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Direct reductive coupling of secondary amides: chemoselective formation of vicinal diamines and vicinal amino alcohols†‡

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We report the first one-pot reductive homocoupling reaction of secondary amides and cross-coupling reaction of secondary amides with ketones to give secondary vicinal diamines and amino alcohols. This method relies on the direct generation of α -amino carbon radicals from secondary amides by activation with trifluoromethanesulfonic anhydride, partial reduction with triethylsilane and samarium diiodide-mediated single-electron transfer. The reactions were run under mild conditions and tolerated several functional groups.

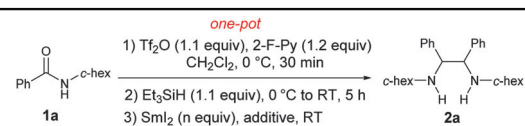
Amides are easily available¹ and highly stable carbonyl compounds. These features make them excellent starting materials and synthetic intermediates for a number of useful transformations,² including amide group-directed C–H functionalization.³ After these transformations, it is often necessary to convert the amide group, which is at a high level of oxidation state, to a functionality at a lower oxidation state. In this regard, chemoselective transformations of amides into amines and ketones *via* C–C bond formation, as a class of redox economical reactions,⁴ have attracted considerable attention.^{5–9} Although significant progress has been made recently after the discovery of the well-known Kulinkovich–de Meijere reaction,⁵ most of the methods involve the chemoselective or controlled generation of electrophilic intermediates such as iminoyl triflates, iminium ions, or nitrilium ions, followed by the capture of these reactive intermediates using π -nucleophiles⁷ or organometallic reagents.^{8,9} If reactive species other than electrophilic iminium ions were generated directly from amides, many other subsequent reactions other than nucleophilic addition could be anticipated. Along these lines, few examples involving the direct generation of

α -amino carbenes¹⁰ or α -amino carbon radicals¹¹ from tertiary amides have been reported. The direct generation of α -amino radicals from the more challenging secondary amides for C–C bond formation has not been reported probably because of the presence of a free N–H group in these amides.

As part of our goal of developing new C–C bond formation reactions that employ stable amides as substrates,^{8,9b,c} we now report the generation of α -amino carbon radicals from secondary amides and the application of these reactive species in the development of the first one-pot synthesis of vicinal diamines and vicinal amino alcohols from secondary amides. Vicinal diamines and vicinal amino alcohols are privileged scaffolds widely present in synthetically useful chiral ligands, auxiliaries and bioactive compounds.¹² Although many methods have been developed for the synthesis of these structural motifs,^{12b,13,14} it is still highly desirable to develop methods that use stable and easily available starting materials.

Our investigation was initiated by examining the reductive homocoupling of benzamide **1a** (Table 1). **1a** was treated sequentially with trifluoromethanesulfonic anhydride (Tf₂O)¹⁵

Table 1 Optimization of reaction conditions for the reductive homocoupling of secondary amides



Entry	Additive	SmI ₂ (equiv.)	% yield ^a (<i>meso</i> : <i>dl</i>) ^b
1	None	3.0	86 (54 : 46)
2	NiI ₂ (1 mol%)	3.0	88 (53 : 47)
3	NiI ₂ (1 mol%)	3.5	88 (53 : 47)
4	NiI ₂ (1 mol%)	2.2	74 (53 : 47)
5	^t BuOH (2 equiv.)	3.0	86 (54 : 46)
6	HMPA (2 equiv.)	3.0	89 (54 : 46)
7	Yb(OTf) ₃ (1 equiv.)	3.0	88 (55 : 45)

^a Isolated yields. ^b Determined by ¹H NMR analysis of the benzylic protons of the mixture obtained from a preliminary column chromatographic separation.

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(1.1 equiv.) and 2-F-Py^{9,16} (1.2 equiv.) at 0 °C for 30 min, Et₃SiH^{17,18} at 0 °C to RT for 5 h, and SmI₂ (ref. 19) (3.0 equiv.) for 5 min. To our delight, the desired diamine **2a** was obtained in 86% yield with a *meso/dl* ratio of 54 : 46 (Table 1, entry 1). No *N*-benzyl-cyclohexylamine as a result of unimolecular reduction was observed. In the presence of a catalytic amount of NiI₂^{19d} (1% mol), a slightly improved yield of 88% was obtained. However increasing the amount of SmI₂ to 3.5 equiv. produced no additional improvement in the yield (entry 3), lowering its quantity to 2.2 equiv. was shown to be detrimental (entry 4). On the other hand, replacing NiI₂ with other additives, including *t*-BuOH, HMPA or Yb(OTf)₃, failed to improve the diastereoselectivity (Table 1, entries 5–7). Hence, 3.0 equiv. of SmI₂ and 1 mol% NiI₂ were determined to be optimal for the reductive coupling reaction.²⁰

