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Cross-coupling of Secondary Amides with Tertiary Amides: The Use of Tertiary Amides as Surrogates of Alkyl Carbanions for Ketone Synthesis

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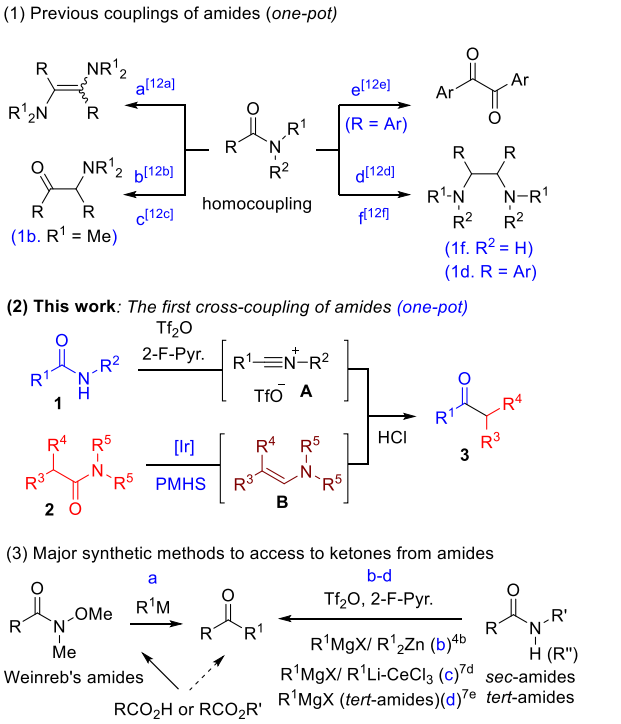
Abstract In recent years, exciting progress has been made in the field of direct transformation of amides, nevertheless, the condensation between two amides remains rare and restricted to homo-coupling reactions. Herein, we report the cross-coupling of secondary amides with tertiary amides, which provides a synthesis of ketones under mild conditions, and features the use of tertiary amides as surrogates of alkyl carbanions. The method relies on the coupling of enamines, generated from tertiary amides by catalytic partial reduction of tertiary amides with Vaska's catalyst, with nitrilium ions, formed in situ from secondary amides via activation with trifluoromethanesulfonic anhydride, and on the subsequent deformylation.

Introduction

Amides are found widespread ranging from proteins to peptides and other natural products, and from pharmaceuticals to materials. A number of methods have been developed for amide synthesis. Thus, amides are widely used in organic synthesis and medicinal chemistry either as starting materials or as synthetic intermediates. As a result, the transformation of amides into other classes of compounds at lower oxidation stages is in high demand. However, due to the low electrophilicity of amide carbonyl group as compare with other carbonyl compounds such as aldehydes, ketones and esters, the direct transformation of amide is underdeveloped. Actually, until very recently, multistep methods have been widely used for amide transformation. [1]

In the past decade, thanks to the contribution[2,3] of research groups of Charette,[4] Movassaghi,[5] Maulide,[2d,e,6] Huang,[2a,7] Chida/ Sato,[8] Pace,[2f,h,9] Dixon,[10] et al,[11] exciting progress has been made in the field of direct transformation of amides,[2] nevertheless, the condensation between two amides remains rare and restricted to homo-coupling reactions.[12] In 1992, Ogawa and Sonoda reported the first deoxygenative homo-coupling of tertiary amides to provide vicinal diaminoalkenes by an unprecedented Sm/SmI_2 system[12a] (Scheme 1, 1a). This was followed by Fleming's reductive homo-coupling of tertiary amides to give enediamines using $PhMe_2SiLi$[12b] (Scheme 1, 1b), Shono's electroreductive homo-coupling of aliphatic amides for the synthesis of α-amino ketones[12c] (Scheme 1, 1c), Harrod's titanocene-catalyzed homo-coupling of tertiary amides in the presence of organosilanes to form vicinal diamines[12d] (Scheme 1, 1d), and Kumagai/ Kawase's Li/ 4,4'-di-*tert*-butylbiphenyl (DBB)-mediated acyloin condensation of *N*,*N*-dimethylbenzamides to yield 1,2-diaryl-1,2-diketones (benzils)[12e] (Scheme 1, 1e). In 2015, our group reported the first reductive homo-coupling of secondary amides to yield vicinal diamines[12f] (Scheme 1, 1f). We disclose herein a method for the cross-coupling of secondary amides with tertiary amides that provides a synthesis of ketones under mild conditions, and features the use of tertiary amides as surrogates of alkyl carbanions.

