

Manganese-Mediated Reductive Transamidation of Tertiary Amides with Nitroarenes

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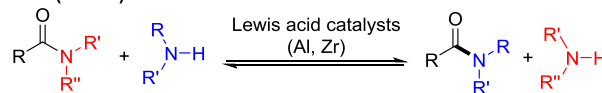
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Supporting Information Placeholder

ABSTRACT: Amides are an important class of organic compounds, which have widespread industrial applications. Transamidation of amides is a convenient method to generate new amides from existing ones. Tertiary amides, however, are challenging substrates for transamidation. Here we describe an unconventional approach to the transamidation of tertiary amides using nitroarenes as the nitrogen source under reductive conditions. Manganese metal alone mediates the reactions and no additional catalyst is required. The method exhibits broad scope and high functional group tolerance.

Amides are ubiquitous in nature and are among the most essential molecules in the chemical and pharmaceutical industries^{1,2} Due to their prevalence and stability, amides are attractive reagents for chemical transformations. Transamidation is a useful method for the diversification of amides.³ However, the amide C-N linkage is unreactive due to resonance stabilization.¹ Various catalytic transamidation methods have been developed, but most of them use primary amides as substrates.^{3,4} A two-step strategy, first conceived by Garg,⁵ is recently employed to transamidate secondary amides by pre-activation with a *tert*-butyloxycarbonyl (Boc) group.⁵⁻⁷ On the other hand, the transamidation of tertiary amides remains challenging due to the steric hinderance around their C-N linkage and no possibility for pre-activation of the nitrogen groups. Only several reports of Lewis acid-mediated or -catalyzed transamidation of tertiary amides are known, however, the scope is narrow.⁸⁻¹⁰ For example, Stahl, Gellman, and co-workers developed Al- and Zr-catalyzed transamidation of tertiary amides, but only *N,N*-dialkyl amides were suitable substrates, and the reactions yielded an equilibrium mixture of reactant and product amides (Figure 1a).¹⁰ An efficient and general method for transamidation of tertiary amides remains hitherto elusive.

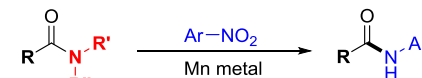
(a) Previous examples of transamidation of tertiary amides with amines (Ref 10)



R = alkyl, aryl R', R'', R, R' = alkyl

- limited scope, handful of examples
- equilibrium mixtures of amide reactants and products

(b) Mn-mediated reductive transamidation of tertiary amides with nitroarenes (this work)



- R = alkyl, aryl R', R'' = alkyl, aryl
- broad scope, high functional group tolerance
 - No equilibrium mixture

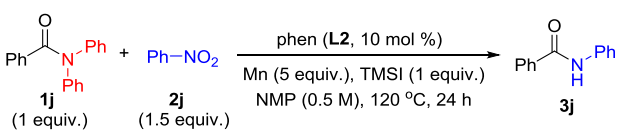
Figure 1. Methods of transamidation of tertiary amides.

To overcome the difficulties in the transamidation of tertiary amides, we decided to employ nitroarenes instead of anilines as the incoming amine reagents. We showed earlier that under reductive conditions the intermediates formed by partial reduction of nitroarene, e.g., nitrosoarene, azoxyarene, and azoarene, could engage in efficient C-N bond forming reactions,^{7,11a-11c} including the transamidation of Boc-activated secondary amides.⁷ We reasoned that since anilines were not involved, the problem of yielding an equilibrium mixture of reactant and product amides, as observed in the Lewis acid-catalyzed transamidation of tertiary amides,¹⁰ could in principle be avoided. Moreover, compared to anilines, nitroarenes are generally more accessible, more stable, and less costly.^{7,11} Here we report the development of a Mn-mediated method that fulfills these promises and is efficient and general for the transamidation of tertiary amides (Figure 1b).

