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Synthesis of Tertiary Amines by Direct Brønsted Acid Catalyzed Reductive Amination

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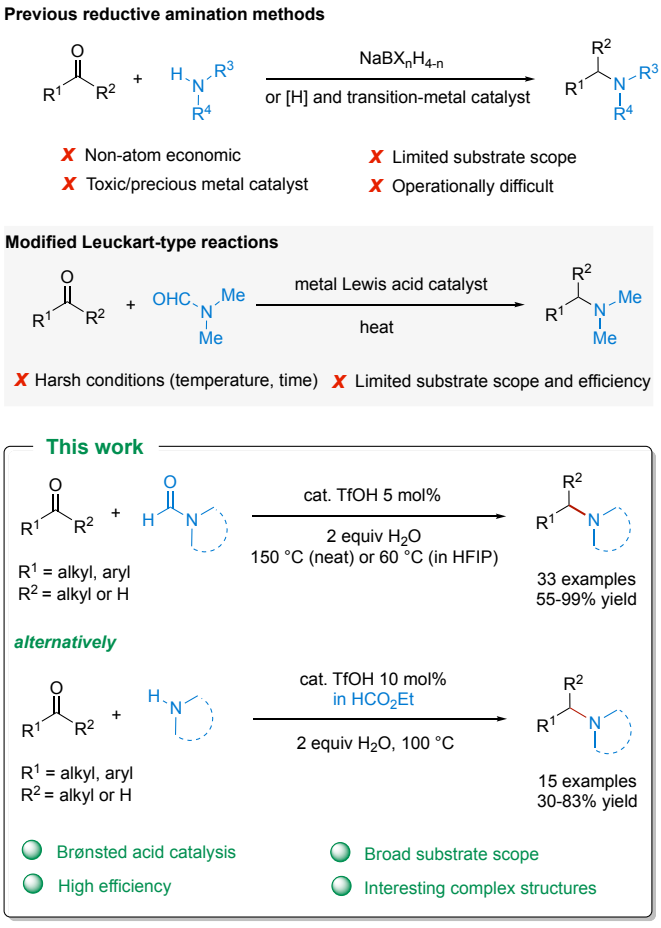
Tertiary amines are ubiquitous and valuable compounds in synthetic chemistry, with a wide range of applications in organocatalysis, organometallic complexes, biological processes and pharmaceutical chemistry. One of the most frequently used pathways to synthesize tertiary amines is the reductive amination reaction of carbonyl compounds. Despite developments of numerous new reductive amination methods in the past decades, this reaction generally requires non-atom-economic processes with harsh conditions and toxic transition-metal catalysts. Herein we report simple yet practical protocols using triflic acid as catalyst to efficiently promote direct reductive amination reactions of carbonyl compounds on a broad range of substrates. Applications of this new method to generate valuable heterocyclic frameworks and polyamines are also included.

Amines are an important class of compounds in organic chemistry and fundamental building blocks of biological processes.[1] Tertiary amines, in particular, appear in a diverse range of naturally occurring compounds and synthetic products such as pharmaceuticals, agrochemicals and functional materials.[2] They have also been used extensively as ligands in organometallic complexes[3] as well as organocatalysts in organic synthesis.[4] Tertiary amines can be synthesized by alkylation or arylation reaction of ammonia or less substituted amines.[5] This method, however, often suffers from over-substitution on the nitrogen centre.[5] Another frequently used synthetic route to tertiary amines is the reductive amination reaction of carbonyl compounds (Scheme 1), which can potentially become a practical process due to diverse carbonyl precursors abundantly available from feedstock chemicals.[6] In the past few decades, there have been numerous new protocols developed to facilitate this chemical transformation.[6a,6b,7] However, they generally involve either non-atom economic processes using excessive amounts of reductants, or harsh conditions, and the use of transition-metal catalysts such as Ir, Cu, Ag, Au, Pd, Ru or Rh for transfer hydrogenation reaction.[6b,6c,8] Hence, more practical and environmentally benign reductive amination procedures are still in demand.

