entry	amide (NR′R″)	SmI_2–H_2O (Hammett ρ)	SmI_2–Et_3N–H_2O (Hammett ρ)	SmI_2–Et_3N–H_2O (Hammett ρ)[c]
1	NH_2 (1° amide)	3.90	1.56	0.52
2	NH*n*-Bu (2° amide)	4.37	3.49	0.13
3	NEt_2 (3° amide)	3.70	2.97	0.59
entry	amide (NR′R″)	SmI_2–H_2O (Taft E_S)	SmI_2–Et_3N–H_2O (Taft E_S)	SmI_2–Et_3N–H_2O (Taft E_S)[d]
1	(2° amides)	0.73	0.52	0.92
2	(3° amides)	2.78	3.16	3.25

[a]For comparison, data for the reduction of aliphatic amides using SmI_2–Et_3N–H_2O are shown. [b]Conditions: [amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C. [c]Data from the reduction of 2-phenylacetamides with SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C. See ref 16 for additional details. [d]Data from the reduction of 3-phenylpropanamides SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C. See ref 16. for additional details.

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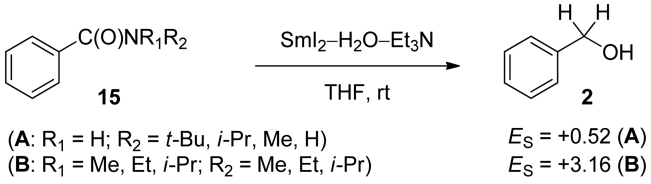
phenylpropanamides using SmI_2–H_2O–Et_3N as determined previously. Thus, these findings indicate that (1) steric factors play a significant role in the reduction of aromatic amides using SmI_2–H_2O; (2) the slower reaction rate with increasing steric hindrance results from inhibition of the coordination of Sm(II) to the amide carbonyl group; and (3) the steric effect in the reduction of aromatic amides using SmI_2–H_2O is similar to that in the reduction of aliphatic amides using SmI_2–H_2O–Et_3N,[16] which is in sharp contrast to the electronic effects observed in these reactions.

SmI_2–H_2O–Et_3N: Taft Studies. To compare the effect of steric stabilization of aminoketyl radical intermediate,[33] Taft correlation studies were conducted in the reduction of aromatic amides using the SmI_2–H_2O–Et_3N reagent (Figure 12). The



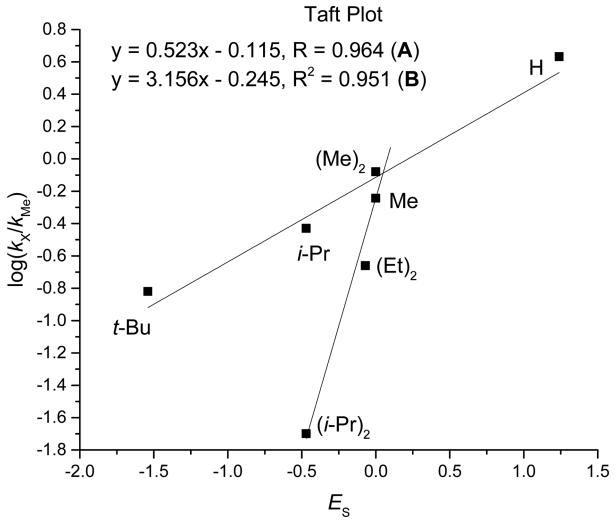


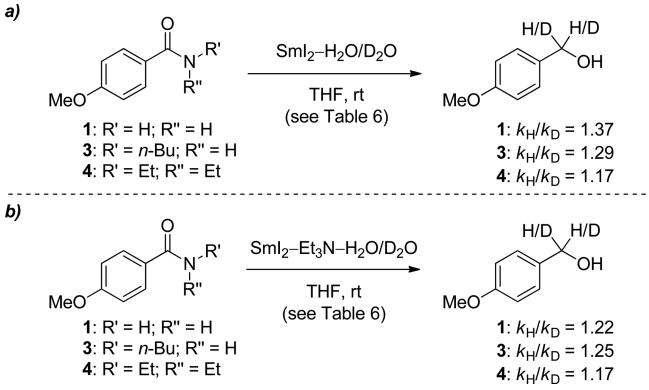
Figure 12. Plot of log k vs E_S for the reduction of *N*-mono and *N,N*-disubstituted benzamides with SmI_2–Et_3N–H_2O. [Amide] = 0.025 M. [SmI_2] = 0.050 M. [Et_3N] = 0.60 M. [H_2O] = 0.60 M. T = 23 °C.

