Chemical Papers (2023) 77:4057–4084
https://doi.org/10.1007/s11696-023-02772-w

REVIEW

Recent advances in transamidation of unactivated amides

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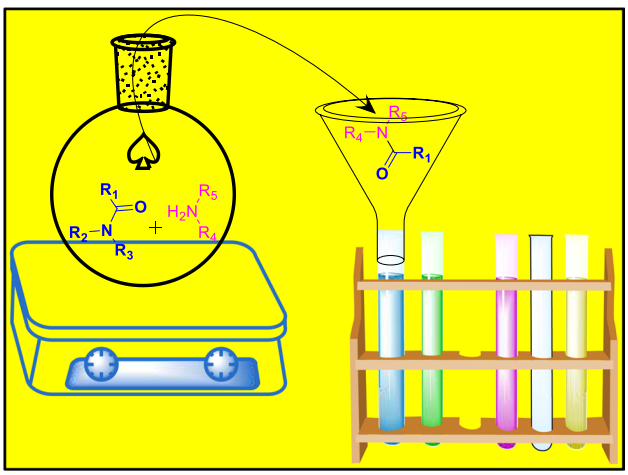
Received: 12 May 2022 / Accepted: 3 March 2023 / Published online: 30 May 2023

Abstract

In recent years, transamidation has been an essential topic in the formation of amide bonds over the conventional route due to chemoselectivity and greenside products. So many groups have disclosed new amide transformation techniques. Transamidation is typically classified into two categories based on amide activation: activated amide and unactivated amide. We conducted a review of the pertinent literature that discusses the cross amidation reactions of unactivated amides employing a variety of reagents, enabling contemporary research professionals to overcome synthetic barriers.

Graphical abstract



Keywords Catalyst · *N*-Formylation · *N*-Acetylation · Transamidation · Unactivated amides

Introduction

Amides are also known as carboxamides, an organic functional group in which amine is directly linked to the carbonyl carbon having the general structure "R^1–CO–NR^2R^3", whereby the variables R^1, R^2 and R^3 can be any organic groups or a hydrogen atom (Acosta-Guzmán et al. 2018; Kolympadi Marković et al. 2020). Amides and their analogues are widely present in biomolecules (Mahesh et al. 2018), natural products (Marchetti et al. 2019), pharmaceuticals (Viveiros et al. 2019; Santos et al. 2020), drugs (Dorr and Fuerst 2018), polymers (Papadopoulos et al. 2020). The amide unit contains drugs that display anthelmintic,

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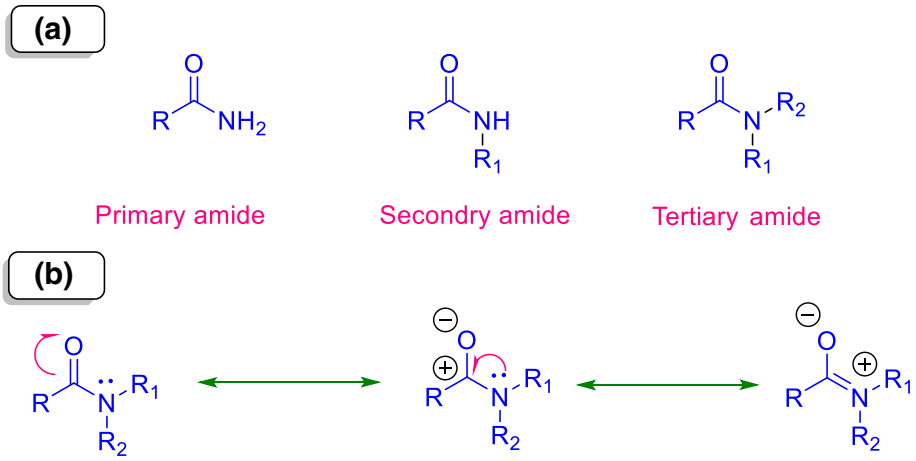


Fig. 1 Category and resonance structures of amides

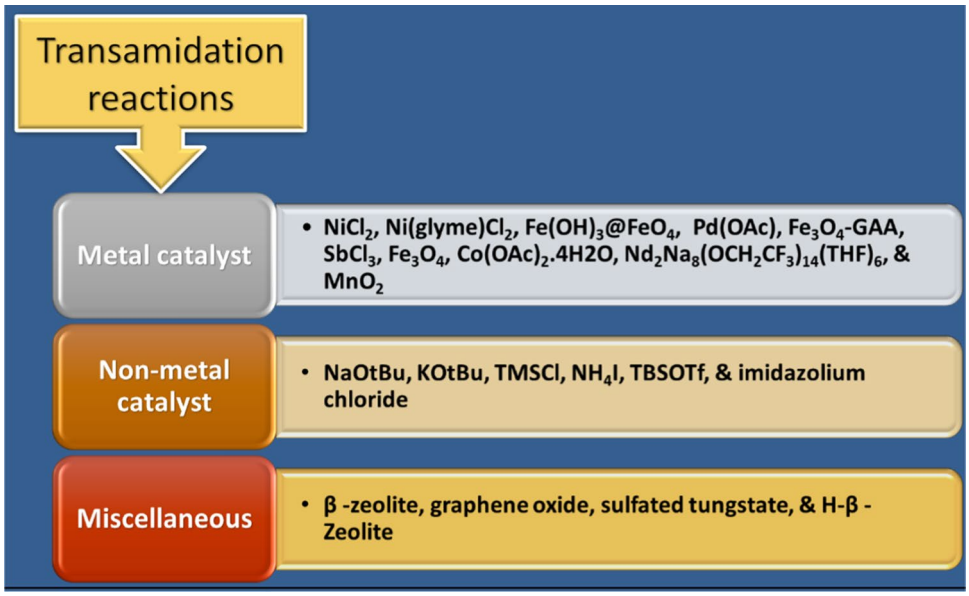
antitumor, antifungal, antispasmodic, herbicide, insecticide, and antibacterial activity (Chaudhari and Gnanaprakasam 2019; Petchey and Grogan 2019; Szostak and Szostak 2019). In biomolecules such as proteins, amides are the key components used to connect two amino acids known as peptide linkages (Miyanaga et al. 2018).

Based on the substituents on the nitrogen atom of amide, they are categorised as primary, secondary and tertiary amides (Fig. 1a). Because of its intermolecular hydrogen bonding (Abraham and Abraham 2017; Han et al. 2017), the order of amides' boiling point and melting point is primary > secondary > tertiary. The amide resonance structure shows the C-N double bond character with its plane geometry (Kemnitz and Loewen 2007), which reveals its stability and inner strength in the presence of other chemical substances (Fig. 1b).

Due to amides' low reactivity, transamidation reactions have been challenging for researchers over the years. Many researchers have activated amides by *N*-substitution of an activated group on the nitrogen atom of amide to boost its reactivity. *N*-tosyl, *N*-Boc, *N*-acetyl, and *N*-triflyl are commonly used as activated groups to activate the unactivated amides. However, this step has disadvantages because it is a two-step reaction, and only primary and secondary amides have predominantly been explored because an activating group can replace the one proton of amide.

On the other hand, multiple groups have published a variety of unactivated amide transamidation approaches utilising various reagents. The main advantage of these approaches is that no activation group is required for the amide transformation. Furthermore, these methods do not produce any side products that may be employed as activating groups. The only byproduct of this coversion is the elimination of amide's amine (Fig. 2). In a single step, these procedures can convert amides into other amides. These methodologies are mostly chemoselective reactions.

Transamidation reagents list



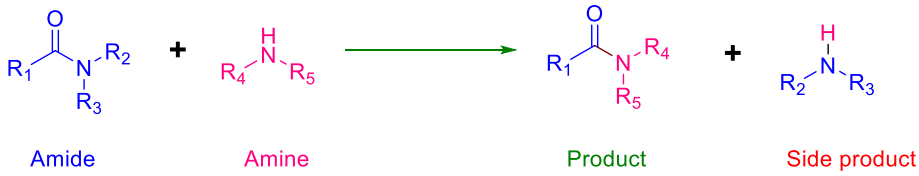


Fig. 2 Unactivated amide reaction

The preceding chart summarises the metal, non-metal, and miscellaneous reagents used to carry out the transamidation reactions discussed in this article.

Literature study

Following that, we discussed a summary of the literature that reported trans amidation reactions, categorising them as metal, non-metal, and miscellaneous catalysts, in which we systematically summarised optimisation studies and reaction scope of all previously covered articles.

Metal catalysed

Gellman and Stahl group demonstrated a metal-catalysed (Sc, Ti and Al metals) transamidation of amides under moderate conditions (Eldred et al. 2003). In 2005, the Stahl group published a report on titanium(IV)-mediated transamidation of unactivated primary amide (Kissounko et al. 2005).

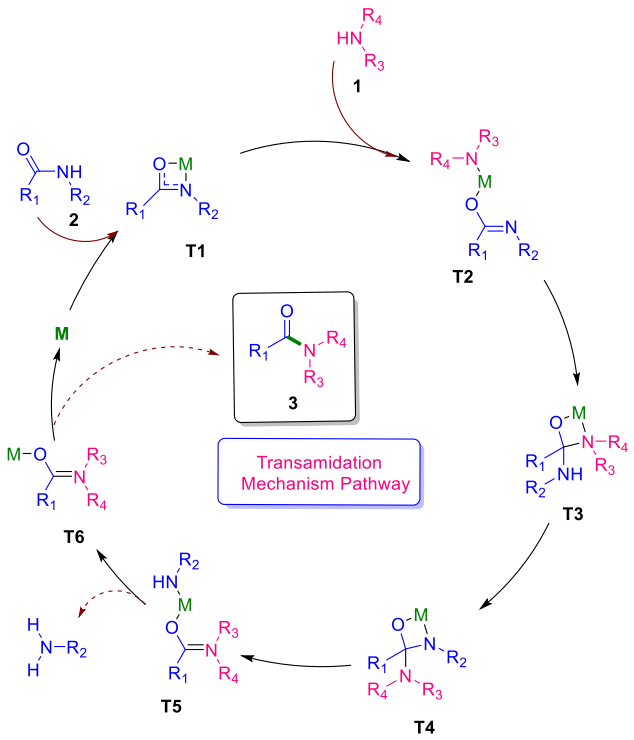


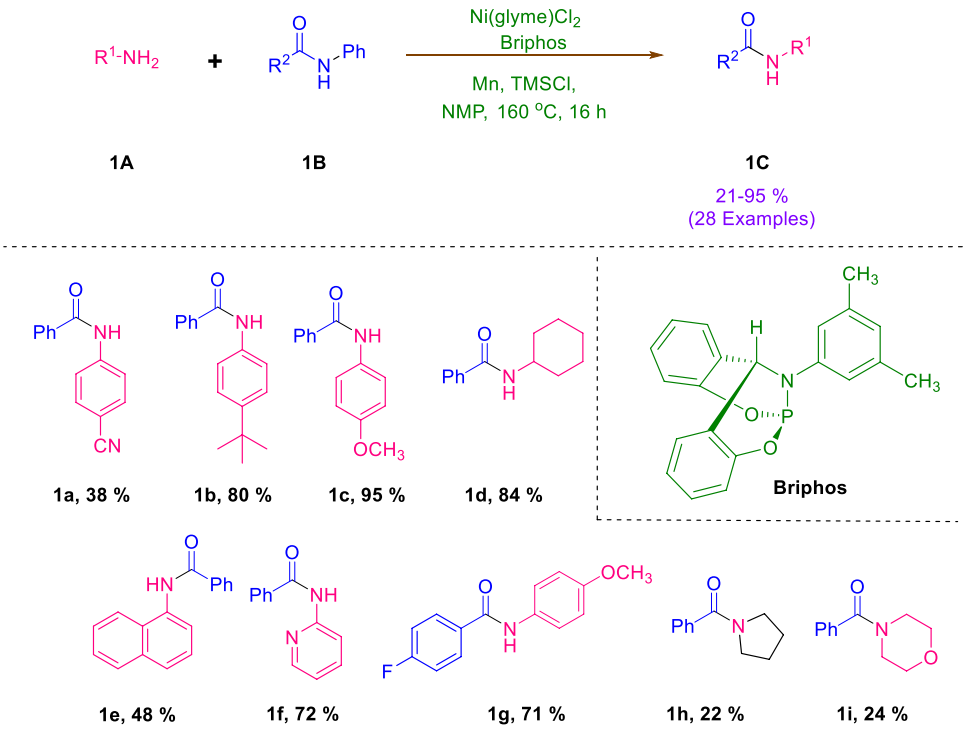
Fig. 3 Proposed metal-catalysed transamidation mechanism pathway between primary or secondary amides with secondary amines

The following year, they explained a mechanistic pathway of secondary carboxamide transformation mediated by metal (aluminium), which had been proven by ^{1}H and C^{13} NMR data (Hoerter et al. 2006, 2008). The next year, the same researchers also concluded a difference between amidine versus amide formation through transamidation of primary amines with secondary amide. They explained how the reaction circumstances affect the transamidation's final product (Kissounko et al. 2007). They published additional research on the Zr-catalyzed unactivated tertiary amide transamidation reaction (Stephenson et al. 2009).

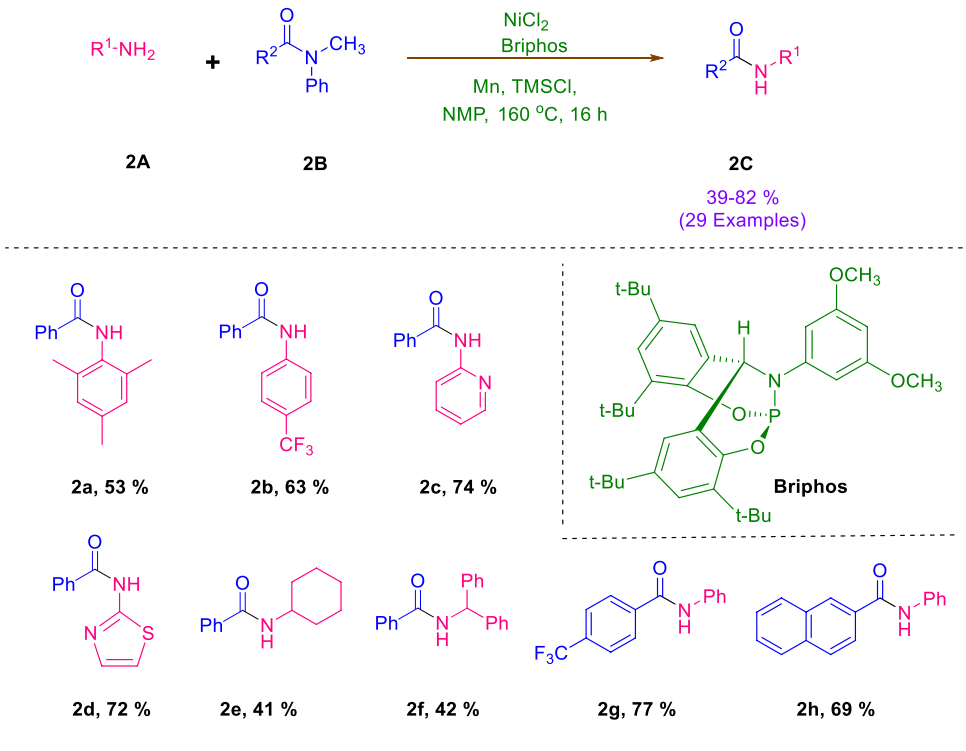
In the metal catalysed transamidation, the metal activates the amides due to its poor electrophilic nature. We proposed a general metal catalyst mechanism to explain the transformation based on previous mechanistic experiments and research (Hoerter et al. 2006, 2008), as shown in Fig. 3. Initially, metal (**M**) activates the amide bond of amide **2** to generate amidate complex **T1**, which can be synthesised from free metal. When the complex **T1** is treated with amine **1**, the Cu–N bond of **T1** is cleaved, resulting in the unstable species **T2**. Usually, basic ligand amines exchange with the amide, resulting in protonated free ligands; it has been proposed in other similar mechanisms. **T2** annulates occur due to intramolecular interactions between the amine nitrogen atom and the carbonyl carbon atom, leading to intermediate **T3**, which is in equilibrium with its isomer **T4**. **T3** can regenerate **T2** in the same way that **T4** can produce **T5** (an isomer of **T2**). As a result, the removal of amine generates the **M** complex species **T6**. Eventually, **T6** splits to give the transamidated product **3,** and the **M** catalyst is used for the next cycle.