Recently, attention has been brought back to modifications of the Leuckart reaction[9] in which formic acid and its ester or



Scheme 1. Direct Brønsted acid catalysed reductive amination

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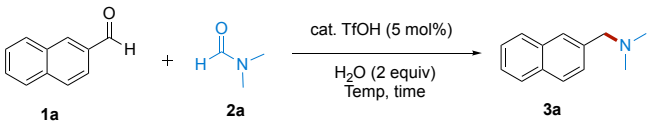
amide derivatives are used as efficient reductants for the reductive amination.[9-10] The main drawback of Leuckart-type reactions is that they require extremely high temperature, an issue can potentially be addressed by using suitable catalysts and solvents. Among those studies, *N*,*N*-dimethylformamide (DMF) is a compound of particular interest as it acts not only as a good solvent for the reaction but also the dimethylamino group source, in addition to being the reductant.[11] Methods employing DMF generally work with precious transition metal complex[8f,10k,10l] or metal Lewis acid catalysts,[10b,12] which facilitate the *in situ* hydrolysis of DMF to dimethylamine and formic acid. The former reacts with carbonyl compounds to form *N*,*N*-dimethyliminimum intermediates, which are reduced by formic acid to form the target dimethylaminated products. Thus, we believe that, in principle, a Brønsted acid should be able to promote the same transformation. To the best of our knowledge, however, no direct Brønsted acid catalyzed reductive amination method has been reported, except for some non-systematic examples with unsatisfactory outcomes in literature.[12] Herein we discuss the development of simple yet practical protocols using triflic acid as catalyst to efficiently promote reductive amination reactions of carbonyl compounds on a broad range of substrates (Scheme 1). Our procedure is not only applicable to DMF but also other formamides to form a diverse library of tertiary amine products. Several applications of this new method to generate valuable products such as complex *N*-heterocycles and polyamines are also included in this work.

To investigate the possibility of using a Brønsted acid to catalyze the reductive amination of carbonyl compounds, 2-naphthaldehyde (**1a**) was used as the model substrate with DMF (**2a**) as the amine source, reductant and solvent. A range of readily available Brønsted acids were tested as catalysts for this reaction (see Table S1 in the ESI for more details)[13] at 10 mol% loadings. Triflic acid, a super Brønsted acid,[14] showed superior efficiency in comparison to other acids. We subsequently carried out optimization studies with this catalyst (see Table S2 in the ESI for more details).[13] Elevated temperatures were required to facilitate the chemical transformation to satisfactory outcomes within reasonable reaction times. The reaction worked best in DMF at 150 °C with 5 mol% TfOH (see entry 1, Table 1). Two equivalents of water were found to be sufficient to mediate the reaction, whilst previous methods required excess amounts.[12] Lowering the catalyst loading led to longer reaction times but the overall product yield was not significantly affected by this parameter (see Table S2 in the ESI).[13]

In order to aim for a broader substrate scope later on where the formamide is less readily available and cannot be used as solvent, we also explored the effect of solvents when using DMF only as a reactant. Many of the tested solvents resulted in lower efficiency than DMF itself (Table 1). Interestingly, fluorinated alcohols[15] such as TFE and HFIP[16] and a typical ionic liquid[17] [bmim]PF_6, which are known for their highly ionizing ability, gave excellent outcomes even at lower reaction temperatures (entries 8-12, Table 1). A quick optimization study on HFIP as reaction solvent identified a set of conditions (entry 12, Table 1)

Table 1. Optimization of NHC-promoted Appel-type reactions[a]