Taft correlation study obtained by plotting log(k_{obs}) vs E_S in the same series of *N*-mono- and *N,N*-disubstituted benzamides showed positive slopes of +0.52 (R^2 = 0.96) and +3.16 (R^2 = 0.95) for the reduction of secondary and tertiary amides, respectively. These results suggest that (1) the reduction of tertiary benzamides using SmI_2–H_2O–Et_3N is subject to similar steric effects as the reduction of aliphatic amides using the same reagent system (slope of +3.25) and (2) the reduction of secondary benzamides using SmI_2–H_2O–Et_3N is less sensitive to the steric effect of *N*-substituents than the reduction of aliphatic secondary amides using SmI_2–H_2O–Et_3N (slope of +0.92) and secondary benzamides using SmI_2–H_2O (slope of +0.73). Overall, these findings suggest that Sm coordination to the amide bond using SmI_2–H_2O–Et_3N is similar to using SmI_2–H_2O.[13,14]

Table 7 summarizes steric effects observed in the reduction of aromatic amides using SmI_2–H_2O and SmI_2–H_2O–Et_3N.

Kinetic Isotope Effect Studies. Kinetic isotope effect studies in the reduction of aromatic amides using SmI_2–H_2O (Scheme 2A) and SmI_2–H_2O–Et_3N (Scheme 2B) were conducted by intermolecular competition.[34] Studies on KIE in Sm(II)-mediated reactions have been published.[24d,23a]

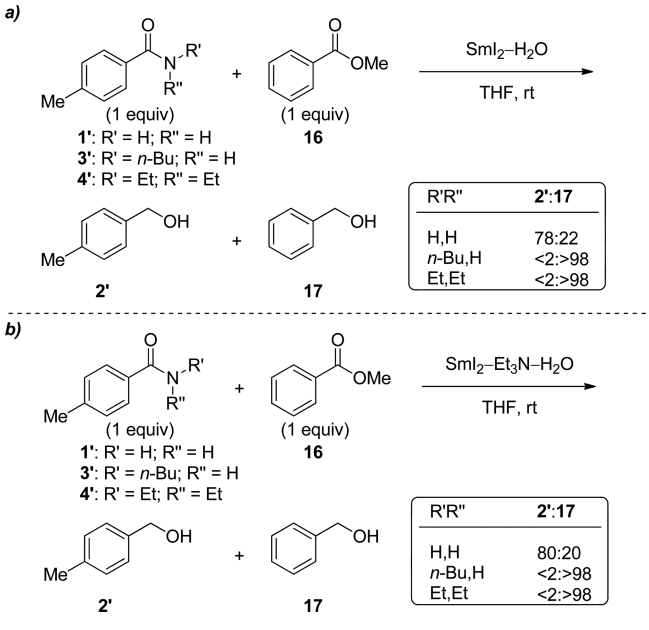
Scheme 2. Kinetic Isotope Effect Studies in the Reduction of Aromatic Amides to Alcohols: (a) SmI_2–H_2O; (b) SmI_2–Et_3N–H_2O



Selectivity Studies. Amides are the least reactive carboxylic acid derivatives due to $N_{lp} \rightarrow \pi^*_{CO}$ conjugation.[35] As a consequence, direct reduction of amides in the presence of other carboxylic acid functional groups remains a significant challenge.[1−5]

Selectivity studies in the reduction of aromatic amides using SmI_2–H_2O (Scheme 3A) and SmI_2–H_2O–Et_3N (Scheme 3B) demonstrate that selective reduction of primary amides in the presence of an aromatic ester group may be possible; in contrast, selective aromatic ester reduction in the presence of secondary and tertiary aromatic amides is observed. Previous studies established that esters are reduced at a similar rate as carboxylic acids using Sm(II)-based reagents.[16,9d] The high

Scheme 3. Selectivity Studies in the Reduction of Aromatic Amides to Alcohols vs Reduction of Esters: (a) SmI_2–H_2O; (b) SmI_2–Et_3N–H_2O



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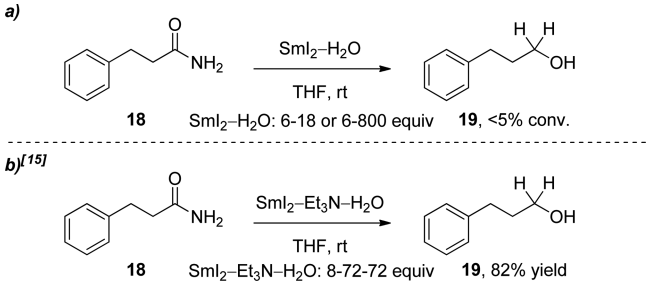
selectivity for the reduction of primary amides is synthetically significant because efficient reduction of these substrates to alcohols using metal hydrides[4] or catalytic hydrogenation[5] is currently unknown. Thus, the reduction of aromatic amides follows the same trends of reactivity as the reduction of aliphatic carboxylic acid derivatives using Sm(II) reagent systems.[16]

Full selectivity for the reduction of aromatic amides in the presence of aliphatic amides using SmI_2–H_2O is observed (Scheme 4A).[19,20a] Full selectivity (>50:1) in the reduction of