Yu et al. (2018) developed a metal-catalysed transamidation reaction between *N*-Phenyl-substituted 2° benzamide and 1° amines (Scheme 1). The researcher examined different nickel catalysts during the optimisation study, but Ni(glyme)Cl_2 showed better conversion. The authors observed that the highest yield of transamidated products was obtained when Briphos-Ni(glyme)Cl_2 was used as the ligand-catalyst combination and NMP as the solvent. They performed reactions of numerous amines with amide under optimised conditions and found that the *para*-substituted anilines showed a much better yield than *ortho* substitutes. However, the reaction had failed with 2,6-diisopropylaniline due to steric hindrance. They reported that hetero-aromatic, bulky anilines and aliphatic amines performed well in this procedure. Moreover, the authors studied the scope of amide

Scheme 1 Ni-catalysed transamidation of 2° benzamide derivatives with amines

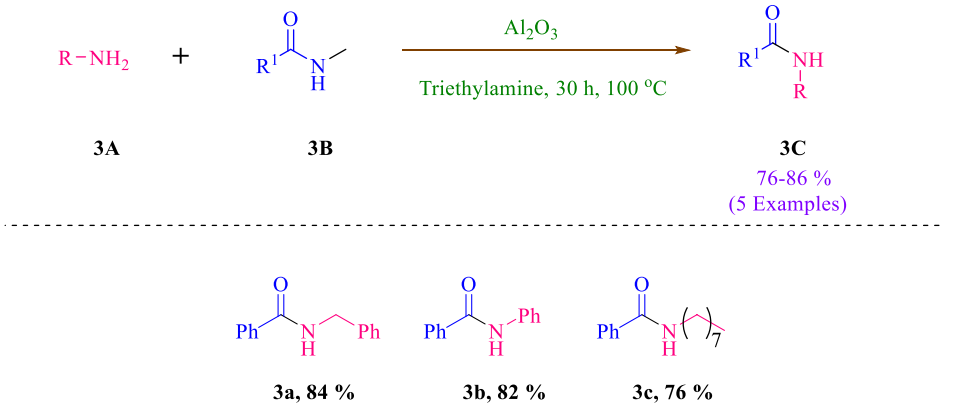


Scheme 2 Ni-catalysed transamidation of 3° benzamide derivatives with amines



by bringing the different substitutions on the phenyl ring and found them compatible under standard conditions. They also tried reaction with 2° amines, which showed a poor yield of the desired product (**1Ch** and **1Ci**). Finally, the author concluded by the control experiment that the electron-donating

Scheme 3 Al-catalyzed transamidation of secondary amide



amine and the electron-withdrawing benzamide have been triggering the reaction.

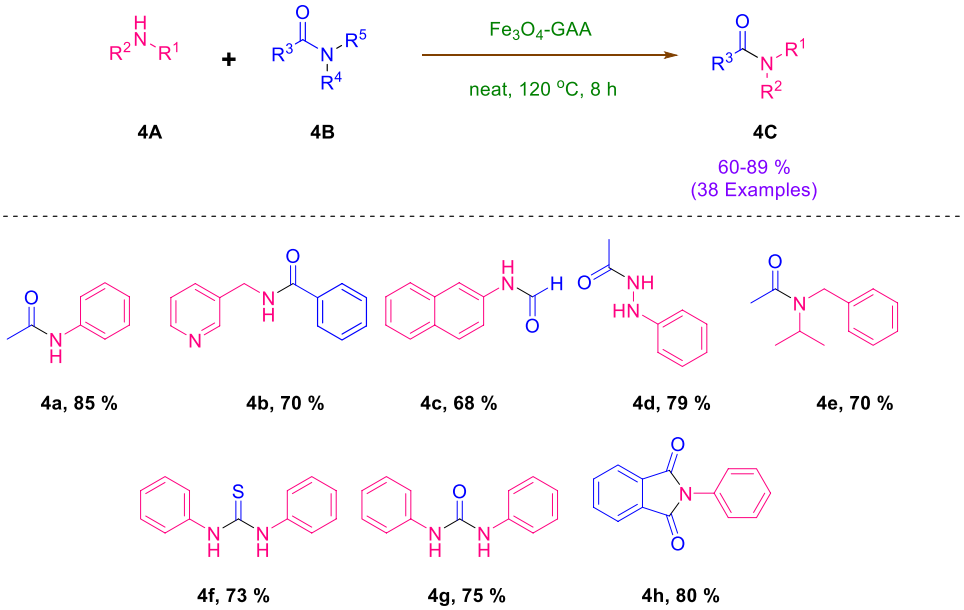
The same group also reported a transamidation of *N*-methyl-*N*-phenylbenzamide derivatives and primary amines using a similar condition (Scheme 2) (Yang et al. 2020). The authors used trimethylsilyl chloride as an activator to investigate several nickel (II) species in the presence of manganese. They concluded from optimisation studies that $NiCl_2$ delivered the best yield with the help of methoxy substituted *t*-Bu-briphos. This method worked well with electron-withdrawing and donating groups substituted aniline. Heterocyclic and aliphatic amines also had yielded a good yield of transamidation products. However, the bulky group substituted aliphatic amines had generated a moderate yield due to steric hindrance. Furthermore, the diversity of amides used in this reaction resulted in moderate to good desired products. The researchers conducted some experiments to demonstrate the relevance of *N*-methyl and *N*-benzyl in activating the amide for this transamidation. In 2021, Qu et al. reported a Ni catalysed transamidation of amides and sulfonamides with nitro compounds via reductive cross-coupling (Qu et al. 2022).

Ali et al. (Ali et al. 2022) established a methodology in which unactivated secondary amides can be converted to another amide (Scheme 3). The researchers observed that a recyclable amphoteric catalyst Al_2O_3 had enhanced the amide scope during this transformation. During catalyst screening, they found Aluminium catalyst performed well as compare to other metal catalyst (Sn, Cu, Nb, Ce and Ti). Several organic solvents investigation were conducted during process optimization, and it was determined that triethylamine as a solvent produced the highest yield of the desired amide product. Additionally, the transition state of the reaction and energy calculated using Gaussian09 software at the DFT level, HUMO, and LUMO. Furthermore, their analysis of the reaction scope concluded that arylamines with electron reach groups yielded more product than electron-deficient groups. In 1994, Bertrand and his team established a aluminium chloride mediated transamidation reaction (Bon et al. 1994). The reaction initiated with aluminium chloride-amine complexes followed by supported transformation of primary, secondary and tertiary amides to another amides.

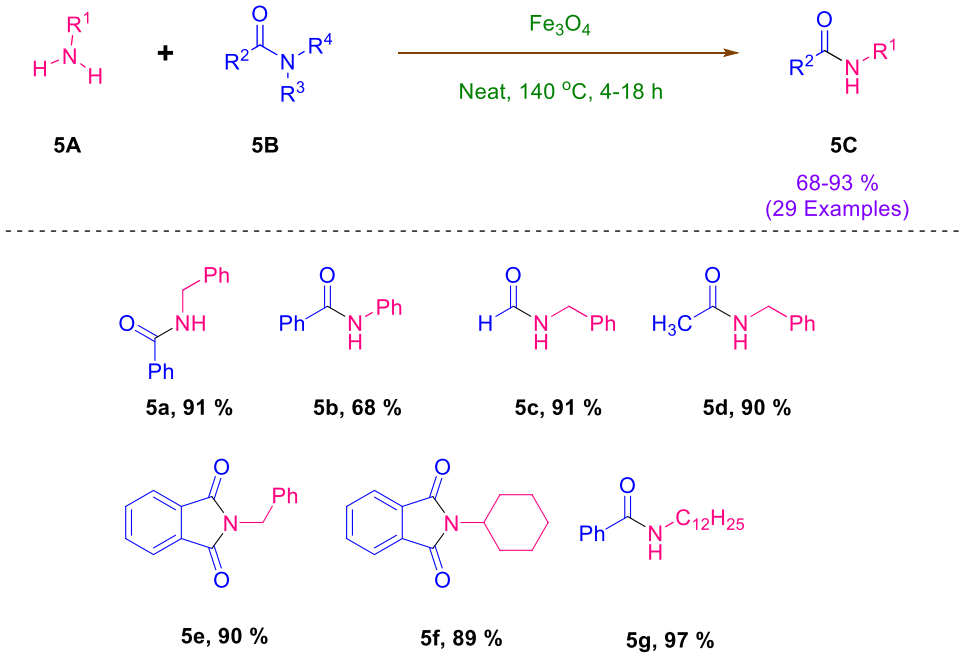
One more methodology of recyclable magnetic nanoparticle of Fe_3O_4-Guanidine acetic Acid (Fe_3O_4-GAA) catalysed transamidation reported by same group (Kazemi Miraki et al. 2016) (Scheme 4). They attached -COOH of guanidine acetic on magnetic nanoparticle during catalyst preparation. In addition, the resultant Fe_3O_4-GAA-immobilised magnetic particle was also confirmed by FT-IR spectra, SEM image, vibrating sample magnetometer, and X-ray diffraction. Catalysts performed effectively in the absence of solvent, according to the researchers. Indeed, they reported that the reaction of electron-donating (OCH_3 and CH_3) and withdrawing (Cl and Br) substituted anilines with acetamide, urea, and thiourea formed targeted amides in good to excellent yields. However, benzamide produced a moderate to a good yield of amide transformation. It's also worth mentioning that this organocatalyst can be re-used up to six times without losing its catalytic activity.

In 2016, another example of unactivated amides being transamidation by iron-mediated was disclosed. Shankarling and colleagues (Thale et al. 2016) synthesized transamide products with the Fe_3O_4 nanocatalyst, which they re-used six times without decreasing its efficiency (Scheme 5). The researchers noted that Fe_3O_4 catalysts performed effectively in the absence of a solvent and produced the desired product in a high yield. However, the outputs of those processes that took place in the presence of solvents were almost useless. Indeed, the additional catalysts Al_2O_3, MgO, and ZnO were also examined, but none of them could compete with Fe_3O_4. They obtained a converted amides yield between 68 and 98% by reacting benzamide with aromatic and aliphatic amines. Interestingly, the yield observation revealed that

Scheme 4 Fe-catalysed transamidation of carboxamides, phthalimide, urea and thiourea



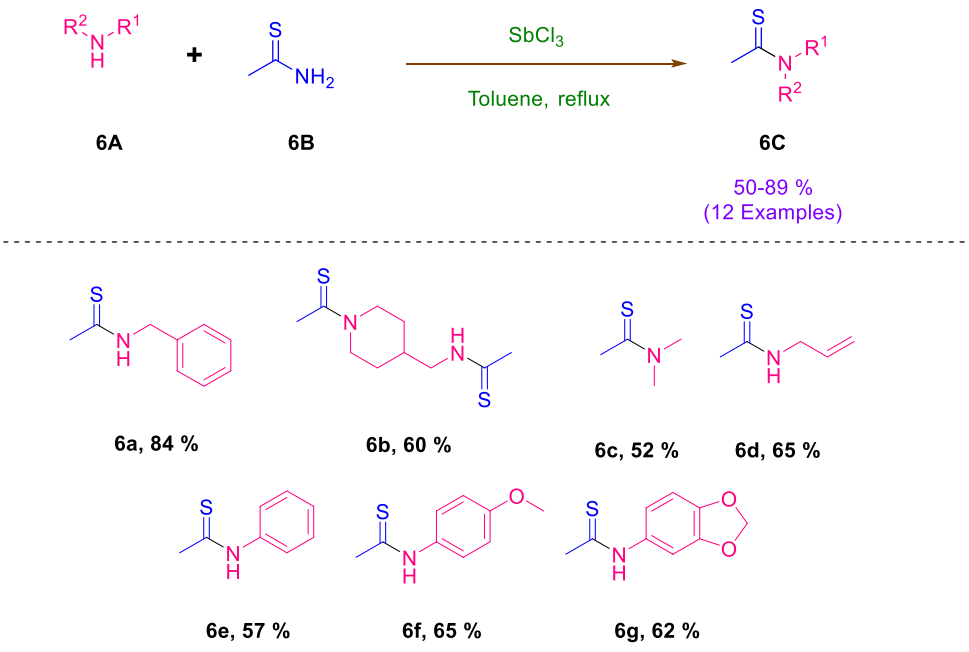
Scheme 5 Fe-catalysed transamidation of carboxamides, phthalimide, urea and thiourea



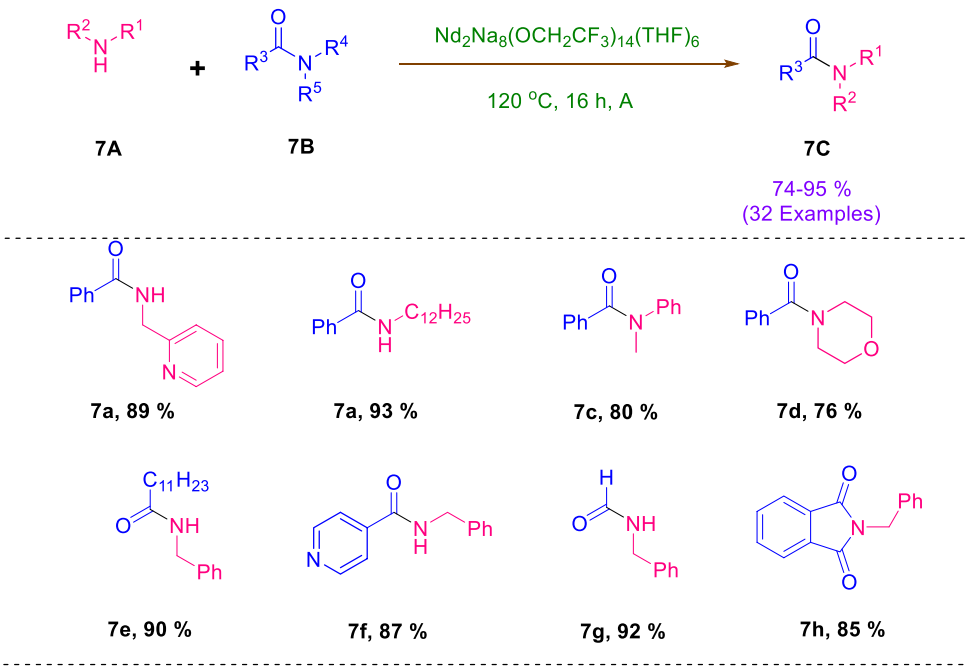
aliphatic amines produced more yield than aromatic amines. It's important to note that they had good results with benzylamine derivatives after transamidation with acetamide, formamide, and phthalimide.