1a 2a 3a

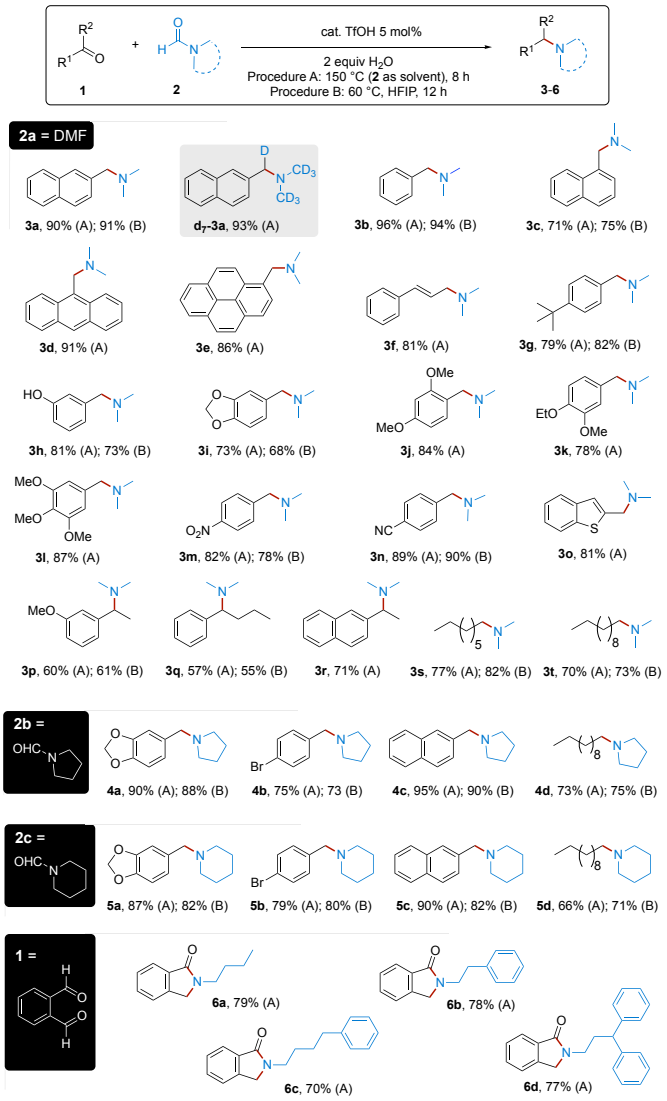
Entry[a]	Solvent	DMF (equiv)	Temp	Time (h)	Yield[b]
1	**neat**	**~ 13 (1.0 mL)**	**150 °C**	**8**	**90%**
2	-	2	150 °C	8	39%
3	-	5	150 °C	8	51%
4	Toluene	5	120 °C	8	19%
5	DCE	5	100 °C	8	41%
6	MeCN	5	100 °C	8	37%
7	EtOH	5	100 °C	8	34%
8	TFE	5	100 °C	8	62%
9	HFIP	5	60 °C	8	67%
10	[bmim]PF_6	5	150 °C	8	64%
11	HFIP	5	60 °C	24	86%
12	**HFIP**	**5**	**60 °C**	**12**	**91%**
13	HFIP	5	40 °C	24	40%
14	HFIP	5	25 °C	24	21%
15	HFIP	5	25 °C	96	63%

[a] Reaction conditions: catalyst TfOH (0.05 mmol), aldehyde **1a** (1.0 mmol), water (2.0 mmol) and DMF (**2a**) in solvent (0.5 mL) in a screw-cap 4 mL reaction vial; [b] Yield of isolated product.

with comparable results to the optimal setup in DMF solvent (entry 1, Table 1, also see Tables S2 and S3 in the ESI for more details).[13] Based on the practicality of the reaction setups, we identified two optimal sets of conditions as in entry 1 (Table 1, *Procedure A*) with DMF solvent and entry 12 (Table 1, *Procedure B*) with HFIP solvent. These two procedures can be used interchangeably with similar efficiencies, as subsequently demonstrated in this work.

Having these optimal conditions in hand, we set out to investigate the applicability of this TfOH-catalyzed reaction on other carbonyl compounds. Gratifyingly, the reaction worked very well on a diverse range of substrates (Scheme 2, top) using DMF as solvent and amination reagent. Both Procedures A and B proved to be practical. Aromatic aldehydes generally afforded the corresponding benzylic tertiary amines in high to excellent yields (**3a**-**3n**, Scheme 2, top). Electron-donating or electron-withdrawing substituents did not seem to have any significant effect on the reaction outcomes (**3h**-**3n**). A heteroaromatic aldehyde also reacted smoothly to give corresponding product in high yield (**3o**). Aromatic ketones are less reactive and resulted in slightly lower product yields (**3p**-**3r**) due to side-reactions. Reactions with aliphatic substrates seemed to be complicated with side processes but still afforded tertiary amine products with satisfactory outcomes (**3s**-**3t**). When d_7-DMF was used instead of normal DMF, product **d_7-3a** was obtained in excellent yield, confirming the reductive role of the formamide as the deuterium ended up on the benzylic position.

