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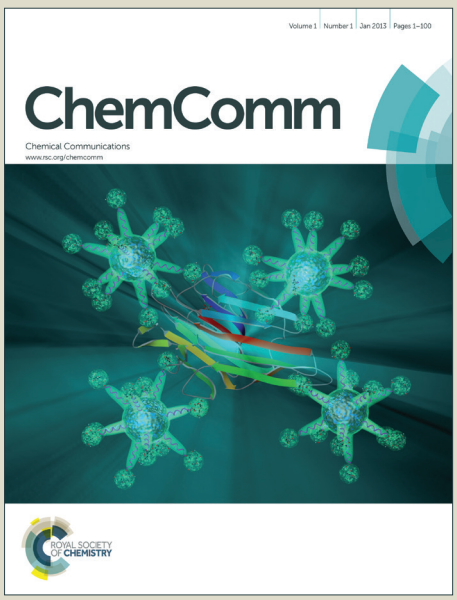

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ARTICLE TYPE

Direct Reductive Coupling of Secondary Amides: Chemoselective Formation of Vicinal Diamines and Vicinal Amino Alcohols † ‡

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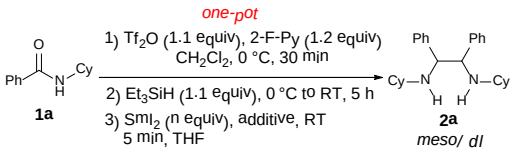
We report the first one-pot reductive homocoupling reaction of secondary amides and cross-coupling reaction of secondary amides with ketones to give secondary vicinal diamines and amino alcohols. This method relies on the direct generation of α-amino carbon radicals from secondary amides by activation 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 available[1] 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 lower oxidation state. In this regard, chemoselective transformation 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 progresses have 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 capturing these reactive intermediates with π-nucleophiles[7] 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 carbenes[10] or α-amino carbon radicals[11] from tertiary amides were 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 these reactive species for 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 (Tf_2O)[15] (1.1 equiv) and 2-F-Py[16,9] (1.2 equiv) at 0 °C for 30 min, Et_3SiH[17,18] at 0 °C to RT for 5 h, and SmI_2[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-cyclohexamine as a result of unimolecular reduction was observed. In the presence of a catalytic amount of NiI_2[19d] (1 %

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



entry	additive	SmI_2 (equiv)	% yield[a] (*meso:dl*)[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 yield; [b] Determined by ^{1}H NMR analysis of the benzylic protons of the mixture obtained from a preliminary column chromatographic separation.

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† Dedicated to Professor Henri-Philippe Husson on the occasion of his 75th birthday

‡ Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI:10.1039/b000000x/

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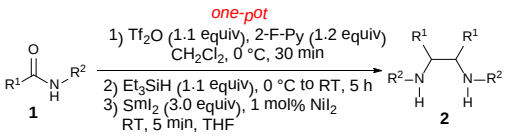
mol), a slightly improved yield of 88% was obtained. However increasing the amount of SmI_2 to 3.5 equiv produced no additional benefit for the yield (entry 3), lowing its quantity to 2.2 equiv was shown to be detrimental (entry 4). On the other hand, replacing NiI_2 with other additives, including *t*-BuOH, HMPA or $Yb(OTf)_3$ failed to improve the diastereoselectivity (Table 1, entries 5–7). Hence, the use of 3.0 equiv of SmI_2 and 1 mol% NiI_2 was determined to be the optimal conditions for the reductive coupling reaction.[20]

With the reaction conditions optimized, 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, 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 that bear 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.

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



entry	substrate (R^1, R^2)	product (%)[a]	*meso*:*dl*[b]
1	**1a** (Ph, *c*-hex)	**2a** (88)	53:47
2	**1b** (4-MeC_6H_4, *c*-hex)	**2b** (90)	55:45
3	**1c** (4-MeOC_6H_4, *c*-hex)	**2c** (80)	61:39[c]
4	**1d** (4-FC_6H_4, *c*-hex)	**2d** (86)	56:44
5	**1e** (4-ClC_6H_4, *c*-hex)	**2e** (88)	57:43
6	**1f** (4-BrC_6H_4, *c*-hex)	**2f** (79)	54:46
7	**1g** (4-$CF_3C_6H_4$, *c*-hex)	**2g** (81)	54:46
8	**1h** (4-NCC_6H_4, *i*-Pr)	**2h** (58)	55:45
9	**1i** (4-$MeO_2CC_6H_4$, *i*-Pr)	**2i** (41)	54:46
10	**1j** (Ph, *n*-Bu)	**2j** (71)	70:30
11	**1k** (Ph, *i*-Bu)	**2k** (83)	60:40
12[d]	**1l** (Ph, *c*-propyl)	**2l** (66)	78:22
13	**1m** (Ph, *c*-pentyl)	**2m** (88)	55:45
14	**1n** (Ph, *i*-Pr)	**2n** (93)	58:42
15	**1o** (4-MeC_6H_4, *i*-Pr)	**2o** (94)	59:41
16	**1p** (Ph, *t*-Bu)	**2p** (0)	-
17	**1q** (Ph, Ph)	**2q** (0)	-
18	**1r** (2-thienyl, *c*-hex)	**2r** (65)	60:40
19[e]	**1s** (*c*-hex, Bn)	**2s** (54)	52:48