Porras et al. (2015) published their work on cross-amidation between thioacetamide and amines using $SbCl_3$ catalyst (Scheme 6). Thioacetamide was shown to be compatible with both aliphatic and aromatic amines in this study. Furthermore, secondary aliphatic amines were yielded less yield in more time than primary aliphatic amines. However, in the case of aromatic amines, the transamidation results were obtained a moderate to good range. Additionally, aromatic amine conversion takes longer than aliphatic amine conversion. The authors also attempted to broaden the thioamide scope from aliphatic to aromatic, but no changes occurred. They also reported a phthalimide and benzylamine reaction, but the yield was substantially lower after more time was spent on it. Same group also reported a Fe(III)-catalysed transamidation of unactivated carboxamides in the presence of water (Becerra-Figueroa et al. 2014).

Scheme 6 Sb-catalysed transamidation of thioacetamide

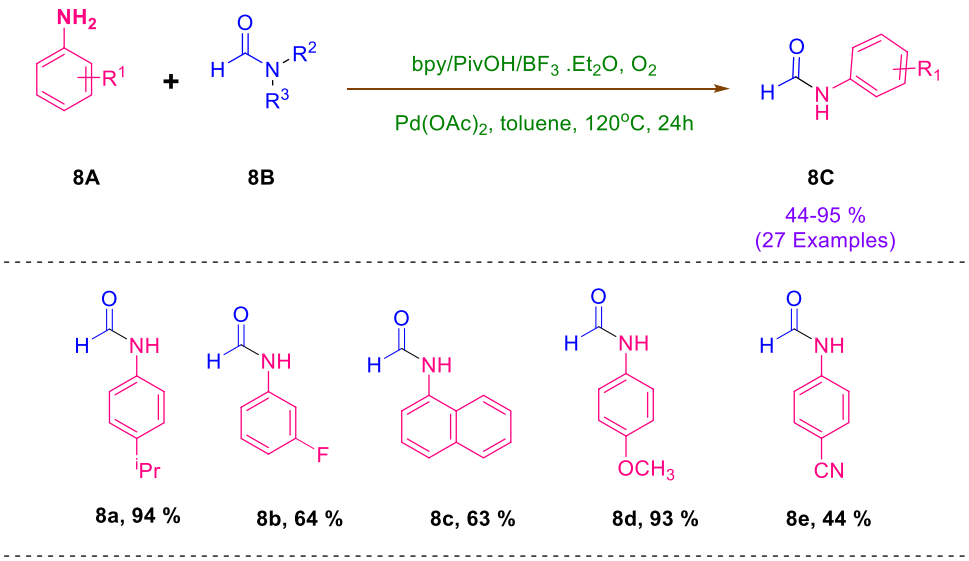


Scheme 7 Multimetallic catalysed transamidation reaction between benzamide and amine



Sheng et al. (2017) got the idea to perform the multimetallic catalysed transamidation reaction after investigating the previous literature (Haak et al. 2010; Delferro and Marks 2011; Valdez et al. 2014; Serrano-Plana et al. 2015) (Scheme 7). Researchers examined different lanthanoids catalysts while standardising reaction conditions and found that $Nd_2Na_8(OCH_2CF_3)_{14}(THF)_6$ was the most effective catalyst. They also observed that heterobimetallic lanthanide/sodium alkoxide complexes performed better during transamidation than monometallic lanthanide complexes. Furthermore, this approach helped researchers to obtain a satisfactory yield of transamidated products from 1° and 2° aromatic, aliphatic, and heterocyclic amines on treatment with a benzamide. Notably, the reported protocol showed that benzylamine and long-chain aliphatic amine were compatible with the reaction of aromatic and heteroaromatic carboxamides. In 2005, Calimsiz et al. (2005) reported a lanthanide-catalysed transamidation reaction

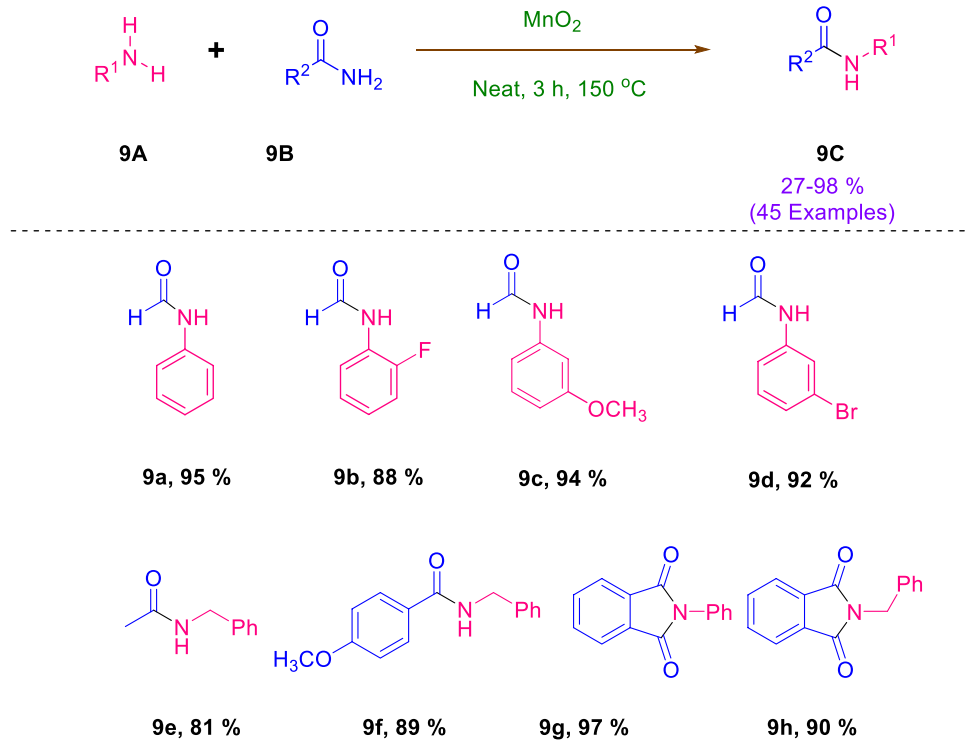
Scheme 8 Pd-catalysed transamidation between carboxamide of DMF and anilines

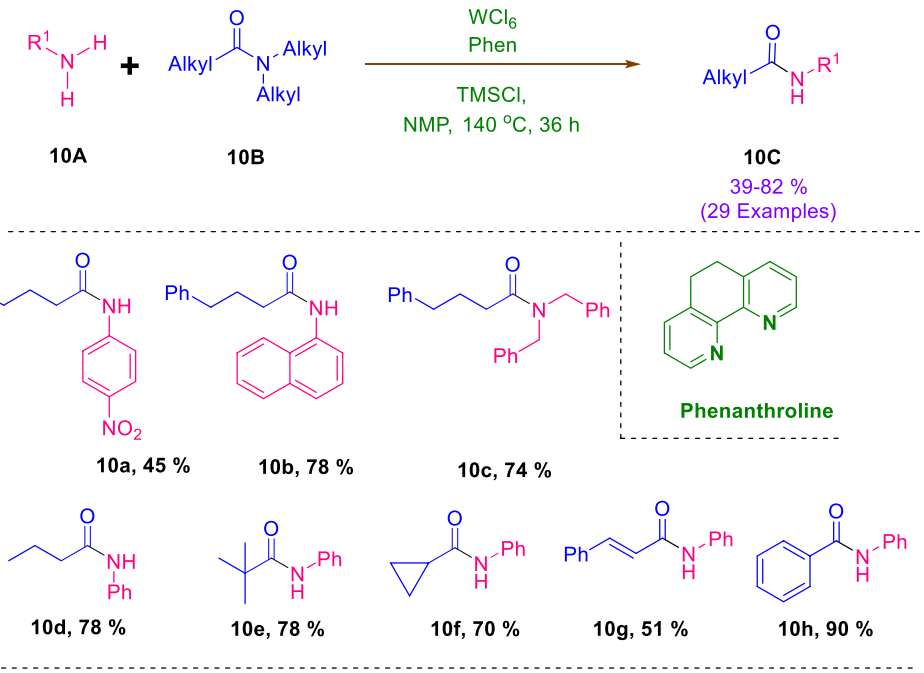


of tert-butyl *N*-Boc-(2S,3S,4R)-dimethylpyroglutamate derivatives. This process provided a selective replacement of a Boc group with Fmoc group on the lactam followed by $Eu(OTf)_3$-mediated transamidation reaction of the Fmoc-protected lactam in the presence of ammonia and dimethylaluminium chloride.

Gu et al. (2015) developed a novel method of palladium catalysed reaction among DMF derivatives and substituted 1° anilines (Scheme 8). The study utilises several ligands and also organic acids and Lewis acids as additives at different temperatures to standardise the reaction. In addition, the optimisation study revealed that the addition of additives has a significant effect on product yield. The electron-donating substituted aniline yielded a higher yield than electron-deficient substituted anilines. Moreover, para-substituted anilines were more comfortable with this transformation than ortho- and meta-substituted. Additionally, the bulky group produced a moderate yield

Scheme 9 Mn-catalysed transamidation of primary carboxamides and phthalimide





Scheme 10 W-catalysed transamidation of tertiary alkyl amides with amines

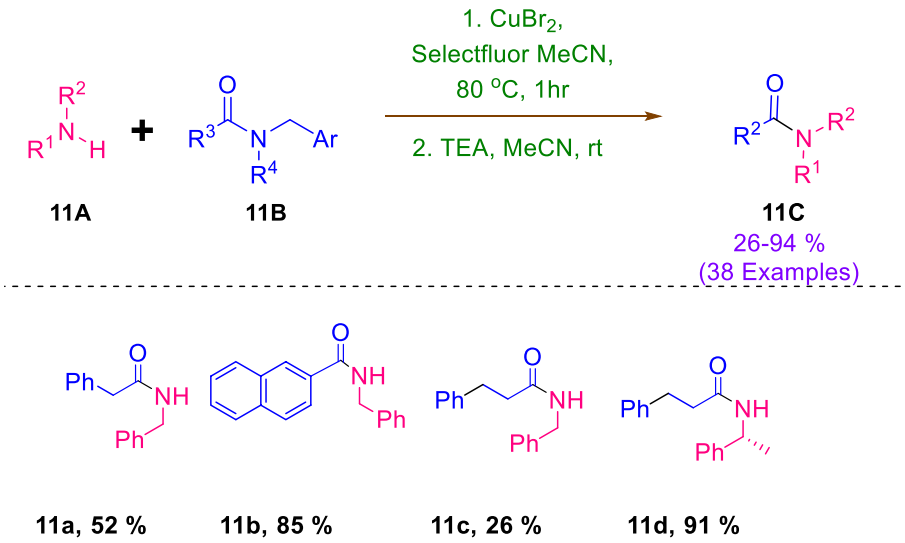
of the desired product due to steric hindrance. Furthermore, formamide derivatives produced moderate to good results in this conversion. The researcher observed that the transamidation yield was lowered due to the bulky replacement on the nitrogen atom of amides. In a subsequent analysis, they tried different amide derivatives with aniline, and the study concluded that formyl derivatives were more compatible than acetyl derivatives.

Bhanage and his colleagues reviewed the literature on manganese oxide applications and found that it is a good oxidant as well as an excellent catalyst in organic reactions (Che et al. 2011; Vanjari et al. 2013; Singh et al. 2014). They established a transamidation method of a broad range of primary amides and amines utilising MnO_2 as a catalyst, based on the previous research (Yedage et al. 2015) (Scheme 9). This process showed excellent tolerance to aromatic amines that were substituted with electron-donating and withdrawing groups during the treatment with formamide. However, ortho-substituted anilines had produced a lower yield than meta- and para-substituted anilines. Similarly, meta and para substitutions were found to be more efficient than ortho substituents during the transformation of substituted benzamides. Furthermore, the protocol showed the compatibility of phthalimides with aromatic and aliphatic amines. As a consequence, the authors were able to scale up their technique to the grams scale and obtain a good yield of transamide product.