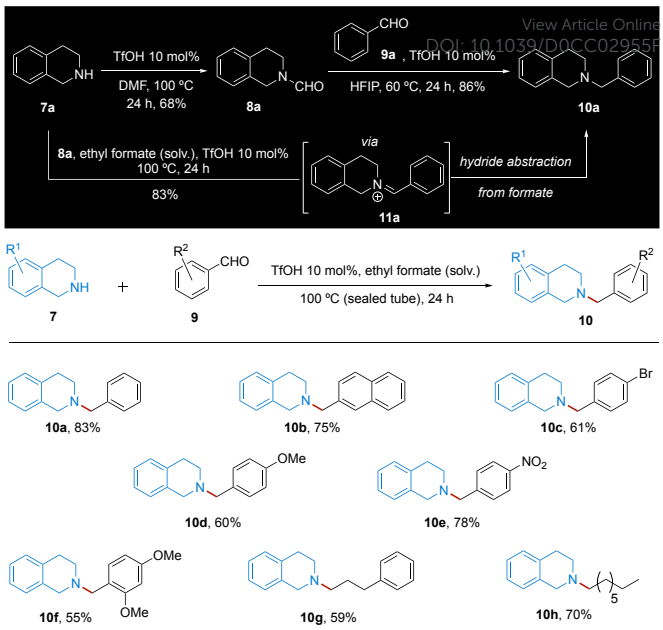
Other formamides[18] were also examined for this triflic acid catalyzed reductive amination reaction. Under similar reaction conditions developed in Table 1, 1-formyl pyrrolidine (**2b**) and 1-formyl piperidine (**2c**) also reacted smoothly with aldehydes to give the corresponding products **4** or **5** (Scheme 2, middle).



Scheme 2. Substrate scope of the TfOH-catalyzed reductive amination reaction with DMF and other formamides.

Again, both procedures with **2b** or **2c** as solvents or with HFIP worked relatively well with comparable efficiencies. Preliminary studies with some ketones only led to very sluggish reactions with these formamides, giving less than 50% conversion after several days, so we did not further extend the reaction scope to this type of substrates. Interestingly, when phthalaldehyde was used in conjunction with mono *N*-substituted formamides (Scheme 2, bottom), we observed the formation of isoindolinone derivatives **6a**-**6d** as major products. Presumably, the reaction proceeded through a sequential reductive amination reaction on the first aldehyde moiety followed by the oxidative lactamization on the second aldehyde to form the isoindoline framework. Similar cyclization reactions have been reported for some other Lewis acid catalytic methods.[6b,6c,8c,8e]

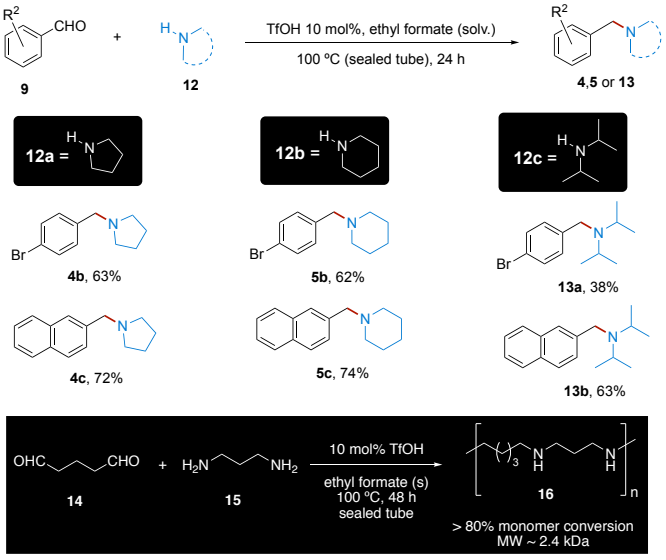
In a subsequent attempt to extend the method to the synthesis of tetrahydroisoquinolines (THIQs), which are the backbones of many biologically valuable compounds, we synthesized *N*-formyl THIQ (compound **8a**, Scheme 3). This compound was produced via transamidation reaction of THIQ **7a** with DMF,[19] which was conveniently catalyzed by the same TfOH catalyst.[13]



Scheme 3. Reductive alkylation of tetrahydroisoquinoline with aldehydes and ethylformate.