Scheme 4. Selectivity Studies in the Reduction of Amides to Alcohols: Aromatic vs Aliphatic Amides



secondary and tertiary aromatic amides in the presence of the corresponding aliphatic amides using SmI_2–H_2OEt_3N is observed, while primary amides give modest selectivity (4:1) (not shown).[16] Moreover, other aliphatic carboxylic acid derivatives are not reduced by the SmI_2–H_2O reagent, providing synthetically valuable selectivity.[19,20a] Although aliphatic amides are reduced to alcohols using SmI_2–H_2O–Et_3N (Scheme 4B),[16] reduction of aromatic amides in the presence of aliphatic amides using SmI_2–H_2O–Et_3N is readily accomplished.[16]

Relative Reactivity Order. On the basis of our work, the relative reactivity order of aromatic carboxylic acid derivatives to alcohols using Sm(II)-based reagents can be summarized as shown in Figure 13. Noteworthy features include (1) facile

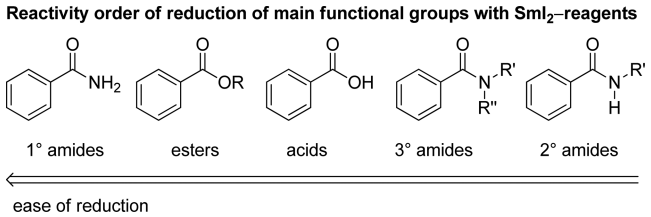


Figure 13. Relative reactivity order in reduction of main functional groups using SmI_2-based reagents.

reduction of primary benzamides, most likely driven by Sm coordination to the amidic nitrogen,[35] and (2) the ability to tune the relative rate of reduction by *N*-substitution in secondary and tertiary benzamides.

CONCLUSIONS

In conclusion, this paper describes extensive insights into the mechanism of the SmI_2–H_2O and SmI_2–H_2O–amine-mediated reduction of aromatic benzamides (primary, secondary and tertiary) to alcohols via selective N–C bond amide cleavage. The mechanistic experiments showed that the rate and selectivity of the reduction depends on the water concentration and the type of amide undergoing the reduction. As discussed above, primary benzamides undergo rapid reduction with SmI_2–H_2O and SmI_2–H_2O–amine systems with excellent N–C/C–O scission selectivity. Steric effects of *N*-substituents contribute to the reactivity of secondary and tertiary benzamides. In general, SmI_2–H_2O–amine gives higher reduction selectivity than SmI_2–H_2O; however, the reactivity of simple unhindered secondary and tertiary amides is similar using both Sm(II) reagent systems.

The study also provides extensive insights into the stability of benzylic aminoketyl radicals generated in the reduction of aromatic amides. Our data demonstrate that these radicals are significantly more stable than the corresponding aminoketyl radicals generated by single-electron transfer to unactivated aliphatic amides. However, little difference in terms of steric effect of the substituents on the stability of aminoketyl radicals from aromatic and aliphatic amides has been found. The present reaction allowed us to compare the electronic and steric effects involving aminoketyl radicals between SmI_2–H_2O and SmI_2–H_2O–amine reagents for the first time. Selectivity studies were used to determine the relative reactivity order of carboxylic acid derivatives with Sm(II)-based reagents. These similarities and differences between the reagent systems will have important implications for the design and optimization of new reductive processes involving the SmI_2–H_2O and SmI_2–H_2O–amine-mediated reduction of amides to alcohols and reductive umpolung cyclizations via aminoketyl radicals as a key step. Studies aimed at this direction are underway in our laboratories, and these results will be reported shortly.

EXPERIMENTAL SECTION

General Methods. All products and staring materials used in this study are commercially available or have been previously reported.[15,16] The products were identified using ^{1}H NMR, GC, and GC–MS analysis and comparison with authentic samples. The reaction progress was quantified by ^{1}H NMR and/or GC–MS analysis using internal standards after workup unless stated otherwise. Characterization data for all alcohol products have been previously reported. All experiments were performed using standard Schlenk techniques under argon atmosphere. All solvents were purchased at the highest commercial grade and used as received or after purification by passing through activated alumina columns or distillation from sodium/benzophenone under nitrogen. All solvents were deoxygenated by freeze–pump–thawing or sparging with argon prior to use. Samarium(II) iodide was prepared as described previously.[23a] Samarium metal was purchased as −40 mesh and stored at room temperature in a closed container on a bench prior to use. 1,2-Diiodoethane was stored at 4 °C and used after purification as described previously. All other chemicals were purchased at the highest commercial grade and used as received. Reaction glassware was oven-dried at 140 °C for at least 24 h or flame-dried prior to use, allowed to cool under vacuum and purged with argon (three cycles). Other general methods have been published.[24a]

Procedure A. Effect of Water Concentration. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. A previously published procedure was followed.[23a] Samarium(II) iodide (THF solution, 0.10 M, 6 equiv) was added followed by H_2O (50–1600 equiv) with vigorous stirring, which resulted in the formation of a characteristic burgundy-red color of the $SmI_2(H_2O)_n$ complex (n > 5 with respect to SmI_2). A solution of substrate (stock solution in THF, 0.20 M, 0.10 mmol) was added, and the reaction mixture was vigorously stirred under argon for 5 min. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture until decolorization to white had occurred. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and NaOH (1 N, 30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The sample

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was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC−MS to obtain conversion and yield using internal standard (CH_3NO_2 or 1,3,5-trimethoxybenzene) and comparison with authentic samples.