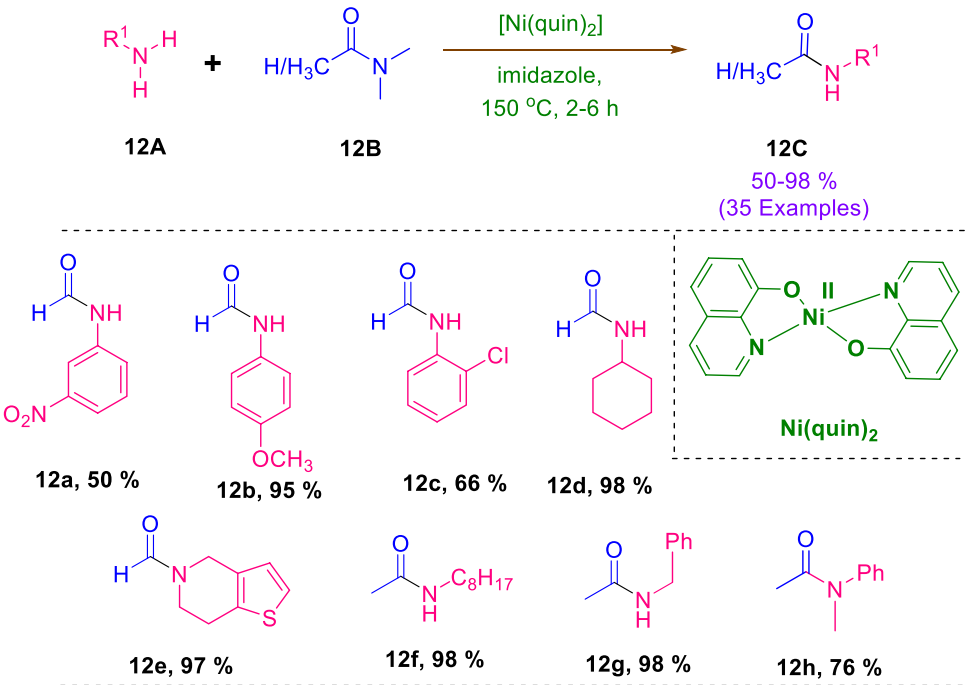
Recently, Feng et al. reported a tungsten-catalyzed conversion of tertiary alkyl amides to another amide in the presence of NMP utilising phenanthroline as a ligand (Feng et al. 2021) (Scheme 10). Compared to other metal catalysts such as Al, Fe, Zr, and Mo, the tungsten catalyst produced the best results during the process optimization study. In addition, the yield was decreased when they performed the experiments in each absence of ligand, catalyst and TMSCl. This approach had a wide scope of anilines containing electron-donating groups (CH_3, OCH_3, SCH_3, CO_2CH_3, *i*-Pr and *t*-Bu), halogen (F, Cl and Br), electron-withdrawing groups (CF_3, CN, NO_2, CO_2H and $COCH_3$) and bulky ring (Naphthyl). Moreover, the aliphatic amines (benzyl, cyclohexyl and cyclopentyl) and heterocyclic amines (indole, pyridine, thiazole and benzothiazole) had also familiar with reaction conditions. Similarly, the various substituted amides had generated transamide products in good to excellent yields. Finally, they concluded from competition studies of primary, secondary, and tertiary amides transamidation that tertiary amides produced more yield than primary and secondary amides. In 2018, the same group reported a manganese-mediated reductive transamidation of unactiavted tertiary amides with nitroarenes (Cheung et al. 2018).

Maruoka and his group reported a selective radical abstraction transamidation of a tertiary amides by a $CuBr_2$/Selectfluor hybrid system (Wang et al. 2020). This reaction proceeded via a radical pathway that involved benzylic carbon radical generated by the selective radical-polar crossover process that involves benzylic carbon radicals in a one-pot fashion (Scheme 11). The observation indicated that $CuBr_2$ and selectfluor system performed well under inert atmosphere at 80 °C to room temperature. The approach uses a wide range of amine substrates, including both electron-withdrawing and electron-donating groups. In 2022, Our group reported a Cu-promoted transamidation of unactivated

Scheme 11 Cu-catalysed transamidation of tertiary amides with amines



Scheme 12 Ni-catalysed transamidation of DMA and DMF with amines

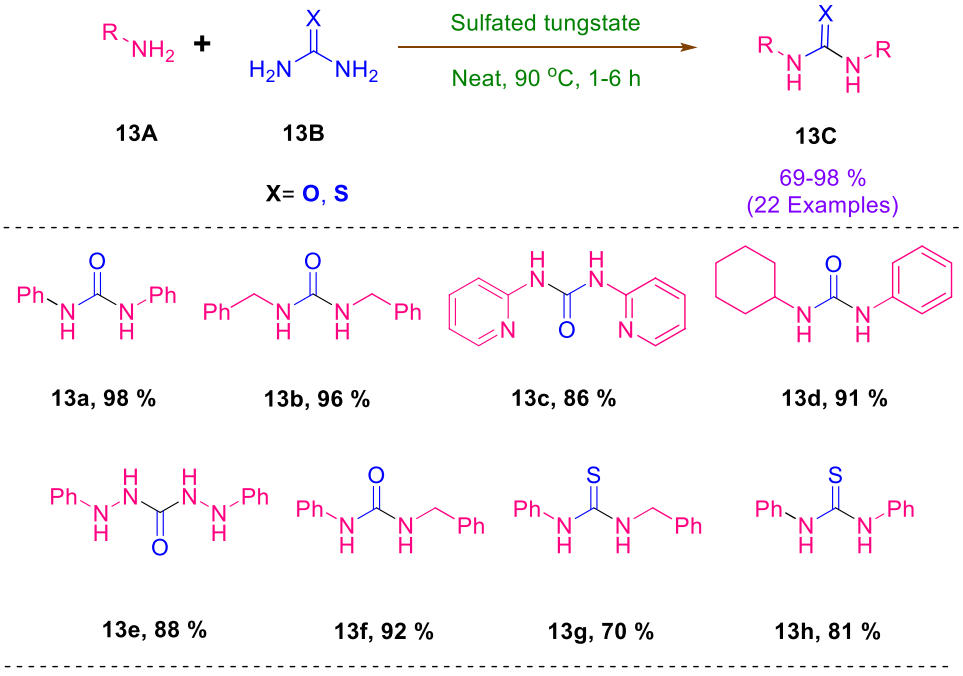


aliphatic amides using TMSCl as a additive (Kumar et al. 2022a, b).

In April 2017, another example of Ni-catalyzed transamidation conversion of DMF and DMA came to light. Sonawane et al. found that a Ni (II)-metal complex with 8-hydroquinoline [Ni(quin)$_2$] was an excellent catalyst for the *N*-formaylation and *N*-acylation of various amines with DMF and DMA (Sonawane et al. 2017) (Scheme 12). The catalyst is efficiently transformed into another amide in the presence of imidazole. Interestingly, the reaction conditions were found to be feasible and did not necessitate the use of an inert atmosphere. The technique is quite versatile since it may be used to *N*-formylate and *N*-acylate of electron-withdrawing (F, Cl, Br, and NO_2) and electron-donating (CH_3 and OCH_3) substituted anilines. Notably, both amide transformations are compatible with linear, cyclic, and heterocyclic aliphatic amines. It has been noted that when electron-withdrawing groups substituted anilines are utilized as coupling partners, the yield is often lowered.

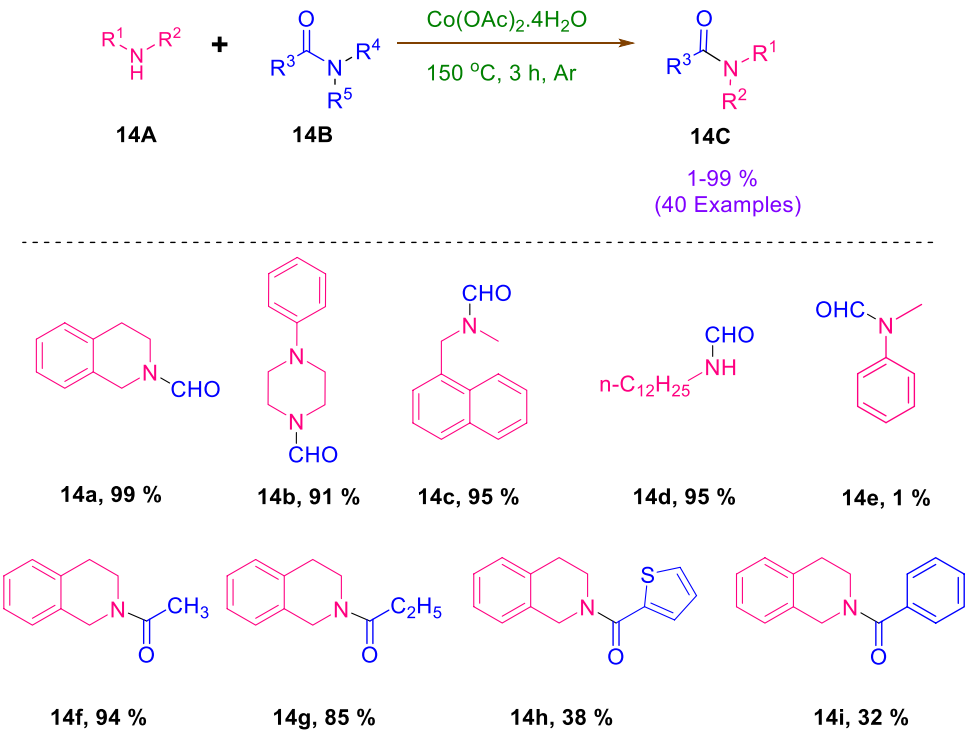
Pathare et al. (2013), Wagh et al. (2018) promoted a transamination of urea and thiourea in the presence of heterogeneous catalyst sulfated tungstate; they recycled and

Scheme 13 Sulfated tungstate catalysed transamidation of N-substituted urea and thiourea

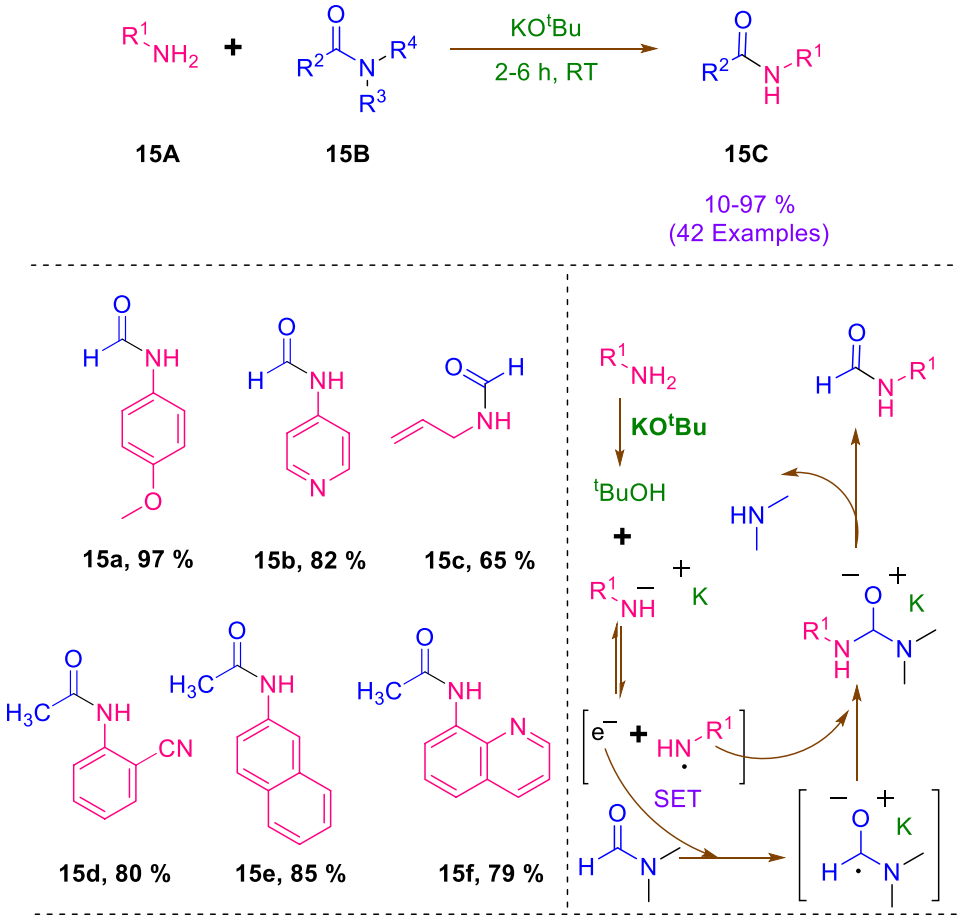


re-used the catalyst 4–5 times without losing efficiency (Scheme 13). After the optimisation study, they obtained 98% of desired urea on the neat reaction between aniline and urea in the presence of 10 wt% of sulfated tungstate at 90 °C within 1.5 h. The method produced transamide symmetrical and unsymmetrical ureas and thioureas from unsubstituted and monosubstituted ureas and thioureas. The researcher obtained an excellent yield of symmetrical and unsymmetrical ureas under the set condition from reacting aniline, aliphatic amines, hetero amines and aryl hydrazides with unsubstituted and monosubstituted ureas. They also

Scheme 14 Cobalt catalysed *N*-formylation and *N*-acetylation reaction



Scheme 15 KO^{t}Bu mediated transamidation reaction of primary and secondary amide



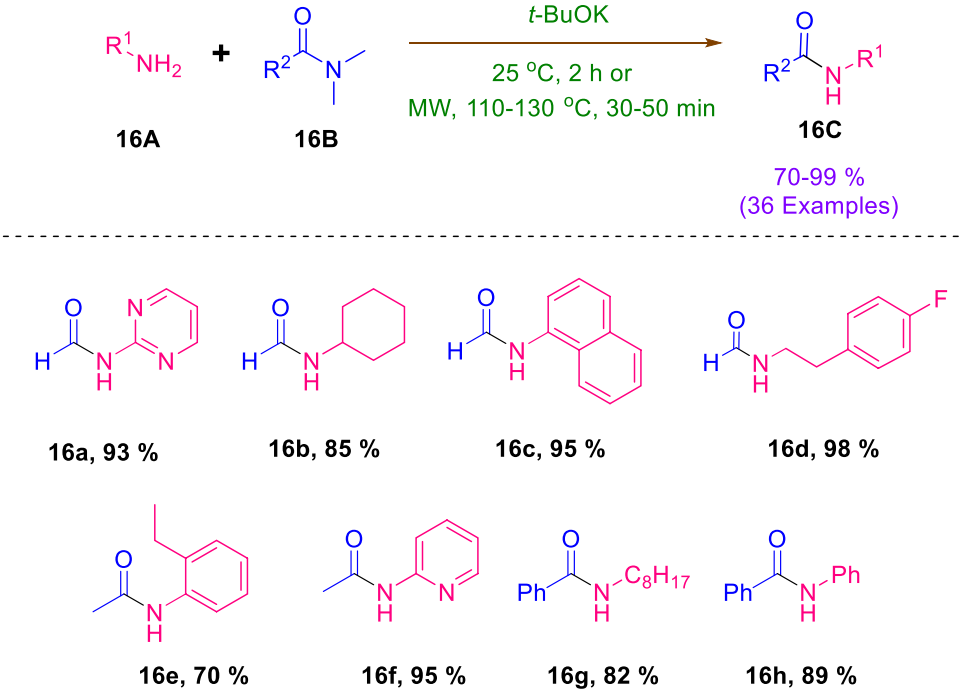
confirmed the similar kind of reactivity of thioureas against different amines.

Ma et al. (2018a, b) used cobalt catalyst to perform *N*-formylation and *N*-acetylation of a variety of amines and carboxamides (Scheme 14). Prior to selecting cobalt catalysts, they screened a variety of transition metal catalysts, including Ni, Cu, Mn, and Fe, of which Co catalyst was found to be the most prevalent for obtaining the best results. This study systematically examined the scope of amines and carboxamides. They formylated 1° and 2° aliphatic amines, and the results indicated that 1° aliphatic amines produced an excellent yield of product. They observed that aromatic amines have no reactivity. Further, the amide scope revealed a predominance of formylation over acetylation; benzamide and thiophen amide exhibited significantly lower reactivity. In 2019, Same group established a $MnCl_2.4H_2O$ promoted transamidation of amides with aliphatic amines (Ma et al. 2019). The reaction performed under inert atmosphere at 150 °C for 10 h.