Scheme 1 Reported methods and our plan for the cross-coupling of Amides



Whilst the organometallic reagents addition to *N*-methoxyl-*N*-methyl amides (Weinreb's amides) is a reliable and widely used method for the synthesis of ketones,[13] actually, it is an indirect method for the transformation of carboxylic acids or esters into ketones. The direct conversion of common amides to ketones is rare. The first approach for the direct transformation of secondary amides to ketones was developed independently by Charette[4b] and our group[7d] in 2012. In 2015, our group reported the first versatile direct transformation of tertiary amides to ketones.[7e] Very recently, our group have developed two organometallic reagent-free syntheses of ketones from secondary

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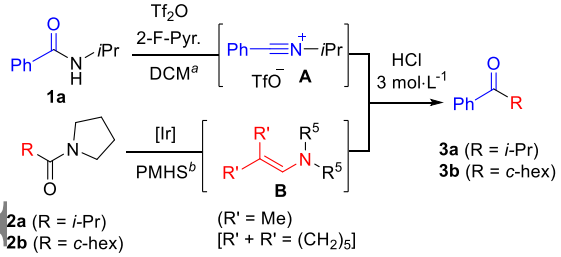
amides.[14] The methods relies on the nucleophilic addition of enamine[14a] or alkenes[14b] with nitrilium ion intermediates, generated in situ from secondary amides, and on the subsequent in situ deformylation. In view of the possibility of catalytic partial reduction of tertiary amides to enamines,[15] the use of the former as precursor of the latter for C-C bond formation was envisaged. Although Vaska's catalyst [IrCl(CO)(PPh_3)$_2$]-catalyzed reductive functionalization of amide carbonyl has been reported by several group,[7f,8c-e,10] to the best of our knowledge, the employment of the possible enamine products as synthetic equivalents of enols or enolates for C-C bond formation is unprecedented.

At the outset, the cross-coupling of secondary amide **1a** and tertiary amide **2a** (2.0 equiv) was examined. In the event, in the presence of 3 mol% of Vaska's catalyst,[16] amide **2a** (2.0 equiv) was reduced with PMHS (6.0 equiv toluene, 30 min) to give, the presumed enamine **B**. The crude enamine was directly used for the addition with nitrilium ion **A**, generated in situ by exposing a CH_2Cl_2 solution of secondary amide **1a** and 2-fluoropyridine to Tf_2O at 0 °C for 20 min.[7b] After being stirred at rt for 3 h, and treated with a 3 M HCl, the desired ketone **3a** was obtained in 19% yield. Increasing equivalent of tertiary amide **2a** from 2.0 to 3.0, and 3.5 resulted in an increase of yield from 19% to 27% and 35%, respectively. No further improvement was observed when 4.0 equiv of **2a** was used. The failure to further increase the yield was attributed to the volatility of the enamine that partially lost during concentration. To check this possibility, amide **2b** was used in place of **2a**. Indeed, when 2.0 equiv of **2b** was use, ketone **3a** was obtained in 27% yield. Encouraged by this result, the equivalent of tertiary amide **2b** was further screened. As can be seen from Table 1, use of 3.5 equiv of **2b** afforded an optimal yield of 82%.