Procedure B. Effect of Other Ligands. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.10 M) was added followed by amine (if applicable) and alcohol with vigorous stirring, which resulted in the color change characteristic to a given Sm(II) complex.[20] A solution of substrate (stock solution in THF) was added, and the reaction mixture was vigorously stirred under argon for a given time. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture until decolorization to white or yellow had occurred. Workup and analysis were performed as described for procedure A.

Procedure C. Effect of *N*-Substituents. An oven-dried vial containing a stir bar was placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.60 mmol, 6.0 equiv, 0.10 M) was added followed by H_2O with vigorous stirring, which resulted in the formation of a characteristic burgundy-red color of the $SmI_2(H_2O)_n$ complex (n > 5 with respect to SmI_2). A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added and the reaction mixture was stirred at room temperature for 30 min. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture. Workup and analysis was performed as described for procedure A. For runs using SmI_2−Et_3N−H_2O complex, samarium(II) iodide (THF solution, 0.60 mmol, 6.0 equiv, 0.10 M) was added followed by Et_3N and H_2O with vigorous stirring, which resulted in the formation of a characteristic dark brown color of the SmI_2−Et_3N−H_2O complex. A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred at room temperature for 5 min. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture. Workup and analysis were performed as described for procedure A.

Procedure D. Relative Reactivity Studies. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.20 mmol, 2.0 equiv, 0.10 M) was added followed by H_2O (50 equiv) with vigorous stirring, which resulted in the formation of a characteristic burgundy-red color of the $SmI_2(H_2O)_n$ complex (n > 5 with respect to SmI_2). A preformed solution of two substrates (each 0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred until decolorization to white had occurred. Workup and analysis was performed as described for procedure A. For runs using SmI_2−Et_3N−H_2O complex, samarium(II) iodide (THF solution, 0.20 mmol, 2.0 equiv, 0.10 M) was added followed by Et_3N (24 equiv) and H_2O (24 equiv) with vigorous stirring, which resulted in the formation of a characteristic dark brown color of the SmI_2−Et_3N−H_2O complex. A preformed solution of two substrates (each 0.10 mmol, 1.0 equiv, stock solution in THF) was added and the reaction mixture was stirred until decolorization to white had occurred. Workup and analysis was performed as described for procedure A.

Procedure E. Determination of Kinetic Isotope Effect. An oven-dried vial containing a stir bar was placed under a positive pressure of argon and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (THF solution, 0.60 mmol, 6.0 equiv, 0.10 M) was added followed by an equimolar mixture of D_2O and H_2O with vigorous stirring, which resulted in the formation of a characteristic burgundy-red color of the $SmI_2(H_2O)_n$ complex (n > 5 with respect to SmI_2). A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added, and the reaction mixture was stirred at room temperature for 30 min. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture. Workup and analysis were performed as described for procedure A. For runs using SmI_2−Et_3N−H_2O complex, samarium(II) iodide (THF solution, 0.60 mmol, 6.0 equiv, 0.10 M) was added followed by Et_3N and an equimolar mixture of D_2O and H_2O with vigorous stirring, which resulted in the formation of a characteristic dark brown color of the SmI_2−Et_3N−H_2O complex. A solution of substrate (0.10 mmol, 1.0 equiv, stock solution in THF) was added and the reaction mixture was stirred at room temperature for 5 min. The excess of Sm(II) was oxidized by bubbling air through the reaction mixture. Workup and analysis were performed as described for procedure A.

Characterization Data. Characterization data for amide and alcohol products have been previously reported.[15,16] ^{1}H and ^{13}C NMR data for the amide and alcohol products used in the current study are presented below for characterization purposes. All amines were assigned by comparison with literature data: phenylmethanamine,[36] *N*-benzylbutan-1-amine,[9c] *N*-benzyl-*N*-ethylethanamine,[37] *N*-methyl-1-phenylmethanamine,[38] *N*-benzyl-2-methylpropan-2-amine,[39] *N*-benzylaniline,[40] *N*-benzylprop-2-en-1-amine,[41] *N*,*N*-dimethyl-1-phenylmethanamine,[42] 1-benzylpyrrolidine,[9c] 1-benzylpiperidine,[3s] 4-benzylmorpholine,[9c] and *N*-benzyl-*N*-isopropylpropan-2-amine.[43] All other alcohols were assigned by comparison with literature data: phenylmethanol,[44] (4-(trifluoromethyl)phenyl)methanol,[45] (4-fluorophenyl)methanol,[45] (4-chlorophenyl)methanol.[46]

4-Methoxybenzamide (Table 1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3 H), 5.93 (br, 2 H), 6.96 (d, J = 8.7 Hz, 2 H), 7.81 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 113.8, 125.4, 129.3, 162.7, 168.9.