The transamidation of *N,N*-diphenyl benzamide (**1j**) with nitrobenzene (**2j**, 1.5 equiv.) was used as the test reaction (Table 1). Using the conditions previously employed for transamidation of Boc-activated secondary amides with nitroarenes,⁷ that is, Ni(glyme)Cl₂ (10 mol%; glyme = ethylene glycol dimethyl ether) as catalyst, terpyridine (10 mol %; terpy, **L1**) as ligand, Mn as reductant (5 equiv.), iodotrimethylsilane (1 equiv.; TMSI) as additive, and *N*-methyl-2-pyrrolidone (NMP) as solvent, the transamidation was actually successful, giving the desired amide product, *N*-phenyl benzamide (**3j**), in 81% yield (Figure 2). A control experiment then

showed that a yield of 64% was obtained in the absence of Ni(glyme)Cl₂ catalyst (Figure 2). We then optimized the Mn-mediated transamidation of **1j** with **2j**. By changing ligand **L1** to 1,10-phenanthroline (phen, **L2**), and increasing the reaction time to 24 h, the yield of **3j** was increased to 80% (Table 1, entry 1). The use of chlorotrimethylsilane (TMSCl) instead of TMSI, **L1** or 2,2'-dipyridyl (**L3**) instead of **L2**, lower loading of Mn (4 equiv.) or TMSI (0.5 equiv.) all led to a modest reduction of yields (Table 1, entries 2-6). Other metal reductants such as zinc, copper, and iron were not effective (Table 1, entries 7-9). Without **L2**, the yield was slightly lower (Table 1, entry 10). As shown below for a few other substrates (Figure 3, **3h**, **3k**, **3m**, **3p**; Figure 5, **3m**), the use of **L2** led to 8-25% higher transamidation yields compared to ligand-less conditions. Thus, **L2** was used for the general protocol to favor the yields. A ligand-less protocol might be more advantageous for specific substrates or applications, but it was not further explored here.

Table 1. Optimization of Mn-mediated transamidation with nitrobenzene^a



Entry	Variations from 'standard conditions'	Yield of 3j % ^b
1	No variation	80
2	TMSCl (1 equiv.) instead of TMSI	67
3	L1 instead of L2	72
4	L3 instead of L2	71
5	Mn (4 equiv.) instead of (5 equiv.)	73
6	TMSI (0.5 equiv.) instead of (1 equiv.)	69
7	Zn (5 equiv.) instead of Mn	0
8	Cu (5 equiv.) instead of Mn	0
9	Fe (5 equiv.) instead of Mn	0
10	No L2	73

(a) 0.25 mmol of **1j** was used for screening of conditions. (b) GC yield of **3j** using *n*-dodecane as an internal standard.

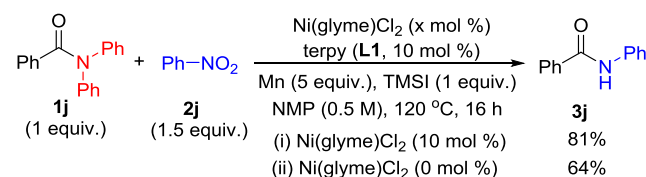


Figure 2. Discovery of Mn-mediated transamidation of tertiary amide with nitrobenzene.

This transamidation method proved to be general (Figures 3-5). A wide range of *N,N*-diaryl and *N*-alkyl-*N*-aryl amides (Figure 3, **AA-1** to **AA-8**), amides bearing heterocycles (Figure 4, **H1-H5**), and *N,N*-dialkyl amides (Figure 5, **DA-1** to **DA-6**) all reacted smoothly with nitroarenes to give the *N*-aryl amide products in good to excellent yields. Electron-rich (**3i**, **3l**, **3w**, **3x**) -neutral (**3j**, **3n**), -deficient (**3m**, **3r**, **3v**, **3y**), and sterically

congested aryl groups (**3ak**), heteroaryl groups (**3o**, **3p**, **3z**), secondary cyclic alkyl groups (**3f**, **3g**, **3aj**, **3al**), as well as primary (**3aa**, **3ab**) and tertiary alkyl groups (**3ao**) could be transferred from the starting to the final amides. Amides substituted by electron-rich (**3e**, **3f**, **3h**, **3o**, **3p**, **3v**, **3x**, **3ah**, **3al**), -neutral (**3j**), -deficient (**3b-3d**, **3n**, **3ab**), and sterically bulky (**3l**) aryl groups, as well as heteroaryl groups such as pyrrole (**3a**), benzodioxole (**3g**), pyridine (**3k**), carbazole (**3w**), benzothiophene (**3ae**), benzoxazole (**3af**), pyrazole (**3ag**), and quinoline groups (**3an**) could be accessed from the corresponding nitro(hetero)arenes. The transamidation method tolerated a wide range of functional groups from both amide and nitroarene partners, such as sulfonamide (**3b**), chloro (**3c**, **3y**, **3ac**, **3ai**), nitrile (**3d**), amino (**3e**, **3o**, **3v**, **3x**), thio (**3ah**, **3al**), fluoro (**3v**, **3ab**), bromo (**3ad**), olefin (**3h**, **3aa**), keto (**3am**) moieties. The protocol allowed gram-scale transamidation without significant diminishment of yield (**3z**).