Non-metal catalysed

Ghosh et al. (2019) reported a strong base potassium *tert*-butoxide mediated transamidation of primary and tertiary amides. Initially, they tried readily available inorganic bases viz KOH, K_2CO_3, Cs_2CO_3, KO^{t}Bu, DBU, and NaOH. Among them, KO^{t}Bu showed the best-desired product yield. They claimed that this method supported amines including aryl, heteroaryl and aliphatic amines, transamidation with amides such as DMF and DMA (Scheme 15). Moreover, the yield observation concluded that the electron-withdrawing group substituted aniline took place more time with less yield as the comparatively electron-donating group substituted aniline. Furthermore, the method features broad substrate scope of amides, including DMA, DMF, trifluoroactamide and benzamide. Finally, they concluded from mechanistic studies that the transmaidtion proceeded through a free-radical pathway.

Tan et al. reported one more t-BuOK-mediated methodology for transamidation of tertiary amide in the same year (Tan et al. 2019) (Scheme 16). The transamidation of DMF proceeds smoothly in the presence of t-BuOK as a base (4.0 equiv) and DMF as solvent at 25 °C for 2 h in an inert environment. However, when DMA and dimethylbenzamide (DMB) are used for transformation, this reaction acts differently because it occurs at 110–130 °C in the microwave for 30–50 min while utilising its diglyme as a solvent and in the presence of t-BuOK. The transamidation of DMF produces



Scheme 16 KO^{t}Bu mediated transamidation reaction of tertiary amide

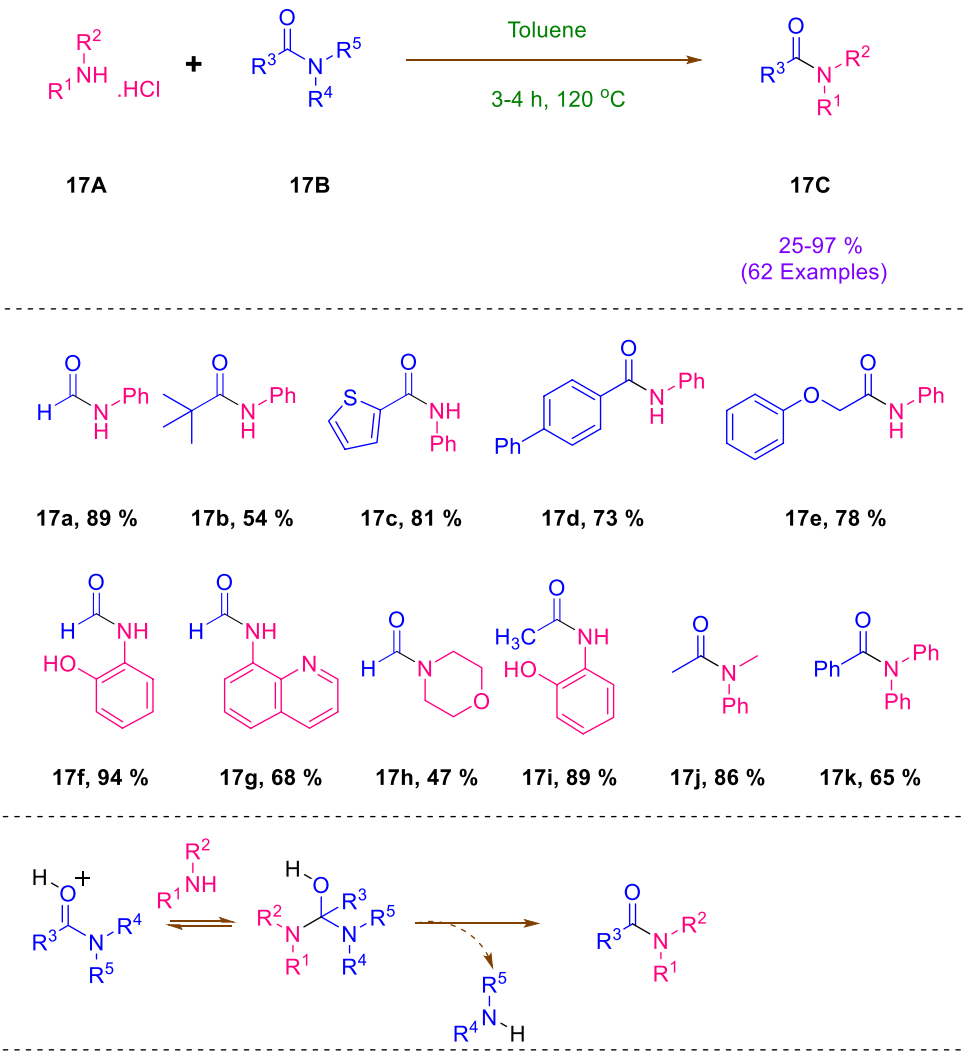
excellent yields of amide compounds. Additionally, the approach utilizes a broad range of amines during the treatment with DMF and DMA, including anilines substituted with electron-withdrawing and electron-donating groups, heteroaromatic, and aliphatic amines. Notably, the procedure's main flaw is that ortho-substituted anilines produced lower yields than other positions. This method follows the same mechanism as Scheme 15.

One methodology reported by our group was the use of amine salt instead of an additional salt additive (Kumar et al. 2021) (Scheme 17). Notably, the simplicity of processing and the moisture and air reliability provided are significant advantages of this technique. In particular, this approach allowed the development of functionalised transamide products from amides, including sterically hindered, aliphatic, heteroaromatic, and aromatic amides. The method is also efficient with primary, secondary, and tertiary amides, yielding good to exceptional converted amide yields. Furthermore, various cyclic and linear aliphatic, heteroaromatic, and aromatic amines are substituted with electron-rich and deficient groups that were compatible as nucleophiles for this amide conversion in the substrate scope. This methodology has additional advantages if it raises the temperature in the case of substituted 2-aminophenols as nucleophiles reacting with amides to produce 2-substituted benzoxazole as a final product (Kumar et al. 2022a, b). The hydrogen ion activates the amide, followed by amines attack as a nucleophile and eliminating the amine as a side product, leading to the final amide product.

One more example of transmaidation conversion of DMF and DMA using metal free conditions, published by Zhang and Xie's (2019) team. Authors found that NH_4I is the best salt to use as a reagent among the other salts evaluated, such as KI, CuI, NH4F, NH_4Cl, and NH_4Br (Scheme 18). They also tried DMSO and *o*-Xylene as solvents but observed low transamidation conversion. Researchers demonstrated an excellent to a good yield of transamidation from a wide range of substituted anilines and DMF. The procedure was less compatible with ortho-substituted anilines when used. Furthermore, the scope of amine with DMA yielded a transamide product with a conversion range of 33–52% utilising 2 equiv of NH_4I. Nevertheless, the range of the reaction is narrow; this approach can only use DMF and DMA.

The transamidation of *N*,*N*-dimethyl amides with various primary amines was also accomplished using the sodium-*tert*-butoxide (NaO^{t}Bu) (Zhang et al. 2020) (Scheme 19). They studied various bases during reaction optimisation and found that NaO^{t}Bu provided the highest yield of transamide product under an inert atmosphere. In addition, the procedure standardisation studies show that base equivalent plays a critical role in the success of conversion. A good to an excellent yield of amides was obtained from aromatic, heteroaromatic, and aliphatic primary amines. The primary disadvantage of this approach is that the base is incompatible with aromatic substitution on the α-position of amide. The mechanistic studies reveal that transamidation does not include a radical pathway in the reaction mechanism like KO^{t}Bu-mediated methodologies.

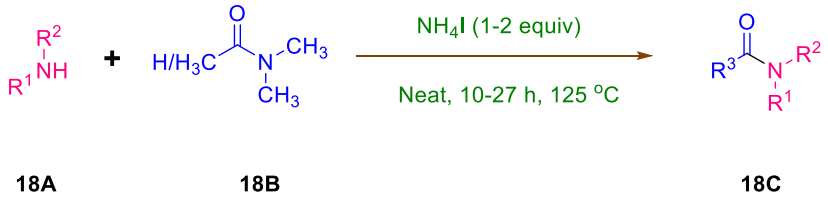
Scheme 17 HCl-mediated transamidation of unactivated amides



Li et al. developed a simple route to achieve transamidation of tertiary amides without involving any hazardous metal catalyst (Li et al. 2019) (Scheme 20). The reaction was carried out by utilising LiHMDS as an additive and toluene as the solvent. Additionally, the reaction carries out using both starting material amide and ester. The comparative studies demonstrate that the transformation from both type of stating material is more effective and efficient, producing more than 80% of the desired product. The reaction scope revealed that this reaction produced an excellent yield of amides from halo, alkoxy, carboxyl and alkyl groups substituted anilines. Notably, the reaction is compatible with aromatic, aliphatic, cyclic amines which yielded the desired transamide products in sound yields. Same group published a chemoselective transamidation of thioamides by NaHMDS at RT (Zuo et al. 2022). Recently, Szostak and Chen collaborator groups reported a transamidation of unactivated tertiary amides using cooperative acid/iodide catalysis through insitu acyl iodide intermediate (Zuo et al. 2022).

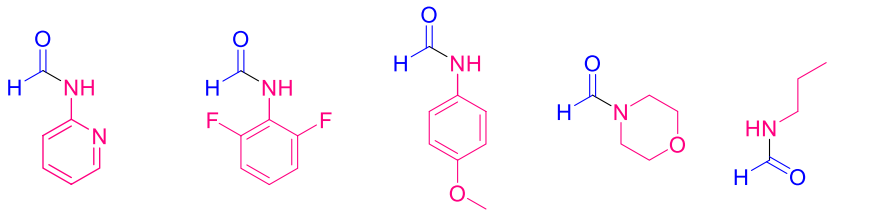
In 2019, Lee and co-workers (Yu et al. 2019) developed a TMSCl mediated transamidation reaction to synthesise transamide products from primary amides (Scheme 21). This protocol demonstrated that TMSCl activates 1° amide, which triggers the transamidation reaction in the presence of NMP as a solvent. Except for TMSCl, no suitable results were obtained during optimisation studies when other silyl lewis acids were used as the additive. Some primary amides bearing phenyl, cyclohexyl, benzyl or even sterical hindered (tert-butyl) groups can be successfully converted under standard conditions. Moreover, aliphatic, heterocyclic, electron-deficient and donating group substituted and even steric hindered aromatic amines can be reacted efficiently with a benzamide. However, when 2,5-disubstituted aniline derivatives were utilised, the intended product was not produced, indicating that electronic and steric factors play a significant role in the success of this reaction. In addition, alkyl-substituted on the *para* position of aniline produced excellent results for transamide products. It was also noteworthy that the aliphatic secondary amine and amides

Scheme 18 NH_4I catalysed transamidation reactions of unactivated amides

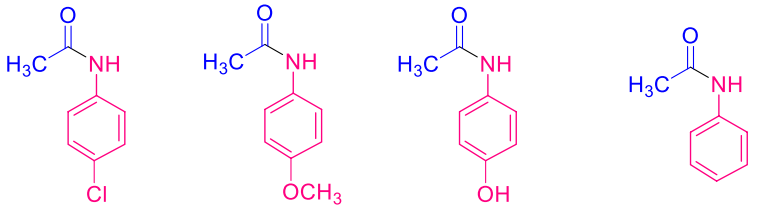


18A 18B 18C

23-94 %
(30 Examples)



18a, 42 % 18b, 54 % 18c, 94 % 18d, 23 % 18e, 62 %

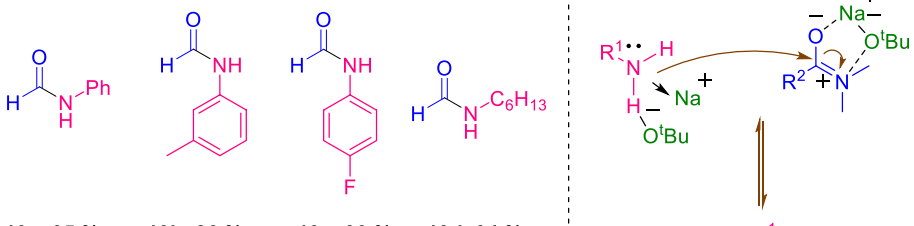


18f, 33 % 18g, 52 % 18h, 29 % 18i, 45 %

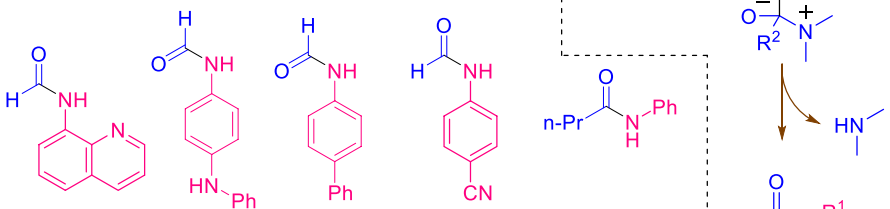
Scheme 19 NaO^tBu-mediated transamidation of amides with a variety of 1° amines

19A 19B 19C

45-90 %
(23 Examples)

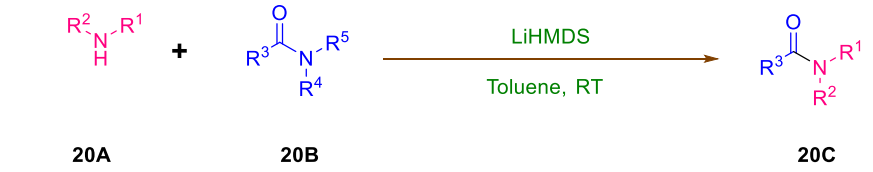


19a, 95 % 19b, 86 % 19c, 90 % 19d, 94 %



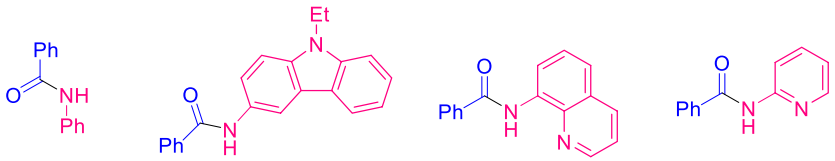
19e, 71 % 19f, 78 % 19g, 75 % 19h, 88 % 19i, 56 %

Scheme 20 LiHMDS-mediated transamidation of amide derivatives with anilines

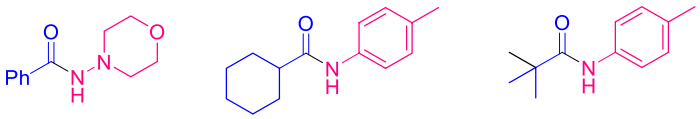


20A **20B** **20C**

70-97 %
(75 Examples)