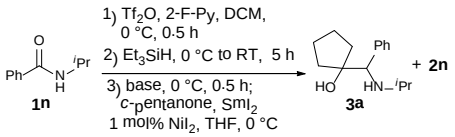
[a] Isolated yield; [b] *Meso*:*dl* ratio, determined by ^{1}H NMR analysis of the benzylic protons of the mixture obtained from a preliminary column chromatographic separation; [c] Determined by ^{1}H NMR analysis of the aromatic protons; [d] The reaction was treated with Tf_2O at −78 °C for 10 min and then at 0 °C for another 10 min; [e] A *N*-benzyl-1-cyclohexylmethanamine was obtained in 20% yield.

During our investigations, we found that the reductive homocoupling reactions also proceeded smoothly in the absence of NiI_2 (see: Electronic Supplementary Information), although the addition of a catalytic amount of this additive did lead to better yields and more consistent results.

Our success with the reductive homocoupling prompted us to turn our attention to the more challenging cross-coupling reactions of secondary amides with ketones. Using 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 SmI_2 or ketone used, or by altering the reaction temperature, were unsuccessful.

Gratifyingly, the addition of 1.5 equiv of Et_3N to the reaction before introducing 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 even higher amount (6.0 equiv), however, did not result in additional yield increase (entry 4). Conversely, changing the amount of SmI_2 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 the using of 1.5 equiv of Et_3N, 3.0 equiv of ketone, and 2.5 equiv of SmI_2.

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_3N	2.0	2.5	67	23
3	**Et_3N**	**3.0**	**2.5**	**76**	**8**
4	Et_3N	6.0	2.5	72	8
5	Et_3N	3.0	2.0	60	10
6	Et_3N	3.0	3.0	71	12
6	Et_3N	3.0	3.5	68	14

[a] isolated yield.

The scope of the cross-coupling reaction was investigated (Table 4). Cyclic ketones with ring sizes ranging from 4 to 8 all reacted efficiently with 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. Reaction of cyclopentanone with the benzamides bearing either electron-donating or electron-withdrawing groups

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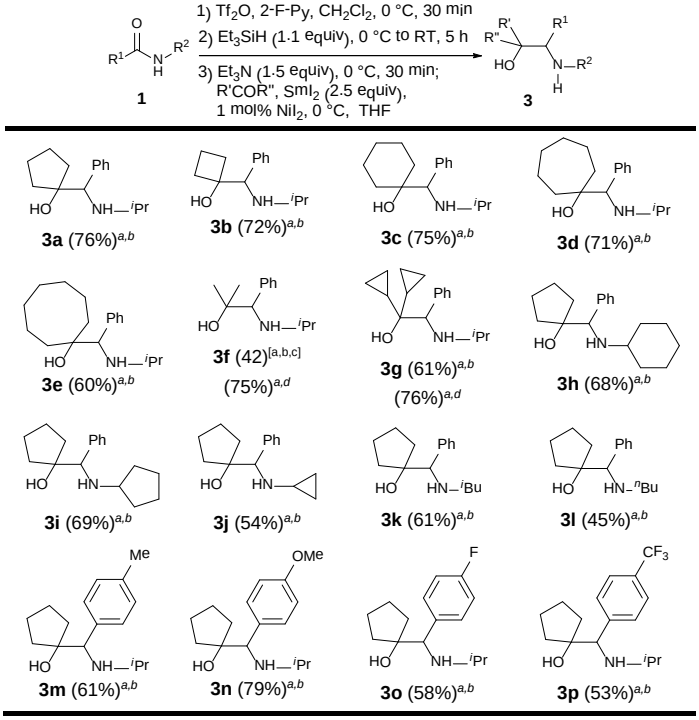
on the benzene ring afforded the expected *vic*-amino alcohols **3m–3p** in 53–79% yields.

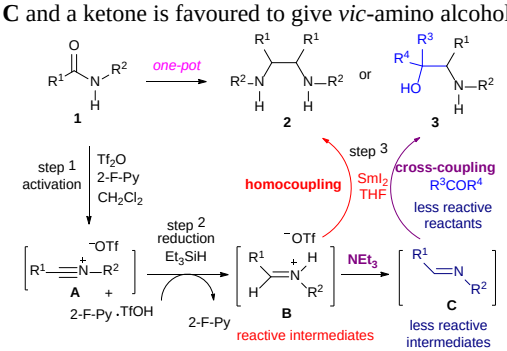
Table 4. One-pot reductive cross-coupling of *sec*-amides with ketones.



[a] isolated yield; [b] ketone/amide ratio = 3.0; [c] homocoupling product **2n** was also obtained in 38% yield; [d] ketone/amide ratio = 8.0.

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**[16,9b-d], 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**.



Scheme 1. A plausible reaction mechanism for the coupling reactions.

In summary, we have demonstrated for the first time that secondary vicinal diamines and vicinal amino alcohols can be constructed 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 or 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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20. For a comparison of more results on the reaction running in the presence or in the absence of NiI_2, see Table 1 in the Electronic Supplementary Information (ESI).

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