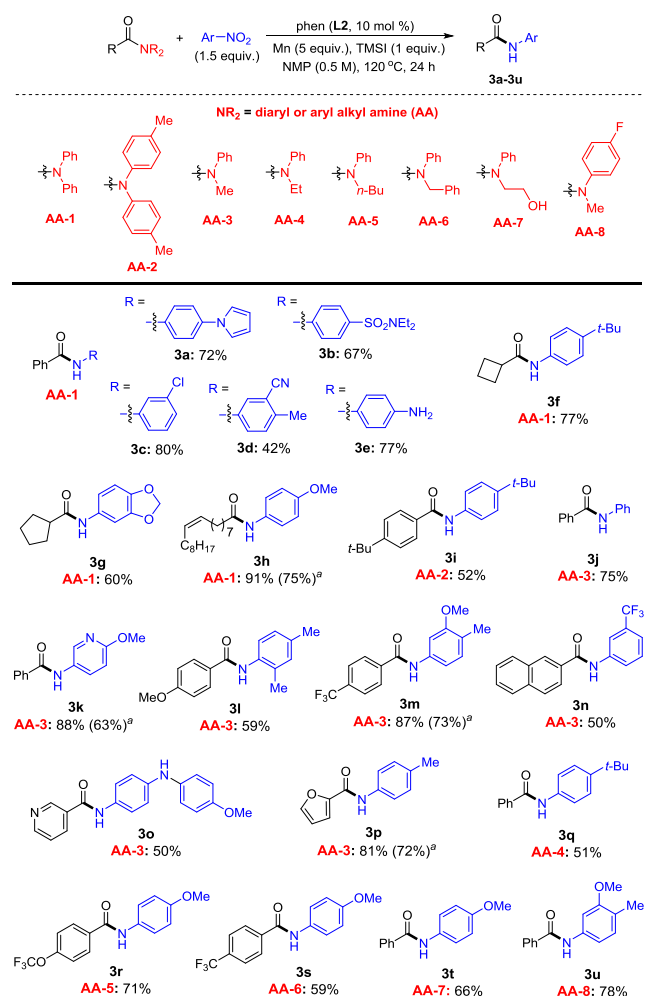


Figure 3. Transamidation of *N,N*-diaryl and *N*-alkyl-*N*-aryl amides with nitroarenes. Isolated yields were shown. (a) Reaction without the addition of phen ligand.

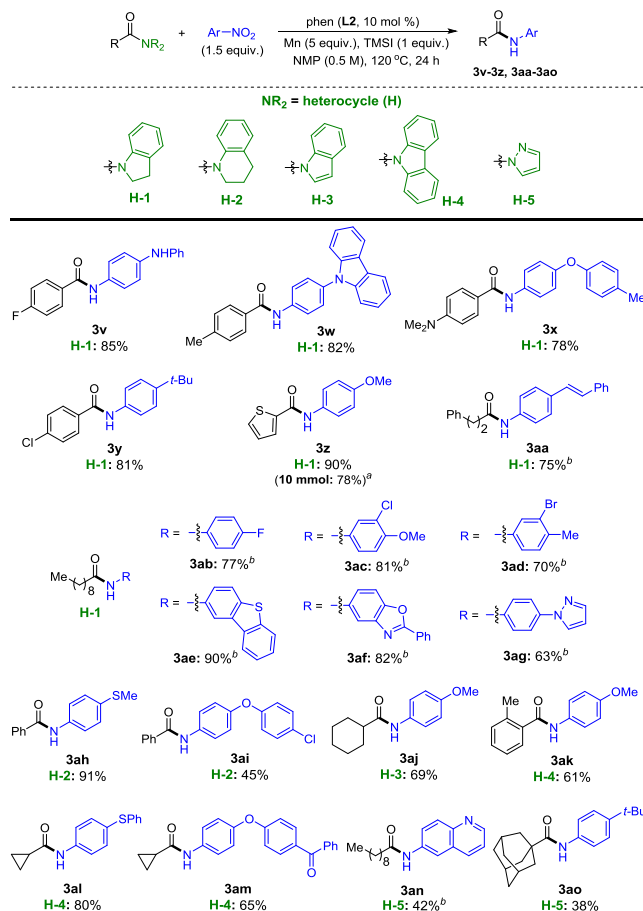


Figure 4. Transamidation of tertiary amides bearing heterocycles with nitroarenes. Isolated yields were shown. (a) 2 days. (b) 16 h.