20a, 93 % **20b, 70 %** **20c, 75 %** **20d, 70 %**

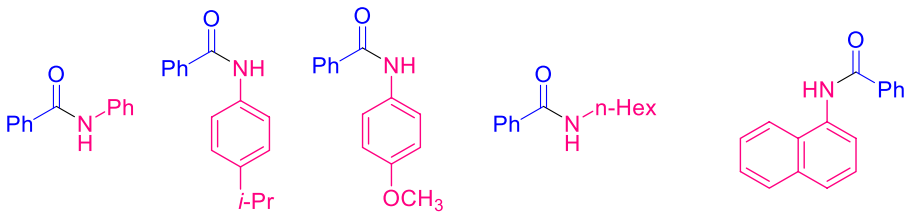


20e, 95 % **20f, 87 %** **20g, 81 %**

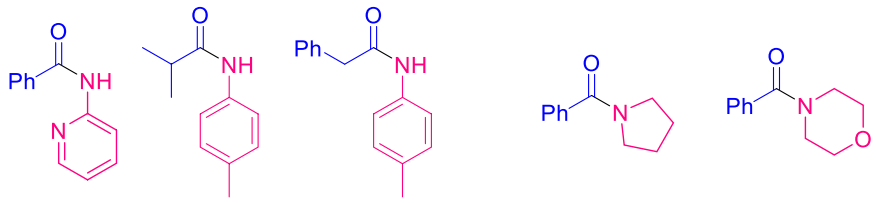
Scheme 21 TMSCl mediated transamidation to synthesise 2° amides

21A **21B** **21C**

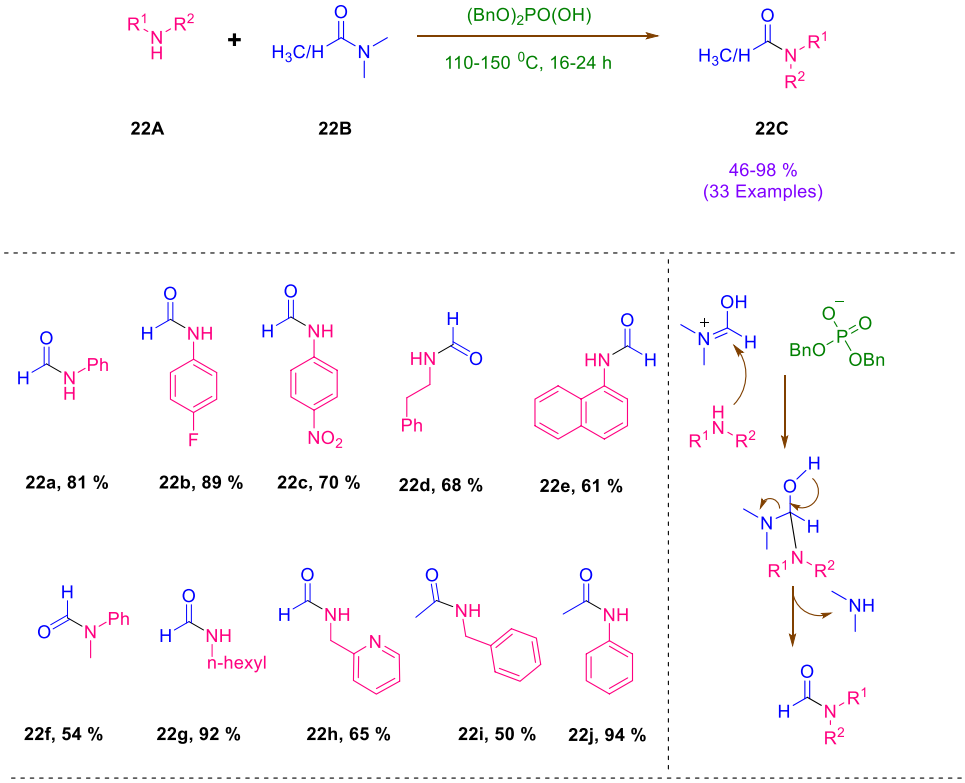
22-92 %
(23 Examples)



21a, 63 % **21b, 91 %** **21c, 65 %** **21d, 84 %** **21e, 32 %**



21f, 42 % **21g, 77 %** **21h, 81 %** **21i, 22 %** **21j, 56 %**



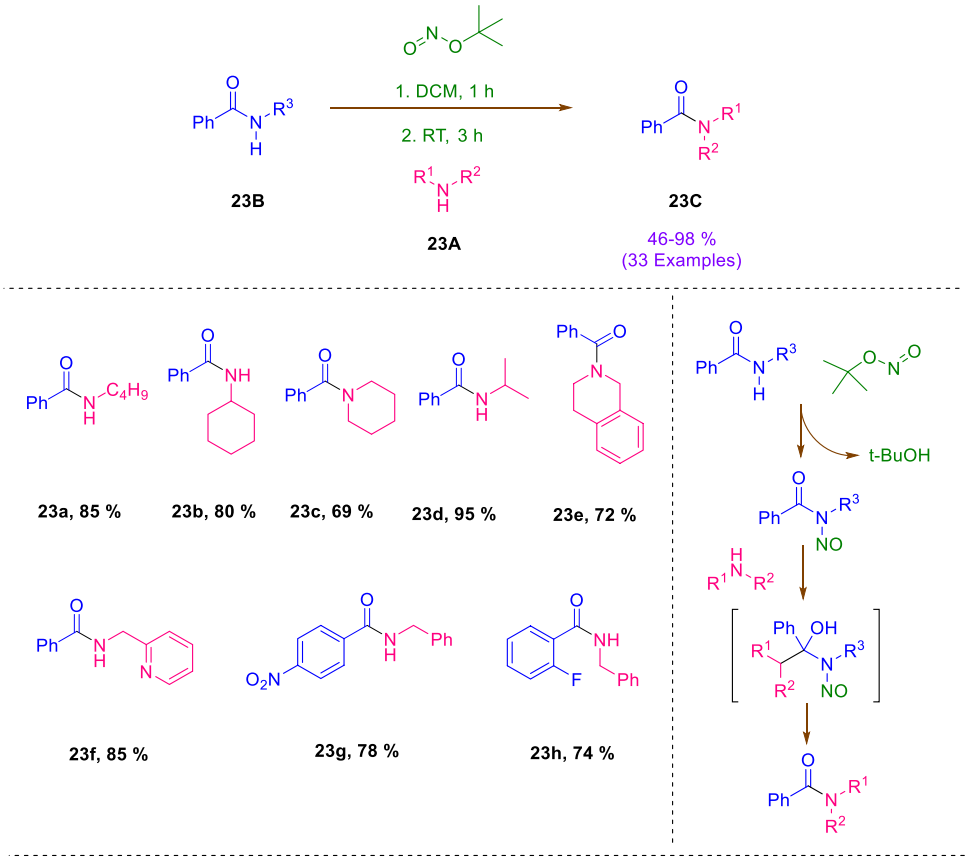
Scheme 22 Organophosphoric acid-mediated transamidation of DMF and DMA

were reacted using NMP/$CHCl_3$ solvent mixture. Further, the control experiment revealed that *N*,*N*-disilyated amides and amines are not active intermediates for transamidation reaction.

Jiang et al. recently reported that phosphoric acid can be employed as a promotor in the transformation of DMF and DMA to transamide compounds (Jiang et al. 2021) (Scheme 22). In neat circumstances at 110–150 °C, they used an organophosphoric acid-mediated amide to amide conversion. Several anilines, including electron-donating and withdrawing group substitution and linear and cyclic aliphatic amines, provide good to exceptional yields of amide products. Interestingly, bromo, nitro, hydroxy, and bulky group substituted aniline and linear and cyclohexyl amines require more time and temperature to react with amides under these acidic circumstances. Furthermore, DMA transamidation occurred around 140–150 °C. This metal-free reaction occurs when an acid activates the amide, followed by a nucleophilic attack on the amine, which results in the amine being eliminated as a side product and the formation of the desired transamide product.

The use of tert-butyl nitrite as a promoter facilitated in situ conversion of the *N*-nitrosamide, which can be held in various amines to generate the final transamide product (Sureshbabu et al. 2019) (Scheme 23). The transamidation reaction was carried out at room temperature in DCM solvent utilising *N*-substituted benzamide amides as the precursor and amines, including linear, cyclic, and secondary aliphatic amines, gave the corresponding transamide product. Surprisingly, transamidation of aniline with *N*-methyl benzamide was unable to complete the transformation. However, secondary amines yielded a lower yield of amide products than primary amines. Additionally, the approach is compatible with the *N*-substitution of benzamide with aliphatic groups such as methyl, ethyl, *n*-propyl, *n*-butyl, cyclohexyl, and benzyl. Furthermore, benzamide substituted with 4-methoxy, nitro, or 2-fluoro effectively converts to other amides. Mechanistically, the tert-butyl nitrite attached with the nitrogen atom of amide to make *N*-nitrosamide as a labile group followed by amine attack as a nucleophile affords the unstable intermediate, which provides transamide product with the release of alkyl *N*-nitrosamine.

Transamidation of amides using iodine and hydroxylamine hydrochloride was recently reported by our group (Girase et al. 2022) (Scheme 24). Both conventional and microwave methods carried out this reaction under neat conditions at 120 °C. The reaction has a wide range of amides, including aliphatic and aromatic, with different *N*-substitutions on amides. Furthermore, aryl, heteroaryl, and aliphatic amines can be easily converted to their amides. The proposed mechanism is quite similar to acid-catalysed transamidation. Initially, the amide is activated by a hydrogen ion and then attacked by hydroxylamine as a nucleophile, resulting in hydroxamic acid and amine elimination as a side product. Iodine then promotes the conversion of the acid intermediate to the nitroso moiety, resulting in the formation of a



Scheme 23 *Tert*-butyl nitrite-mediated transamidation of N-alkyl benzamide

transamide product with the liberation of nitrosyl hydride. Additionally, one more transamidation reported from our group using hydrochloride solution (Dhawan et al. 2021).

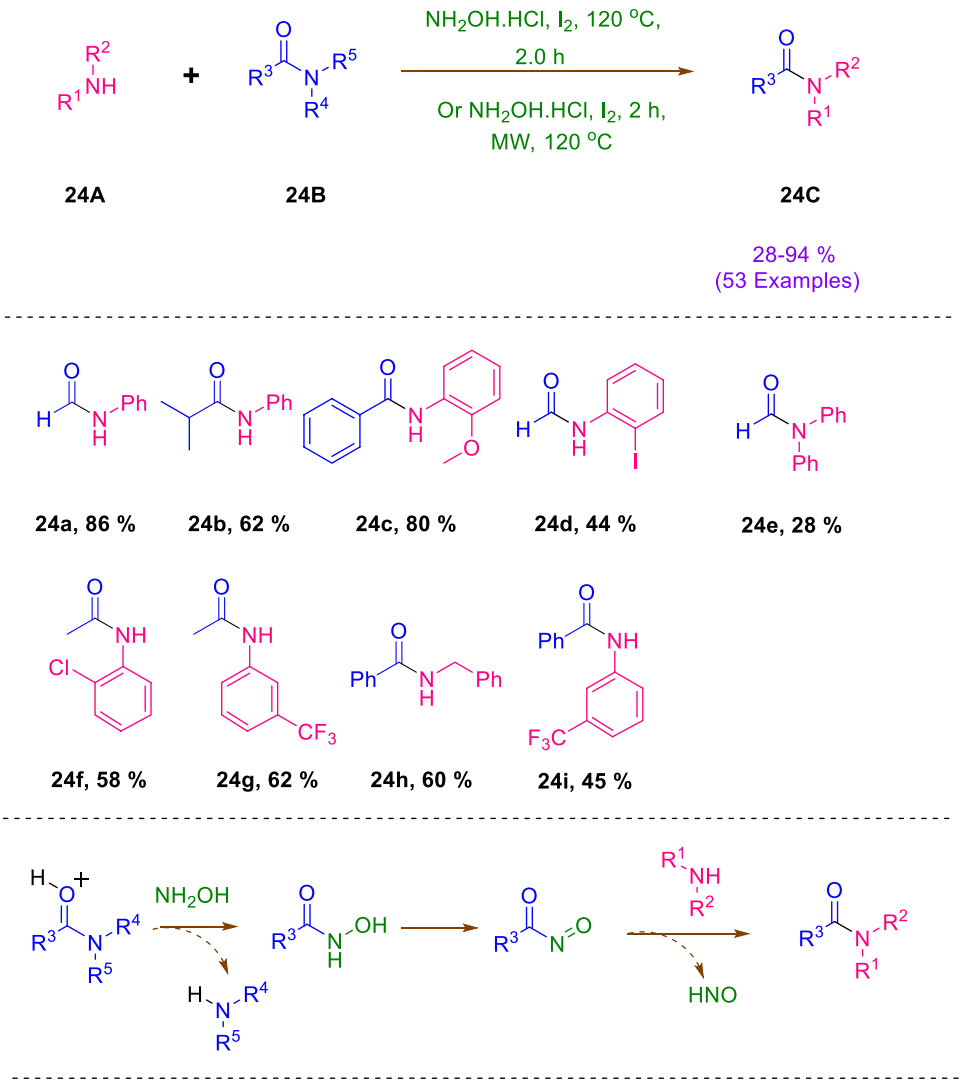
Lewis acids were shown to be involved in the transamidation in metal literature. Sakurai et al. (2019) developed an efficient method to perform the formylation of various amines and hydrazides with the help of *tert*-butyldimethylsilyl triflate (TBSOTf) as an activator (Scheme 25). The optimisation study revealed that silane-based Lewis acids (TMSCl, TMSOTf and TBSOTf) showed better results than other Lewis acids such as BF_3. OEt_2, $AlCl_3$, $TiCl_4$ and $SnCl_4$. The amide products had good to excellent yields and a high tolerance for aliphatic, aromatic, and heteroaromatic hydrazides. Moreover, the same conditions worked for amines, including aliphatic, aromatic, and heterocyclic amines. However, the yield statistics demonstrated that 2° amines had a higher yield than 1° amines. Notably, the additional equivalent of TBSOTf and imidazole were used in the reaction with amines/hydrazines bearing a hydroxy group. According to the proposed mechanism, the amide is activated via lewis acid and then reacts with an amine to form the transamide product.

Compared to metal-mediated transamidation, the salt-mediated conversion reaction has been regarded as a cost-effective approach. Imidazolium chloride had received much attention when Tian et al. (2018) disclosed a method for the transformation of 1° amines with tertiary amides utilizing imidazolium chloride salt as an additive (Tian et al. 2018) (Scheme 26). Anilines with electron-rich and electron-deficient substituents, aliphatic and heteroaromatic amines all reacted to DMA admirably during the reaction scope evaluation. In particular, the nitro substituted anilines yielded less transamide product. Moreover, the study showed that the process is tolerant to amides such as DMF and benzamide. A mechanistic investigation was conducted to clarify the role of imidazolium chloride. The acidic proton of salt activates the amide, and the imidazole serves as a good leaving group to introduce the amine to the amide to obtain the other amide.