Table 1 Optimization of reaction conditions

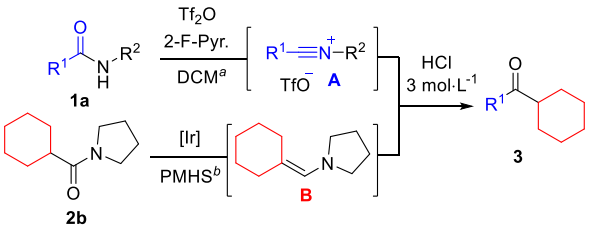


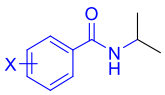
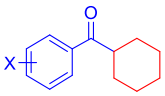
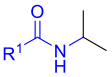
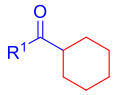
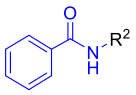
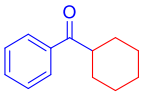
Entry	Tertiary amide **2a**/ **2b**	Yield [c] **3a**	**3b**
1	1.5	-	11%
2	2.0	19%	27%
3	2.5	-	38%
4	3.0	27%	43%
5	3.5	35%	82%
6	4.0	35%	81%

[a] Tf_2O (1.1 equiv), 2-F-Pyr (1.2 equiv), DCM, 0 °C, 20 min; [b] Tertiary amide (n equiv), IrCl(CO)(PPh_3)$_2$ (3.5 mol%), PMHS (2n equiv); [c] Isolated yield.

With the optimized reaction conditions in hand, scope of secondary amides was first surveyed. As can be seen from Table 2, for secondary benzamide derivatives, the reaction tolerated both electron-donating (Me/**1b**, MeO/**1c**) and electron-withdrawing groups (Cl/**1d**, CF_3/**1e**) at *para*-position of benzamide (Table 2, entries 2-5). Significantly, the reaction displayed excellent functional group tolerance and chemoselectivity. Functional groups that are reactive towards organometallic reagents including acetoxy/**1f**, ester/**1g**, cyano/**1h**, tertiary amido/**1i**, ketone/**1j**, aldehyde/**1k**, and nitro/**1l** groups can survive from the reaction (Table 2, entries 6-12), and the reaction took place chemoselectively at the secondary amide group. It is worth mentioning that although such kind of chemoselectivity has been observed by Charette in their elegant synthesis of ketones from secondary amides,[4c] and by our group in the synthesis of enimines/ enones and aromatic ketones[7f,g,l,j], those methods required either the use of high dilution conditions (0.044 M),[4c] or restricted to nucleophilic alkenes/ arenes[7f,g,l,j].

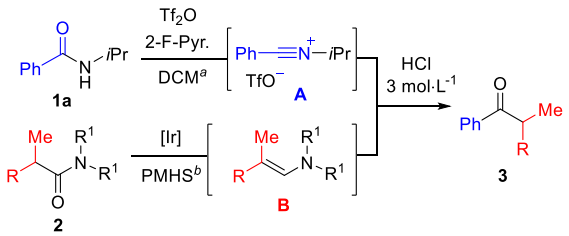
Table 2 Scope of secondary amides

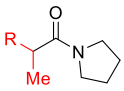
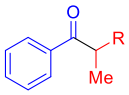
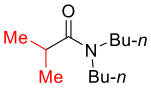
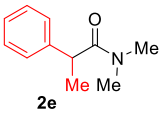
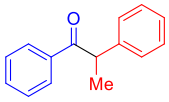
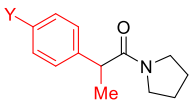
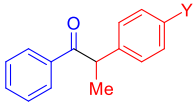


Entry	Secondary amides	Product (Yield)[c]
		