***N*-Butyl-4-methoxybenzamide (Table 2):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 3 H), 1.24−1.37 (m, 2 H), 1.46−1.57 (m, 2 H), 3.34 (q, J = 6.0 Hz, 2 H), 3.76 (s, 3 H), 6.81 (d, J = 8.7 Hz, 2 H), 6.94 (t, J = 4.5 Hz, 1 H), 7.74 (t, J = 9.0 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 20.2, 31.8, 39.8, 55.3, 113.5, 127.1, 128.8, 161.9, 167.3.

***N*,*N*-Diethyl-4-methoxybenzamide (Table 3):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09−1.26 (m, 6 H), 3.13−3.62 (m, 4 H), 3.82 (s, 3 H), 6.90 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 39.6, 43.0, 55.3, 113.7, 128.2, 129.5, 160.3, 171.2.

(4-Methoxyphenyl)methanol (Table 1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (br, 1 H), 3.74 (s, 3 H), 4.54 (s, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 7.22 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 65.1, 114.0, 128.7, 133.2, 159.3.

4-Methoxy-*N*-methylbenzamide (Table 6, entry 3): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02 (d, J = 4.5 Hz, 3 H), 3.87 (s, 3 H), 6.10 (br, 1 H), 6.94 (d, J = 8.5 Hz, 2 H), 7.75 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 55.4, 113.7, 127.0, 128.6, 162.1, 167.7.

***N*-*tert*-Butyl-4-methoxybenzamide (Table 6, entry 7):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 3.85 (s, 3 H), 5.89 (br, 1 H), 6.91 (d, J = 9.0 Hz, 2 H), 7.70 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.9, 51.5, 55.4, 113.6, 128.3, 128.4, 161.9, 166.4.

4-Methoxy-*N*-phenylbenzamide (Table 6, entry 9): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (s, 3 H), 7.00 (d, J = 8.5 Hz, 2 H), 7.16 (t, J = 7.5 Hz, 1 H), 7.39 (t, J = 7.5 Hz, 2 H), 7.65 (d, J = 7.5 Hz, 2 H), 7.76 (br, 1 H), 7.87 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.5, 114.0, 120.1, 124.4, 127.2, 128.9, 129.1, 138.1, 162.5, 165.2.

***N*-Allyl-4-methoxybenzamide (Table 6, entry 11):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 4.09 (t, J = 5.5 Hz, 2 H), 5.17−5.21 (m, 2 H), 5.91−5.99 (m, 1 H), 6.24 (br, 1 H), 6.93 (d, J = 8.5 Hz, 2 H), 7.77 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.4, 55.4, 113.7, 116.5, 126.7, 128.7, 134.4, 162.2, 166.8.

4-Methoxy-*N*,*N*-dimethylbenzamide (Table 6, entry 13): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.04 (s, 6 H), 3.82 (s, 3 H), 6.89 (d, J = 8.5 Hz, 2 H), 7.39 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.5, 39.8, 55.3, 113.5, 128.4, 129.1, 160.6, 171.5

(4-Methoxyphenyl)(pyrrolidin-1-yl)methanone (Table 6, entry 17): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84−1.89 (m, 2 H), 1.92−1.97 (m, 2 H), 3.48 (t, J = 5.5 Hz, 2 H), 3.63 (t, J = 6.5 Hz, 2 H), 3.83 (s, 3 H), 6.89 (d, J = 7.5 Hz, 2 H), 7.51 (d, J = 7.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 26.5, 46.3, 49.8, 55.3, 113.4, 129.2, 129.5, 160.8, 169.4.

(4-Methoxyphenyl)(piperidin-1-yl)methanone (Table 6, entry 19): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48−1.72 (m, 6 H), 3.31−3.76 (m, 4 H), 3.83 (s, 3 H), 6.91 (d, J = 8.0 Hz, 2 H), 7.37 (d, J

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= 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 26.1, 43.4, 48.9, 55.3, 113.6, 128.6, 128.9, 160.5, 170.3.

(4-Methoxyphenyl)(morpholino)methanone (Table 6, entry 21): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51−3.78 (m, 8 H), 3.84 (s, 3 H), 6.92 (d, J = 8.5 Hz, 2 H), 7.39 (d, J = 8.5 Hz, 2 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 43.1, 48.0. 55.4, 66.9, 113.8, 127.4, 129.2, 160.9, 170.4.

***N,N*-Diisopropyl-4-methoxybenzamide (Table 6, entry 23):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04−1.67 (m, 12 H), 3.46−3.92 (m, 2 H), 3.83 (s, 3 H), 6.90 (d, J = 7.5 Hz, 2 H), 7.29 (d, J = 7.5 Hz, 2 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 47.1, 49.1, 55.3, 113.7, 127.5, 131.4, 159.9, 171.0.