Miscellaneous

Hang Gong's (Yin et al. 2019) group have developed a reagent and solvent-free method for the cross amidation reaction between amides and amines (Scheme 27) and proved it

Scheme 24 I_2-mediated transamidation of unactivated amides

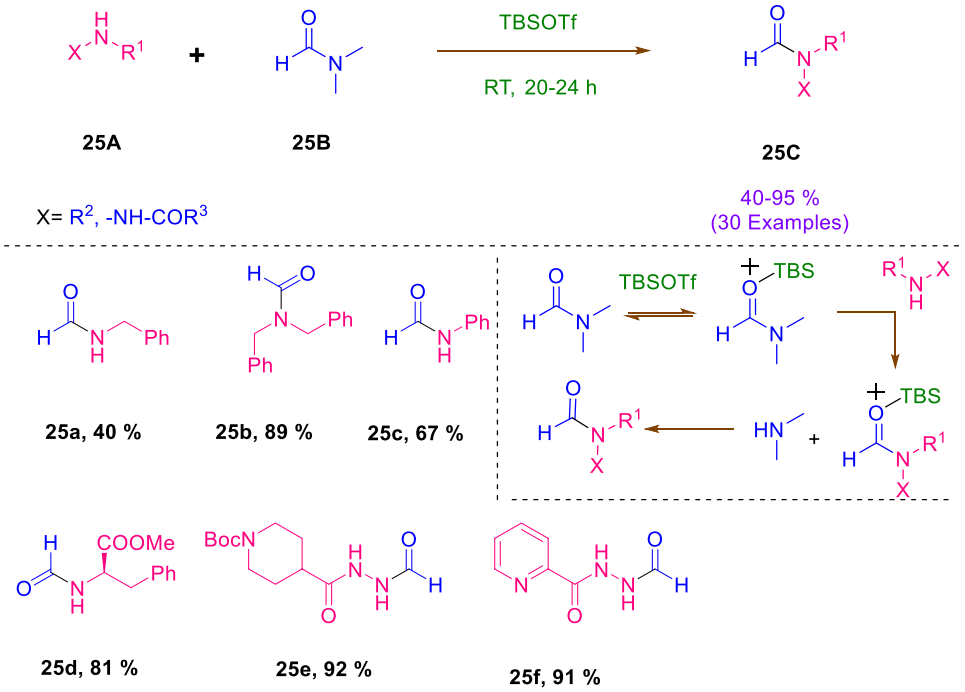


on the gram scale. In the initial phase, they found the best result with simple formamide compared to *N*-substituted ones. The optimisation study revealed that the 10 equivalent of formamide at 150 °C within 24 h produced an excellent yield of formylation on *p*-toluidine. Using this standard condition, they performed formylation on aryl and heteroaryl amines with 60–98% range of yield of the corresponding products. The anilines with various electron-deficient groups such as (NO_2, CN, CF_3, CO_2CH_3), and bulky and heteroaryl amines showed a poor yield of transamide products. The formylation of aliphatic amines was more compatible with DMF at the same temperature for 24–96 h. Further, the competition analysis revealed that the formylation with DMF on aliphatic amine is more preferred over aromatic amine.

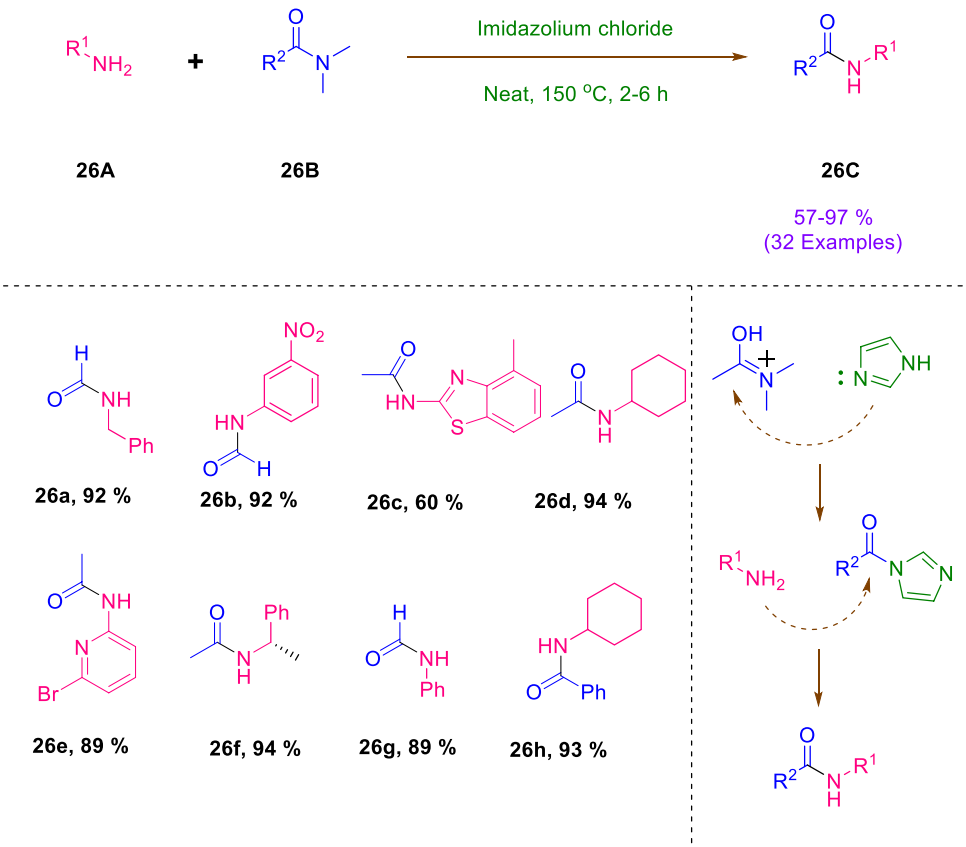
Bensalah et al. (2019) and their teammates developed a green approach to achieve selective transamidation on glycosyl carboxamide derivatives without disturbing any other hydroxy group. They were able to obtain an outstanding yield of the final product without the use of any solvent, reagent, or catalyst, despite the fact that they had tried catalysts such as L-Proline, D-Proline, and hydroxylamine hydrochloride, as well as solvents such as H_2O and DMF. They investigated various aromatic, aliphatic, and cyclic amines and established their compatibility by demonstrating a satisfactory yield (60–94%) of final products (Scheme 28). Primary amines showed a better yield than secondary anilines. On the other hand, they showed well tolerance of glycosyl carboxamide derivatives with different amine reactions.

Durgaiah et al. (2016) developed a novel method to the obtained cross-amidation reaction of unactivated primary amides without using a solvent (Scheme 29). This method used nano zeolite beta as a catalyst that provides large micropore volume, a large-pore channel system used for facelifted acid catalysed reactions. In the reaction optimisation study, they used benzamide and benzylamine as ideal starting materials and treated them in the presence of zeolites, MCM-41 and Montmorillonite. Among them, nanosized zeolite beta provided 93% of respective amide in the 1:2 ratio of

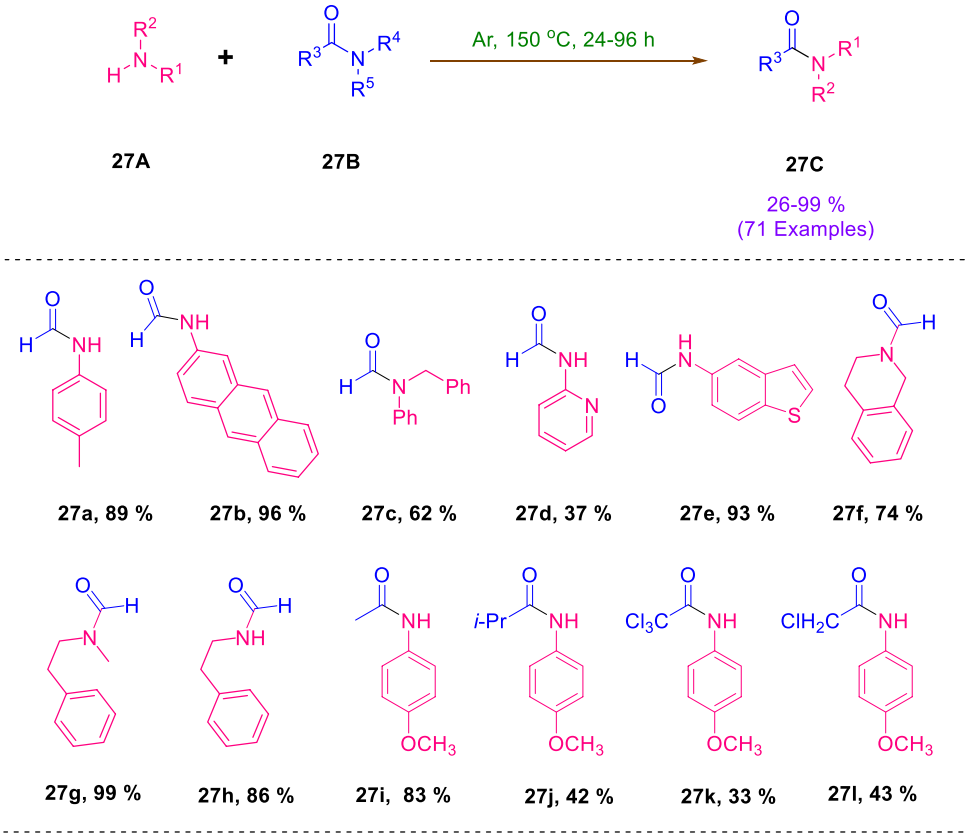
Scheme 25 *Tert*-butyldimethylsilyl triflate (TBSOTf) catalysed transamidation reaction



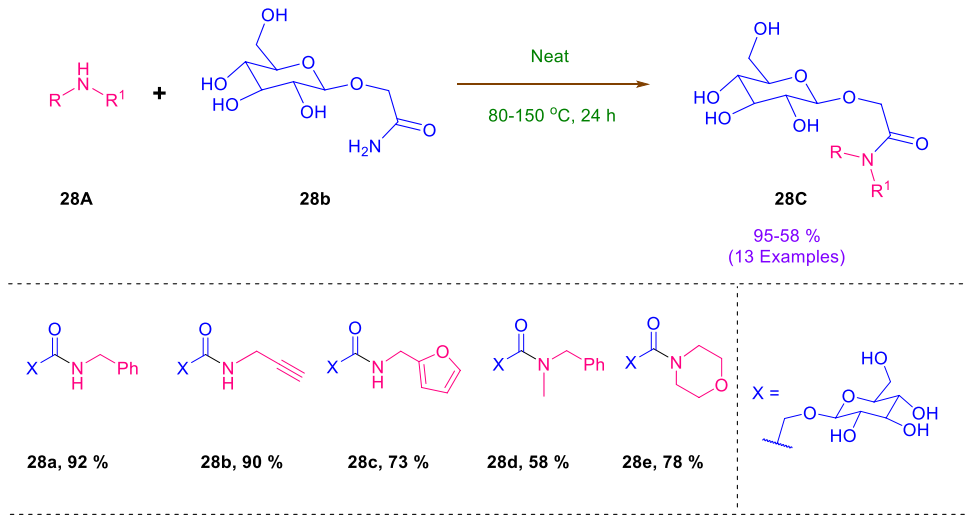
Scheme 26 Imidazolium chloride mediated transamidation reaction of tertiary amides



Scheme 27 Solvent-free method for the cross amidation reaction



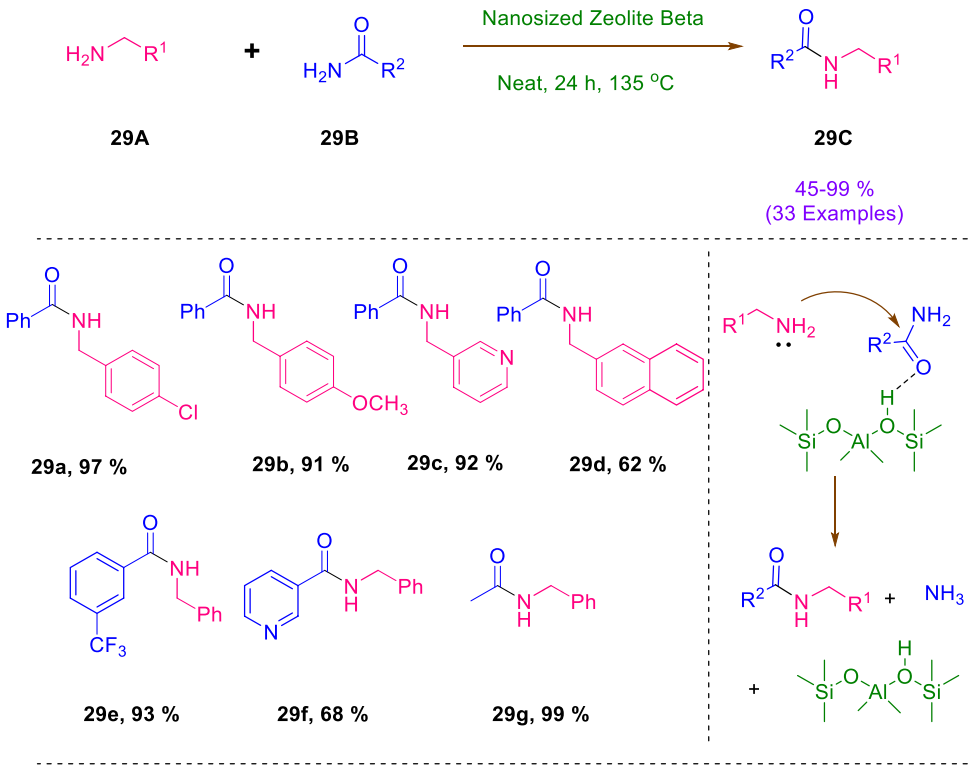
Scheme 28 Green approach to achieving selective transamidation on glycosyl carboxamide



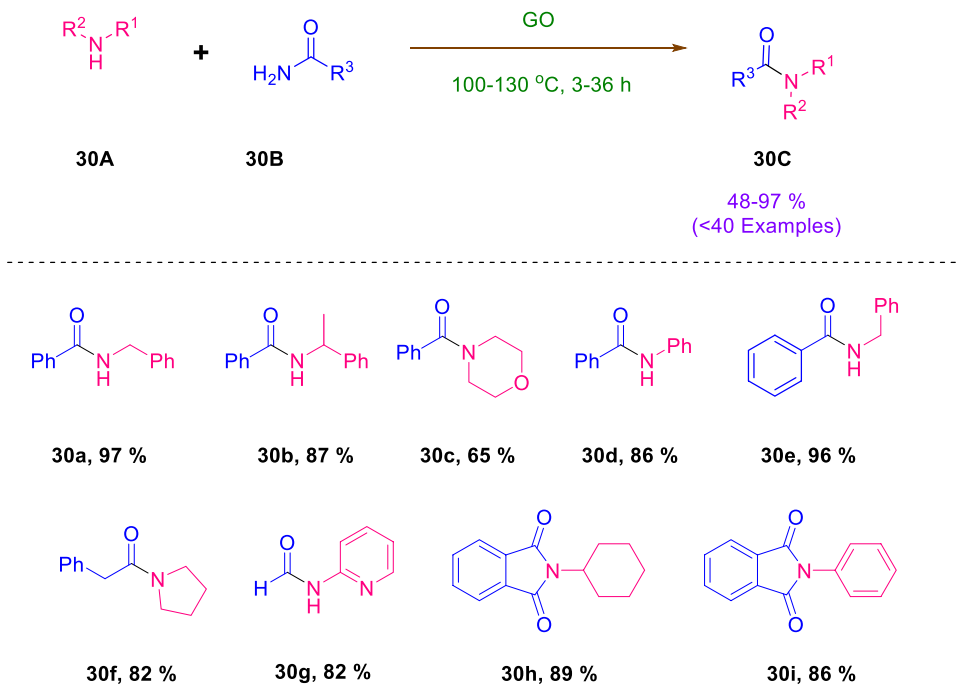
benzamide and benzylamine. The study of reaction scope confirmed that this method tolerated different substituted benzylamines and aliphatic amines viz cyclic and acyclic. It also demonstrated that a wide range of benzamide has been compatible under this method with good to an excellent yield of the final product.