With the optimized reaction conditions in hand, the scope of the one-pot reductive homocoupling reaction was explored by varying the substituents on the phenyl ring and the amidyl nitrogen (Table 2). Electron-donating groups (entries 2 and 3), halogens (entries 4–6), and electron-withdrawing groups (entries 4–7) were shown to be well tolerated on the phenyl ring. A cyano group and an ester, often considered to be sensitive and labile under reductive conditions, were found to be compatible with the current process, furnishing the desired diamine products in moderate yields (entries 8–9). Meanwhile, amides bearing primary (entry 10) and secondary (entries 1–9 and 11–15) alkyl substituents were suitable substrates. The introduction of a sterically hindered *t*-Bu group (entry 16) or a phenyl ring (entry 17), however, completely abolished

product formation. Lastly, non-benzamides such as thiophenyl amide **1r** (entry 18) and cyclohexyl amide **1s** (entry 19) also underwent reductive coupling to produce **2r** in 65% yield and **2s** in 54% yield, respectively. However, the homocoupling of other aliphatic amides gave low yields.

Our success with the reductive homocoupling prompted us to turn our attention to the more challenging cross-coupling reactions of secondary amides with ketones. Under the reaction conditions established for the homocoupling reaction, **1n** was subjected to amide activation and controlled reduction before mixing with 2.0 equiv. of cyclopentanone (Table 3). Under these conditions, the desired cross-coupling product **3a** was obtained in 27% yield, along with the homocoupling product **2n** in 63% yield (entry 1). Attempts to increase the yield of **3a** by varying the amount of SmI₂ or ketone used, or by altering the reaction temperature, were unsuccessful.

Gratifyingly, the addition of 1.5 equiv. of Et₃N to the reaction before the introduction of cyclopentanone dramatically increased the yield of **3a** to 66%, and concomitantly, limited the formation of **2n** to 25% yield (Table 3, entry 2). Increasing the amount of ketone used to 3.0 equiv. (entry 3) further tilted the reaction toward cross coupling (76% of **3a** and 8% of **2n**). Using an even higher amount (6.0 equiv.), however, did not result in an additional increase in yield (entry 4). Conversely, changing the amount of SmI₂ to above or below 2.5 equiv. invariably lowered the amino alcohol formation (entries 5–7). Hence, the best conditions for the cross-coupling reaction consisted of the use of 1.5 equiv. of Et₃N, 3.0 equiv. of ketone, and 2.5 equiv. of SmI₂.

The scope of the cross-coupling reaction was investigated (Table 4). Cyclic ketones with ring sizes ranging from 4 to 8 all reacted efficiently affording good yields (products **3a–3e**, 60–76% yields). Acyclic ketones were also suitable coupling partners; however, 8.0 equiv. of the ketone were needed to ensure a good yield of the amino alcohol. For the amide part, both secondary and primary alkyl *N*-substituents were tolerated with the latter being inferior. The reaction of cyclopentanone with the benzamides bearing either electron-donating or electron-withdrawing groups on the benzene ring afforded the expected *vic*-amino alcohols **3m–3p** in 53–79% yields.

Table 2 One-pot reductive homocoupling of *sec*-amides

Entry	Substrate (R ¹ , R ²)	Product ^a (%)	<i>meso</i> : <i>dl</i> ^b
1	1a (Ph, <i>c</i> -hex)	2a (88)	53 : 47
2	1b (4-MeC ₆ H ₄ , <i>c</i> -hex)	2b (90)	55 : 45
3	1c (4-MeOC ₆ H ₄ , <i>c</i> -hex)	2c (80)	61 : 39 ^c
4	1d (4-FC ₆ H ₄ , <i>c</i> -hex)	2d (86)	56 : 44
5	1e (4-ClC ₆ H ₄ , <i>c</i> -hex)	2e (88)	57 : 43
6	1f (4-BrC ₆ H ₄ , <i>c</i> -hex)	2f (79)	54 : 46
7	1g (4-CF ₃ C ₆ H ₄ , <i>c</i> -hex)	2g (81)	54 : 46
8	1h (4-NCC ₆ H ₄ , <i>i</i> -Pr)	2h (58)	55 : 45
9	1i (4-MeO ₂ CC ₆ H ₄ , <i>i</i> -Pr)	2i (41)	54 : 46
10	1j (Ph, <i>n</i> -Bu)	2j (71)	70 : 30
11	1k (Ph, <i>i</i> -Bu)	2k (83)	60 : 40
12 ^d	1l (Ph, <i>c</i> -propyl)	2l (66)	78 : 22
13	1m (Ph, <i>c</i> -pentyl)	2m (88)	55 : 45
14	1n (Ph, <i>i</i> -Pr)	2n (93)	58 : 42
15	1o (4-MeC ₆ H ₄ , <i>i</i> -Pr)	2o (94)	59 : 41
16	1p (Ph, <i>t</i> -Bu)	2p (0)	—
17	1q (Ph, Ph)	2q (0)	—
18 ^e	1r (2-thienyl, <i>c</i> -hex)	2r (65)	60 : 40
19 ^e	1s (<i>c</i> -hex, Bn)	2s (54)	52 : 48

^a Isolated yields. ^b *meso* : *dl* ratios, determined by ¹H NMR analysis of the benzylic protons of the mixture obtained from a preliminary column chromatographic separation. ^c Determined by ¹H NMR analysis of the aromatic protons. ^d The reaction was treated with Tf₂O at –78 °C for 10 min and then at 0 °C for another 10 min. ^e *N*-benzyl-1-cyclohexylmethanamine was obtained in 20% yield.