1	**1a** (X = H)	**3b** (X = H, 82%)
2	**1b** (X = *p*-Me)	**3c** (X = *p*-Me, 77%)
3	**1c** (X = *p*-MeO)	**3d** (X = *p*-MeO, 80%)
4	**1d** (X = *p*-Cl)	**3e** (X = *p*-Cl, 78%)
5	**1e** (X = *p*-CF_3)	**3f** (X = *p*-CF_3, 77%)
6	**1f** (X = *p*-AcO)	**3g**(X = *p*-AcO, 80%)
7	**1g** (X = *p*-MeO_2C)	**3h** (X = *p*-MeO_2C, 78%)
8	**1h** (X = *p*-NC)	**3i** (X = *p*-NC, 75%)
9	**1i** (X = *p*-$Et_2NC(O)$)	**3j** (X = *p*-$Et_2NC(O)$, 82%)
10	**1j** (X = *p*-$CH_3C(O)$)	**3k** (X = *p*-$CH_3C(O)$, 74%)
11	**1k** (X = *p*-HC(O))	**3l** (X = *p*-HC(O), 76%)
12	**1l** (X = *p*-O_2N)	**3m** (X = *p*-O_2N, 78%)
13	**1m** (X = *m*-Br)	**3n** (X = *m*-Br, 79%)
14	**1n** (X = *o*-Me)	**3o** (X = *o*-Me, NR)
		
15	**1o**. (R^1 = 2-Naphthyl)	**3p** (R^1 = 2-Naphthyl, 86%)
16	**1p** (R^1 = 2-Thienyl)	**3q** (R^1 = 2-Thienyl, 52%)
17	**1q** (R^1 = *n*-$C_{10}H_{21}$)	**3r** (R^1 = *n*-$C_{10}H_{21}$, 76%)
		
18	**1r** R^2 = *c*-Hex	**3b** 89%
19	**1s** R^2 = Et	**3b** 62%
20	**1t** R^2 = allyl	**3b** 43%

[a] Tf_2O (1.1 equiv), 2-F-Pyr (1.2 equiv), DCM, 0 °C, 20 min;[b] Tertiary amide (3.5 equiv), IrCl(CO)(PPh_3)$_2$ (3.5 mol%), PMHS (7.0 equiv); [c] Isolated yield.

Table 3 Scope of tertiary amides in the one-pot coupling with secondary amides



Entry	Tertiary amides	Products (Yield)[c]
		
1	**2a**. R = Me	**3a**. (R = Me, 35%)
2	**2c**. R = Et	**3s**. (R = Me, 72%)
3	 **2d**	**3a**. (R = Me, 71%)
4	 **2e**	 **3t**. (77%)
		
5	**2f**. Y = H	**3t**. (Y = H, 80%)
6	**2g**. Y = Me	**3u**. (Y = Me, 78%)
7	**2h**. Y = MeO	**3v**. (Y = MeO, 82%)
8	**2i**. Y = AcO	**3w**. (Y = AcO, 77%)
9	**2j**. Y = Cl	**3x**. (Y = Cl, 45%)
10	**2k**. Y = MeO_2C	**3y**. (Y = MeO_2C, trace)

[a] Tf_2O (1.1 equiv), 2-F-Pyr. (1.2 equiv), DCM, 0 °C, 20 min;
[b] Tertiary amide (3.5 equiv), $IrCl(CO)(PPh_3)_2$ (3.5 mol%), PMHS (7.0 equiv);
[c] Isolated yield.

The condensation of *meta*-substituted benzamides such as *m*-bromobenzamide **1m** proceeded smoothly to give the desired ketone **3n** in 79% yield (entry 13), whereas *ortho*-substituted benzamides such as *o*-methylbenzamide **1n** failed to yield the desired product (entry 14), which was attributed to steric hindrance. Other aromatic amides such as 2-naphthamide **1o** and thiophene-2-carboxamide **1p** as well as aliphatic amide **1q** turned out to be viable substrates (entries 15-17). As regarding the *N*-substituent in secondary amide **1**, that bearing other secondary alkyl groups such as cyclohexyl (**1r**) worked well (entry 18); a modest yield of 62% was obtained from amide bearing a primary alkyl group such as ethyl group (**1s**) (entry 19), and *N*-allyl amide **1t** afforded the corresponding ketone **3b** in a low yield (43%) (entry 20).