***N*,4-Dimethoxy-*N*-methylbenzamide (Scheme 1):** ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.37 (s, 3 H), 3.57 (s, 3 H), 3.86 (s, 3 H), 6.91 (d, J = 8.5 Hz, 2 H), 7.74 (d, J = 8.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.9, 55.3, 60.9, 113.2, 126.0, 130.5, 161.5, 169.4.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00372.

^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press, 1991. (b) Hudlicky, M. *Reductions in Organic Chemistry*; Ellis Horwood: Chichester, 1984. (c) Seyden-Penne, J. *Reductions by Alumino and Borohydrides in Organic Synthesis*; Wiley: New York, 1997. (d) Andersson, P. G.; Munslow, I. J. *Modern Reduction Methods*; Wiley-VCH: Weinheim, 2008. (e) Addis, D.; Das, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6004.

(2) (a) Ricci, A. *Modern Amination Methods*; Wiley, 2000. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(3) Selected examples of chemoselective amide reductions: (a) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 1770. (b) Das, S.; Wendt, B.; Möller, K.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 1662. (c) Das, S.; Join, B.; Junge, K.; Beller, M. *Chem. Commun.* **2012**, *48*, 2683. (d) Das, S.; Addis, D.; Junge, K.; Beller, M. *Chem. - Eur. J.* **2011**, *17*, 12186. (e) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9507. (f) Das, S.; Zhou, S.; Addis, D.; Junge, K.; Enthaler, S.; Beller, M. *Top. Catal.* **2010**, *53*, 979. (g) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18. (h) Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817. (i) Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem.* **2012**, *4*, 228. (j) Reeves, J. T.; Tan, Z.; Marsini, M. A.; Han, Z. S.; Xu, Y.; Reeves, D. C.; Lee, H.; Lu, B. Z.; Senanayake, C. H. *Adv. Synth. Catal.* **2013**, *355*, 47. (k) Stein, M.; Breit, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 2231. (l) Cheng, C.; Brookhart, M. *J. Am. Chem. Soc.* **2012**, *134*, 11304. (m) Park, S.; Brookhart, M. *J. Am. Chem. Soc.* **2012**, *134*, 640. (n) Hanada, S.; Tsutsumi, E.; Motoyama, Y.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 15032. (o) Motoyama, Y.; Mitsui, K.; Ishida, T.; Nagashima, H. *J. Am. Chem. Soc.* **2005**, *127*, 13150. (p) Sunada, Y.; Kawakami, H.; Imaoka, T.; Motoyama, Y.; Nagashima, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 9511. (q) White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995. (r) Spletstoser, J. T.; White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2007**, *129*, 3408. (s) Tinnis, F.; Volkov, A.; Slagbrand, T.; Adolfsson, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 4562.

(4) (a) Brown, H. C.; Kim, S. C. *Synthesis* **1977**, *1977*, 635. (b) Hutchins, R. O.; Learn, K.; El-Telbany, F.; Stercho, Y. P. *J. Org. Chem.* **1984**, *49*, 2438. (c) Fisher, G. B.; Fuller, J. C.; Harrison, J.; Alvarez, S. G.; Burkhardt, E. R.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 6378. (d) Pasumansky, L.; Goralski, C. T.; Singaram, B. *Org. Process Res. Dev.* **2006**, *10*, 959. (e) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623. (f) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (g) Krackl, S.; Someya, C. I.; Enthaler, S. *Chem. - Eur. J.* **2012**, *18*, 15267.

(5) For recent progress using catalytic hydrogenation under high pressure, see: (a) Balaraman, E.; Gnanaprakasam, B.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2010**, *132*, 16756. (b) Ito, M.; Koo, L. W.; Himizu, A.; Kobayashi, C.; Sakaguchi, A.; Ikariya, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 1324. (c) Ito, M.; Ootsuka, T.; Watari, R.; Shiibashi, A.; Himizu, A.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 4240. (d) John, J. M.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 10377. (e) Cabrero-Antonino, J. R.; Alberico, E.; Drexler, H. J.; Baumann, W.; Junge, K.; Junge, H.; Beller, M. *ACS Catal.* **2016**, *6*, 47. (f) Kita, Y.; Higuchi, T.; Mashima, K. *Chem. Commun.* **2014**, *50*, 11211. (g) Garg, J. A.; Chakraborty, S.; Ben-David, Y.; Milstein, D. *Chem. Commun.* **2016**, *52*, 5285. (h) Rezayee, N. M.; Samblanet, D. C.; Sanford, M. S. *ACS Catal.* **2016**, *6*, 6377. (i) Schneck, F.; Assmann, M.; Balmer, M.; Harms, K.; Langer, R. *Organometallics* **2016**, *35*, 1931.

(6) Recent reviews on SmI_2: (a) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959. (b) Just-Baringo, X.; Procter, D. J. *Acc. Chem. Res.* **2015**, *48*, 1263.