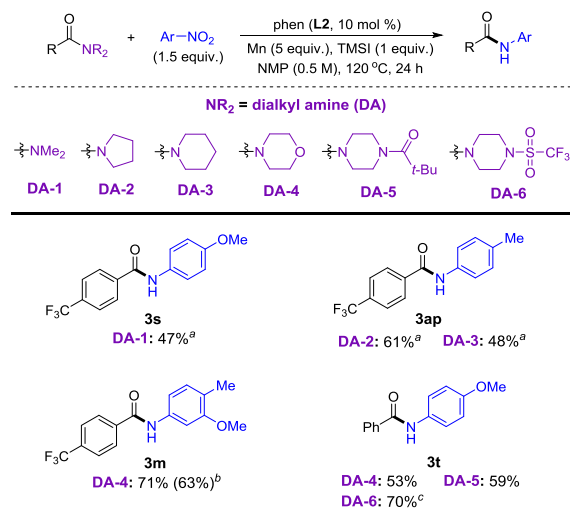


Figure 5. Transamidation of *N,N*-dialkyl amides with nitroarenes. (a) ArNO₂ (3 equiv.), phen (20 mol %), Mn (10 equiv.), TMSI (2 equiv.). (b) Reaction without the addition of phen ligand. (c) 2 days.

The transamidation method was successfully applied to the modification of a bioactive amide **S12**, which was an inhibitor of leukemia cell line,¹² to give a new amide **4a** in 42% yield (Figure 6a). The method was also applied to make an antimicrobial agent **4b**¹³ in 80% yield from a tertiary amide (Figure

6b). These examples highlight the potential utility of this method in medicinal chemistry.

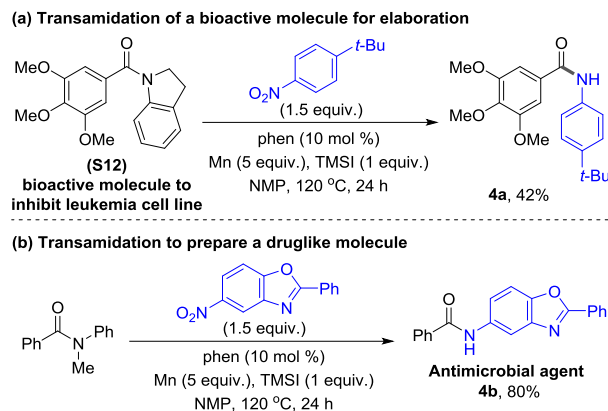


Figure 6. Applications of the present transamidation method in medicinal chemistry.

Although an ultrapure Mn powder (99.9%) was used in this method, a trace amount of Ni (11.6 ppm) and Pd (5.6 ppm) was detected by atomic absorption spectroscopy. To probe the possible catalytic role of these trace metals in the transamidation, a catalytic amount of NiCl₂ or PdCl₂ (2 mol %) was added intentionally to the reaction system. Slightly lower yields of **3m** were obtained (Figure 7, (ii) and (iii)) compared to the parent reaction (87%, Figure 7, (i)). When a lower grade of Mn (97%) was used, **3m** was obtained in a similar yield (82%, Figure 7, (iv)) to the parent reaction. These results suggest that trace amounts of Ni or Pd were unlikely the catalysts for the transamidation.

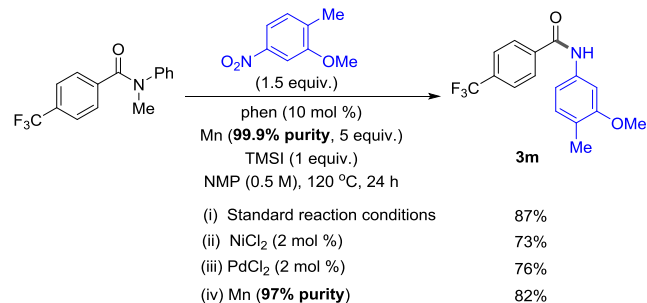


Figure 7. Effect of trace metals and purity of Mn on transamidation.