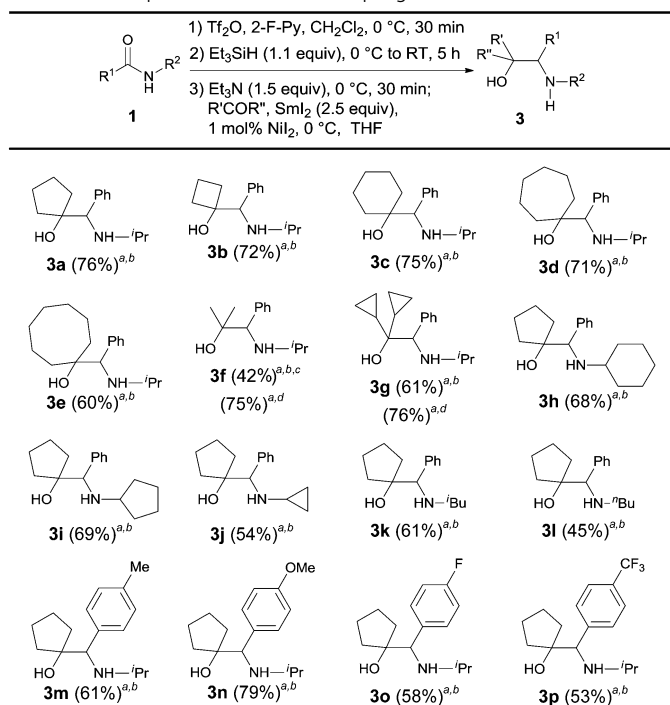
Table 3 Optimization of reaction conditions for the cross coupling of *sec*-amides with ketones

Entry	Base	Ketone (equiv.)	SmI ₂ (equiv.)	Yield ^a (%)	
				3a	2n
1	None	2.0	2.5	27	63
2	Et ₃ N	2.0	2.5	66	23
3	Et ₃ N	3.0	2.5	76	8
4	Et ₃ N	6.0	2.5	72	8
5	Et ₃ N	3.0	2.0	60	10
6	Et ₃ N	3.0	3.0	71	12
7	Et ₃ N	3.0	3.5	68	14

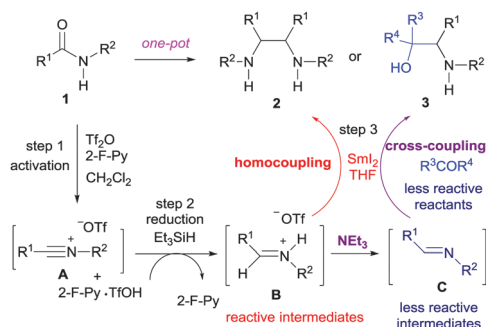
^a Isolated yields.



Table 4 One-pot reductive cross coupling of sec-amides with ketones



^a Isolated yields. ^b Ketone/amide ratio = 3.0. ^c Homocoupling product **2n** was also obtained in 38% yield. ^d Ketone/amide ratio = 8.0.



Scheme 1 A plausible reaction mechanism for the coupling reactions.

A plausible reaction mechanism for the coupling reactions is depicted in Scheme 1. The treatment of secondary amide **1** with Tf_2O yielded reactive nitrilium ion **A**,^{9b-d,16} which is then partially reduced with triethylsilane^{17,18} to give the protonated imine **B**. The highly reactive protonated imine **B** is then subjected to the SmI_2 -mediated homocoupling reaction to give vicinal diamine **2**.

The predominance of **2** in the product profile of the reaction of **1** with cyclopentenone can also be attributed to the predisposition of the highly reactive intermediate **B** to undergo the reductive homocoupling reaction. This undesired homocoupling reaction is suppressed by triethylamine to convert **B** to its less reactive neutral form imine **C**. Having comparable reactivity, the SmI_2 -mediated cross-coupling reaction between imine **C** and a ketone is favoured to give vic-amino alcohol **3**.

In summary, we have demonstrated for the first time that secondary vicinal diamines and vicinal amino alcohols can be

synthesized efficiently from secondary amides through reductive coupling reactions. The method relied on the generation of α -amino carbon radicals from secondary amides through amide activation, controlled reduction, and SmI_2 -mediated single-electron transfer. The homocoupling of the α -amino radical and cross coupling with ketones afforded a variety of vicinal diamines and vicinal amino alcohols, respectively. The more challenging cross-coupling reaction required a careful control of the reactivity of the imine intermediate. Studies that employ other radical acceptors for the α -amino radicals to generate functionalized amines are currently underway and will be reported in due course.

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