(7) Reviews on metal-mediated radical reactions: (a) Szostak, M.; Procter, D. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9238. (b) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (c) Cuerva, J. M.; Justicia, J.; Oller-López, J. L.; Oltra, J. E. *Top. Curr. Chem.* **2006**, *264*, 63. (d) Justicia, J.; Àlvarez de Cienfuegos, L.; Campaña, A. G.; Miguel, D.; Jakoby, V.; Gansäuer, A.; Cuerva, J. M. *Chem. Soc. Rev.* **2011**, *40*, 3525. (e) Streuff, J. *Synthesis* **2013**, *45*, 281. (f) Murphy, J. *J. Org. Chem.* **2014**, *79*, 3731. (g) Meciarova, M.; Tisovsky, P.; Sebesta, R. *New J. Chem.* **2016**, *40*, 4855.

(8) Reviews: (a) Turecek, F.; Julian, R. R. *Chem. Rev.* **2013**, *113*, 6691. (b) Zhurov, K. O.; Fornelli, L.; Wodrich, M. D.; Laskay, Ü. A.; Tsybin, Y. O. *Chem. Soc. Rev.* **2013**, *42*, 5014. (c) Renaud, P.; Giraud, L. *Synthesis* **1996**, *1996*, 913. (d) Aurrecoechea, J. M.; Suero, R. *ARKIVOC* **2004**, 10.

(9) Selected examples of recent SmI_2-mediated reductions: (a) Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 1136. (b) Guazzelli, G.; De Grazia, S.; Collins, K. D.; Matsubara, H.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 7214. (c) Thurow, S.; Lenardao, E.; Just-Baringo, X.; Procter, D. J. *Org. Lett.* **2017**, *19*, 50.

(10) Selected examples of recent SmI_2-mediated cyclizations: (a) Helm, M. D.; Da Silva, M.; Sucunza, D.; Findley, T. J. K.; Procter, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9315. (b) Helm, M. D.; Da Silva, M.; Sucunza, D.; Helliwell, M.; Procter, D. J. *Tetrahedron* **2009**, *65*, 10816. (c) Fazakerley, N. J.; Helm, M. D.; Procter, D. J. *Chem. - Eur. J.* **2013**, *19*, 6718. (d) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964. (e) Yeoman, J. T. S.; Mak, V. W.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 11764. (f) Yeoman, J. T. S.; Cha, J. Y.; Mak, V. W.; Reisman, S. E. *Tetrahedron* **2014**, *70*, 4070. (g) Li, Z.; Nakashige, M.; Chain, W. J. *J. Am. Chem. Soc.* **2011**, *133*, 6553. (h) Breitler, S.; Carreira, E. M. *Angew. Chem., Int.*