Next, scope of tertiary amide was examined. Although the aforementioned reaction of amide **1a** with **2a** afforded ketone **3a** in a low isolated yield (35%), this ketone could be obtained in 71% yield from the corresponding *N*,*N*-dibutylamide **2d** (Table 3, entry 1). Moreover, the reaction of its one-carbon higher homologue **2c** produced the corresponding ketone **3s** in 72% yield (entry 2). These results are in support of our assumption about the relationship between volatility of enamine **B** generated from tertiary amide **2** and yield of ketone **3**.

α-Arylacetamides **2e-2h** are also viable substrates for the coupling with secondary amide **1a**, which afforded the corresponding ketones **3t-3v** in 77-82% yields (Table 3, entries 4-7). It is worth noting that *N*,*N*-dimethylamide bearing a phenyl group (**2e**), the corresponding enamine being less volatile, served as an effective surrogate of the corresponding alkyl carbanion to yield ketone **3t** in good yield (77%, entry 4). Notably, tertiary amide bearing an acetoxy group (**2i**) also reacted smoothly to produce the functionalized ketone **3w** in 77% yield (entry 8). *para*-Chlorophenylacetamide **2j** reacted to give **3x** in a modest yield (45%, entry 9), whereas from ester-bearing amide **2k**, only trace of ketone **3y** was observed (entry 10).

Conclusions

We have achieved the first cross-coupling of secondary amides with tertiary amides. This novel transformation of amides established a novel synthesis of ketones from common amides. Remarkably, through this protocol, we demonstrated the feasibility of employing neutral and highly stable tertiary amides as surrogates of highly basic secondary alkyl carbanions. This ensured the reaction be run under mild conditions. As a result, the reaction showed excellent chemoselectivity and functional group tolerance on the secondary amide partner at normal concentration. Moreover, the tertiary amide partner was shown to tolerate sensitive functional groups such as acetoxy group. Work is in progress in our group to further extend this chemoselective reaction, and the results will be reported in due course.

Experimental

General procedure for cross-coupling of secondary amides with tertiary amides:

To a 0.2 M solution of $IrCl(CO)(PPh_3)_2$ in toluene (9 mL; 0.0175 mmol of [Ir]) was added a tertiary amide (1.75 mmol) and PMHS (777 mg, 3.5 mmol) at 25 °C. After being stirred for 15 min, the resultant residue was washed ten times with ether (50 mL in total), and the combined organic phases were filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford an essentially pure enamine, which was used as it was. Then into a dry 25-mL round-bottom flask equipped with a

magnetic stirring bar were added successively a secondary amide (0.5 mmol, 1.0 equiv), 2 mL of anhydrous CH_2Cl_2 and 2-fluoropyridine (0.6 mmol, 1.2 equiv) under an argon atmosphere. After being cooled to 0 °C, trifluoromethanesulfonic anhydride (Tf_2O) (155 mg, 93 μL, 0.55 mmol, 1.1 equiv) was added dropwise via a syringe and the reaction mixture was stirred for 10 min. To the resulting mixture, the crude enamine was added dropwise at 0 °C. The mixture was allowed warming-up to room temperature and stirred for 3 h. The reaction was quenched with an aqueous HCl solution (3.0 M, 5.0 mL) and stirred for 5-6 h at room temperature. The organic layer was separated and the aqueous phase was extracted with ethyl ether (3×10.0 mL). The combined organic layers were washed with brine (3×3.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc) to afford the desired ketone.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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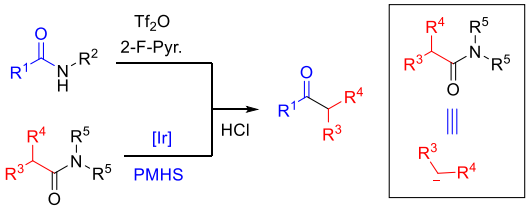
Cross-coupling of Secondary Amides with Tertiary Amides: The Use of Tertiary Amides as Surrogates of Alkyl Carbanions for Ketone Synthesis



We report the cross-coupling of secondary amides with tertiary amides, which provides a synthesis of ketones under mild conditions, and features the use of tertiary amides as surrogates of alkyl carbanions.

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