During the transamidation, nitrobenzene could be reduced to nitrosobenzene, *N*-phenyl hydroxylamine, azobenzene, and anilines under the reductive conditions.^{7,11a-11c} To probe their potential roles as intermediates in transamidation, the reactions of these species with tertiary amide under conditions relevant to the transamidation were monitored. When nitrobenzene **2j** was used as the substrate, the transamidation had a yield of 80% (Table 1, entry 1). When *N*-phenyl hydroxylamine or aniline was used as the substrate, no transamidation occurred (Figure 8, (i) and (ii)). Thus, *N*-phenyl hydroxylamine and aniline are unlikely intermediates. When nitrosobenzene was used as the substrate and in the presence of 2 equiv. of Mn, the yield of transamidation was 30%, while azobenzene was formed as a byproduct in 50% yield (Figure 8, (iii)). When 4 equiv. of Mn was used as reductant for the reaction with nitrosobenzene, the yield of

transamidation was improved to 74% (Figure 8, (iii)). These results suggested that nitrosoarene was a possible intermediate, but likely through a further reduction to azobenzene. Indeed, in the absence of an amide substrate, 3 equiv. of Mn was sufficient to reduce nitrobenzene to azobenzene in 61% isolated yield. This reduction required TMSI, which might serve to deoxygenate nitrobenzene. Azobenzene was then tested as the substrate. In the presence of only 2 equiv. of Mn and 10 mol% TMSI, a high yield of 86% for transamidation was achieved (Figure 8, (iv)). If TMSI was omitted, the transamidation had an even higher isolated yield of 91%. Thus, TMSI is not necessary for the Mn-mediated reaction of azobenzene with an amide to form a new amide. Taking together, these results all support azobenzene as an active intermediate in the transamidation. The mechanism of the reaction is subjected to a further, dedicated study.

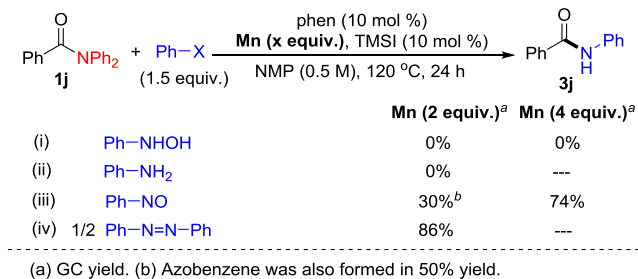


Figure 8. Evaluation of the nitrogen-containing intermediates derived from nitrobenzene for transamidation.

In a few cases (e.g., **3d**, Figure 3), the yields of transamidation were lower than 50%. Although anilines were excluded as the general intermediates, it was possible that for the combinations of substrates leading to lower yields, anilines were produced and the transamidation suffered from equilibration. To probe this possibility, the starting amide (**1d**) was treated with the aniline analogue of the nitroarenes partner under the transamidation conditions, but no transamidation occurred (Figure S1). Moreover, **3d** was treated with 2 equiv. of diphenylamine under the transamidation conditions. If equilibration was operative, then a certain amount of **1d** would be generated. However, no formation of **1d** was observed. Similar experiments were conducted for the case of **3t** (**DA-4**, Figure 5), where the transamidation yield was modest (53%). Again, neither forward nor reverse transamidation occurred with aniline and dialkylamine, respectively (Figure S1). These results exclude anilines as intermediates for reactions where the yields were modest. Instead, the lower yields of those reactions might be attributed to steric hindrance for bulky substrates (**3ak**, **3l**, **AA-6**) or competitive binding of metal ions by coordinative functional groups (**3o**, **3d**, **3ag**, **3an**, **H-5**).

In conclusion, an efficient and broad-scope method for transamidation of tertiary amides has been developed. The method employs readily available nitroarenes as amine surrogates and inexpensive Mn metal as reductant. A wide range of electronically and sterically unbiased tertiary alkyl and aryl amides are suitable substrates. High functional group tolerance is achieved on both the amide and nitroarene reaction partners. The method can be used for the rapid derivatization of tertiary amides, which has potential applications in medicinal and materials chemistry. Azoarene was identified as a likely intermediate for transamidation.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Experimental and spectral data (PDF).

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Notes

The authors declare no competing financial interests.

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