While *N*-formyl THIQ **7a** could also react with benzaldehyde **9a** to produce *N*-benzyl THIQ **10a** as expected, we discovered that it is also possible to form **10a** from a direct TfOH-catalyzed reductive coupling reaction of **7a** and **9a** in ethyl formate solvent (Scheme 3). This transformation is interesting as reductive amination reactions mediated by ethyl formate have never been investigated in detail in literature.[6-8]

Presumably, the most likely pathway for this reaction could be that the secondary amine **7a** reacted with aldehyde **9a** to give an iminium intermediate (**11a**). **11a** could then be reduced to the product by the formate ion generated *in situ* from the hydrolysis of ethyl formate under Brønsted acid catalyzed conditions. We cannot rule out the possibility that intermediate **8a** could also be concomitantly generated in the reaction mixture by the formylation reaction of **7a** with ethyl formate



Scheme 4. Other ethyl formate promoted reductive aldehyde-amine coupling reactions

under the same conditions.[19] Either way, we were able to produce a series of *N*-alkylated THIQs by reacting aromatic or aliphatic aldehydes with *N*-unsubstituted THIQ (**7a**) in ethylformate with 10 mol% TfOH catalyst (Scheme 3). Furthermore, the application of these conditions on the direct coupling reaction of other secondary amines (**12a**-**c**) and some selected aldehydes (**9**) in ethyl formate also gave very encouraging outcomes (Scheme 4), which demonstrates the generality of this protocol. More interestingly, preliminary studies with glutaraldehyde (**14**) and 1,3-diaminopropane (**15**) under similar conditions showed that iterative reductive amination reaction in ethyl formate is possible to produce PEG-type polyamines (**16**, Scheme 4).[13] These promising results pave the way for a new approach to valuable polyamines, which will be further investigated in our future work.

In conclusion, we report simple yet practical protocols using triflic acid as catalyst to efficiently promote direct reductive amination reactions of carbonyl compounds on a broad range of substrates to produce tertiary amines. This new method can give access to valuable heterocyclic systems such as isoindolinones and tetrahydroisoquinolines, or can be potentially applicable to the synthesis of polyamines.

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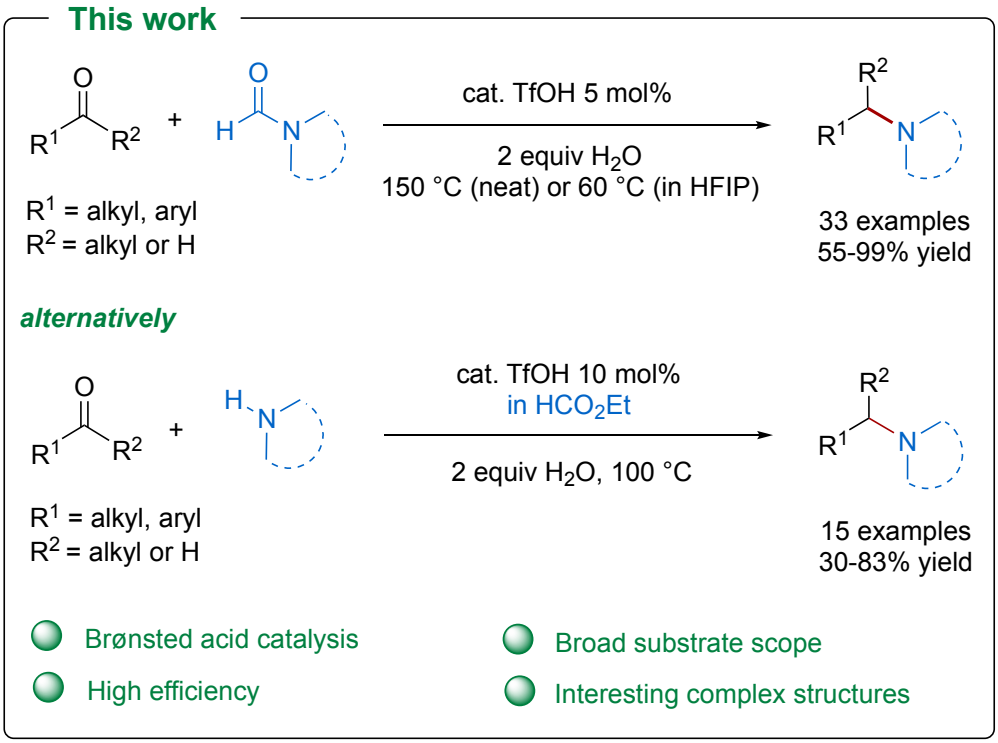

Triflic acid efficiently promotes the reductive amination reactions of carbonyl compounds on a broad range of substrates.