DOI: 10.1021/acs.joc.7b00372
J. Org. Chem. 2017, 82, 6528−6540

Ed. **2013**, *52*, 11168. (i) Just-Baringo, X.; Clark, E.; Gutmann, M. J.; Procter, D. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 12499.
(11) Classic review on carbonyl umpolung: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.
(12) (a) Renaud, P.; Sibi, M. *Radicals in Organic Synthesis*; Wiley-VCH, 2001. (b) Chatgilialoglu, C.; Studer, A. *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Wiley-Blackwell, 2012. (c) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; Wiley-VCH, 1996. (d) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717. (e) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, J. *Synlett* **1992**, *1992*, 943.
(13) (a) Tsuruta, H.; Yamaguchi, K.; Imamoto, T. *Chem. Commun.* **1999**, 1703. (b) Evans, W. J. *Inorg. Chem.* **2007**, *46*, 3435.
(14) Laurence, C.; Gal, J. F. *Lewis Basicity and Affinity Scales: Data and Measurement*; Wiley: Chichester, 2009.
(15) Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 2268.
(16) Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Org. Chem.* **2014**, *79*, 11988.
(17) Szostak, M.; Spain, M.; Procter, D. J. *J. Org. Chem.* **2014**, *79*, 2522 and references cited therein.
(18) (a) Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2002**, *43*, 7197. (b) Dahlén, A.; Hilmersson, G. *Chem. - Eur. J.* **2003**, *9*, 1123. (c) Dahlén, A.; Hilmersson, G. *J. Am. Chem. Soc.* **2005**, *127*, 8340. (d) Ankner, T.; Stålsmeden, A. S.; Hilmersson, G. *Chem. Commun.* **2013**, *49*, 6867 and references cited therein. For a recent mechanistic study, see: (e) Yitzhaki, O.; Hoz, S. *Chem. - Eur. J.* **2015**, *21*, 9242.
(19) Review on chemoselective SmI_2 reductions: Szostak, M.; Spain, M.; Procter, D. J. *Chem. Soc. Rev.* **2013**, *42*, 9155.
(20) For reviews on additives to SmI_2, see: (a) Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Commun.* **2012**, *48*, 330. (b) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, *2004*, 3393. (c) Kagan, H. B.; Namy, J. L. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Ed. Kobayashi, S.; Springer: 1999; p 155.
(21) For a seminal study on the effect of water on SmI_2-mediated reductions, see: Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008.
(22) Kamochi, Y.; Kudo, T. *Chem. Lett.* **1993**, *22*, 1495.
(23) Selected mechanistic studies: (a) Szostak, M.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2014**, *136*, 8459 and references cited therein. (b) See ref 16. (c) Chopade, P. R.; Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2004**, *126*, 44. (d) Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2005**, *127*, 18093. (e) Tarnopolsky, A.; Hoz, S. *J. Am. Chem. Soc.* **2007**, *129*, 3402. (f) Amiel-Levy, M.; Hoz, S. *J. Am. Chem. Soc.* **2009**, *131*, 8280. (g) Upadhyay, S. K.; Hoz, S. *J. Org. Chem.* **2011**, *76*, 1355.
(24) (a) Shi, S.; Szostak, M. *Org. Lett.* **2015**, *17*, 5144. (b) Shi, S.; Lalancette, R.; Szostak, M. *Synthesis* **2016**, *48*, 1825. (c) Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. *Chem. - Eur. J.* **2016**, *22*, 11949. (d) Shi, S.; Szostak, R.; Szostak, M. *Org. Biomol. Chem.* **2016**, *14*, 9151 and references cited therein.
(25) (a) Huang, H. M.; Procter, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 7770. (b) Huang, H. M.; Procter, D. J. *J. Am. Chem. Soc.* **2017**, *139*, 1661.
(26) Meng, G.; Shi, S.; Szostak, M. *Synlett* **2016**, *27*, 2530.
(27) Reviews: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (c) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (d) Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474. (e) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (f) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (g) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (h) Petronijevic, F. R.; Nappi, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 18323. (i) Fava, E.; Nakajima, M.; Nguyen, A. L. P.; Rueping, M. *J. Org. Chem.* **2016**, *81*, 6959.
(28) Selected examples of electron-transfer reactions to carboxylic acid derivatives using Sm(II) and other reductants: (a) Hou, Z.; Fujita, A.; Zhang, Y.; Miyano, T.; Yamazaki, H.; Wakatsuki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 754. (b) Evans, W. J.; Ulibarri, T.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 219. (c) Honda, T.; Ishikawa, F. *Chem. Commun.* **1999**, 1065.
(29) Balasubramaniam, S.; Aidhen, I. *Synthesis* **2008**, 3707.
(30) Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96. (b) Jaffé, H. H. *Chem. Rev.* **1953**, *53*, 191.
(31) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
(32) (a) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979. (b) Chapman, N. B.; Shroter, J. *Advances in Linear Free Energy Relationships*; Plenum Press, 1972.
(33) For computational studies on the geometry of ketyl radicals, see: (a) Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1656. (b) Kefalidis, C. E.; Perrin, L.; Maron, L. *Eur. J. Inorg. Chem.* **2013**, *2013*, 4042.
(34) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066 and references cited therein.
(35) Greenberg, A., Breneman, C. M., Liebman, J. F., Eds. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Wiley: New York, 2000.
(36) Shao, Z.; Fu, S.; Wei, M.; Zhou, S.; Liu, Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 14653.
(37) Molander, G. A.; Gormisky, P. E.; Sandrock, D. L. *J. Org. Chem.* **2008**, *73*, 2052.
(38) Cardullo, F.; Donati, D.; Fusillo, V.; Merlo, G.; Paio, A.; Salaris, M.; Solinas, A.; Taddei, M. *J. Comb. Chem.* **2006**, *8*, 834.
(39) Yagafarov, N. Z.; Usanov, D. L.; Moskovets, A. P.; Kagramanov, N. D.; Maleev, V. I.; Chusov, D. *ChemCatChem* **2015**, *7*, 2590.
(40) Elangovan, S.; Neumann, J.; Sortais, J.-B.; Junge, K.; Darcel, C.; Beller, M. *Nat. Commun.* **2016**, *7*, 12641.
(41) Kennemur, J. L.; Kortman, G. D.; Hull, K. L. *J. Am. Chem. Soc.* **2016**, *138*, 11914.
(42) Mukherjee, D.; Shirase, S.; Mashima, K.; Okuda, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 13326.
(43) Hauser, A.; Bohlmann, R. *Synlett* **2016**, *27*, 1870.
(44) Ogata, O.; Nakayama, Y.; Nara, H.; Fujiwhara, M.; Kayaki, Y. *Org. Lett.* **2016**, *18*, 3894.
(45) Wei, Y.; Liu, S. X.; Mueller-Bunz, H.; Albrecht, M. *ACS Catal.* **2016**, *6*, 8192.
(46) Tan, X.; Wang, Y.; Liu, Y.; Wang, F.; Shi, L.; Lee, K. H.; Lin, Z.; Lv, H.; Zhang, X. *Org. Lett.* **2015**, *17*, 454.

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