Researchers have recently drawn their attention to carbon nanomaterials because of their exceptional thermal, optical, mechanical, and electronic properties. They kept in that mind Patel et al. (2019) explored graphene oxide as a heterogeneous catalyst to conduct transamidation reactions. Researchers have systematically first fixed catalyst amount during reaction optimisation, followed by solvent choice and

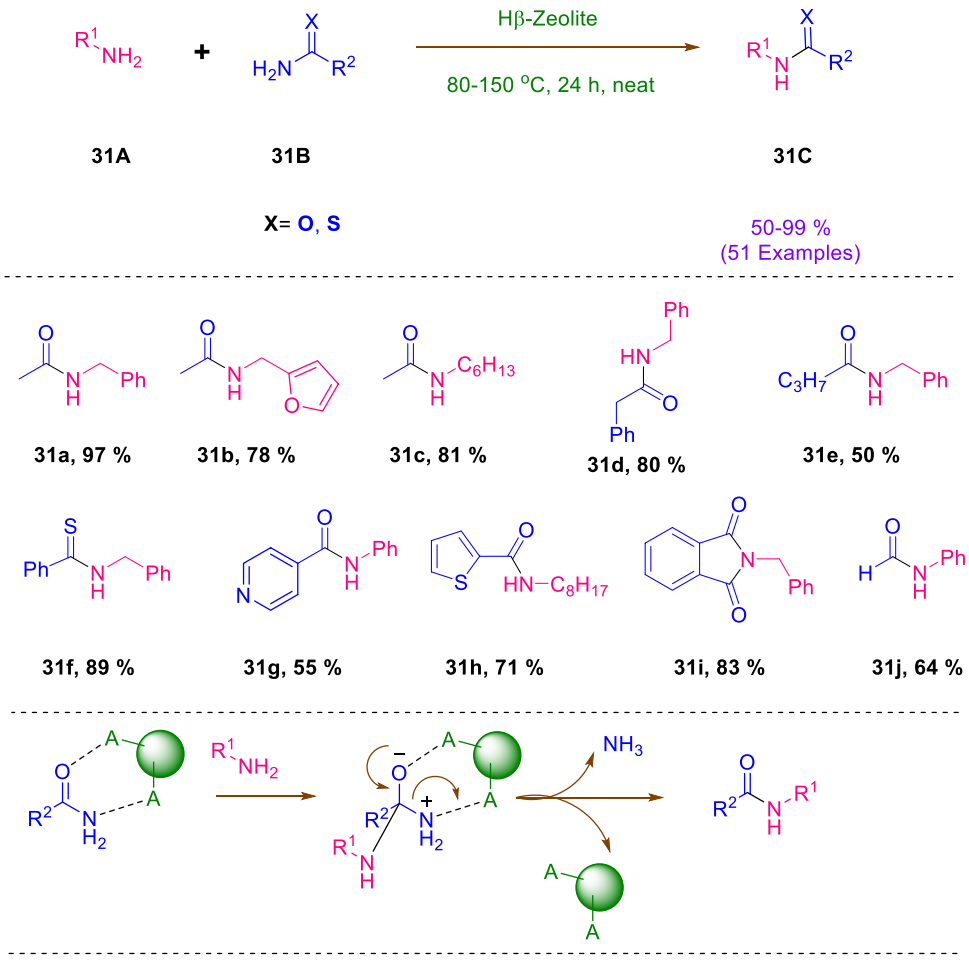
Scheme 29 Nano zeolite beta catalysed transamidation of amides



Scheme 30 Graphene oxide assisted transamidation of unactivated amides



temperature adjustment. Additionally, other carbon nanomaterials were also tried, and the best results were obtained using 20% of graphene oxide at 130 °C. The reaction obtained 97–76% yield of the desired compound from aryl-substituted benzylamine and unsubstituted benzamides, wherein substituted benzamides showed comparatively



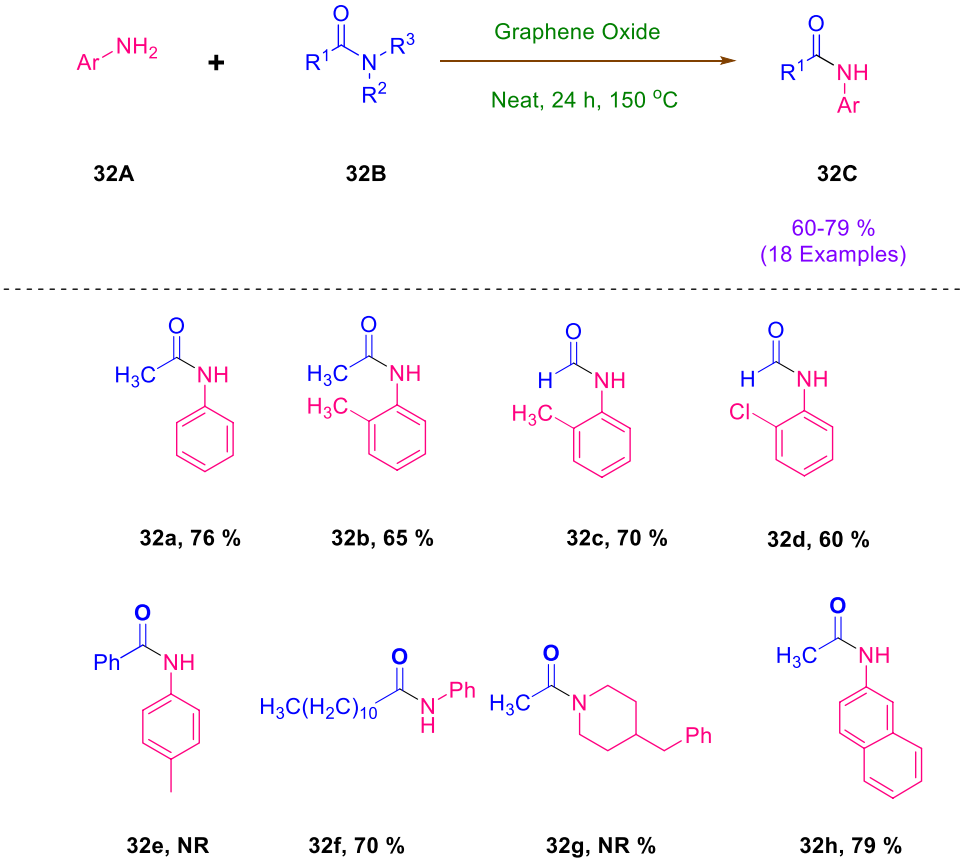
Scheme 31 H-β-Zeolite, assisted transamidation of amides and thioamides

lower transformation (Scheme 30). The method is also compatible with the reactivity of branched-chain and cyclic aliphatic amines. Further, the reaction scope of formamides and the results confirmed the compatibility of aryl, heteroaryl, aliphatic and cyclic amines are suitable for conversion. Interestingly, researchers also showed the tolerance of phthalimide and thioamides with amines. Notably, the dimer transamide product obtains in the treatment of urea. The advantage of this mode is more selective toward aliphatic amines over aromatic and heterocyclic amines at the end of the study.

Rao et al. (2015) used H-β-Zeolite to assist the transamidation reaction of unactivated primary amides with amines under solvent-free conditions (Scheme 31). The optimisation experiments confirmed that solvent-free condition is more effective than the presence of solvent at 130 °C. The method generated a significant yield of the respective desired products from various substituted benzylamine/aniline. This study concludes that aliphatic amines showed a better result than aryl amines in reaction with acetamide. The yield of transamide product was less when a long chain substituted amide on the alpha position was used for conversion. Afterwards, they showed the compatibility of phthalimide and heteroaryl amide on treatment with a wide range of amines. Similarly, they also tried this method on thioamides and results shown its transformation into the desired product in good to excellent yields.

Bhattacharya et al. (2018) developed a metal-free and environmentally safe approach for transamidation. The researchers utilised a heterogeneous catalyst, graphene oxide (GO) that efficiently absorbs reactive molecules and accelerates the reaction (Scheme 32). During the optimisation of the process, they performed a reaction in the presence of organic and inorganic solvents at various temperatures using GO catalysts, but the results did not meet the predicted yield. Notably, the neat condition with the same amount of catalyst at 150 °C produced a high yield of the target product. The method generated a range of converted formamides and acetamides products from the reaction of aromatic anilines with various aliphatic carboxamides. In contrast, the reaction of an aliphatic amine with carboxamides failed to

Scheme 32 Graphene oxide-catalysed *N*-formylation and *N*-acetylation

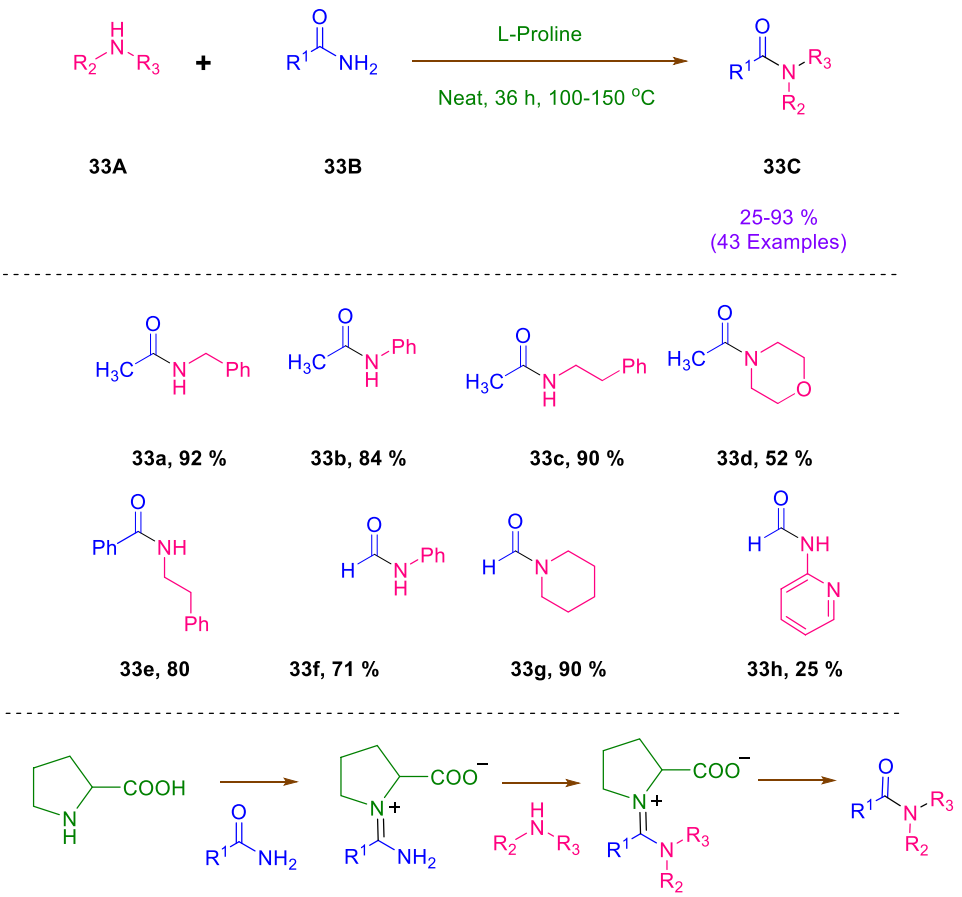


produce the respective transamide product. Additionally, this approach is selective for aromatic amines. Similarly, Ma et al. reported *N*-formylation of amine employing graphene oxide as metal-free recyclable carbocatalyst (Ma et al. 2018a, b).L-proline catalysed transamidation of carboxamides with amines was reported by Rao et al. (2013) (Scheme 33). During the reaction optimization studies, they found that transformation performed better in neat conditions than in the presence of a solvent and that L-proline had been generated the best results when compared to other amino acids. Aliphatic amines and other substituted primary anilines had been successfully *N*-acetylated. The yield study explained that the secondary aliphatic amines yielded less when acetylated than primary amines. Furthermore, the *N*-acetylation of aniline was carried out at 150 °C rather than 100 °C. Furthermore, the transamidation of benzamide with aliphatic and aromatic amines was carried out successfully at 150 °C. Notably, the conditions of transamidation change with α-substitution of amides. In addition, Yang et al. examined a study of mechanistic pathway on L-proline catalysed transamidation of unactivated amide with benzylamine via density functional theory calculations (Yang et al. 2014).

Conclusion

The amide moiety is an important functional group in chemical, pharmacological, and biological chemistry. Several researchers have focused on its synthesis; alternative methods for amide synthesis remain elusive. While novel and recent methods for amide activation are available, simple activation of the C–N bond in amides via coordination with metals or interaction with small molecules remains a crucial alternative in amide bond synthesis. Herein, we examined unactivated amides in transamidation processes and explored many examples in this article. We believe that this review will assist researchers, provide motivation for future work, and help in their knowledge of several recently described transamidation mechanisms.

Scheme 33 L-proline-catalysed transamidation of amides



Acknowledgements The authors are thankful to the Discipline of Pharmaceutical Sciences, College of Health Sciences, University of KwaZulu-Natal (UKZN), Durban, South Africa, for providing all the necessary facilities. R.K. gratefully acknowledges National Research Foundation-South Africa (NRF-SA) for funding this project (Grant No. 129247).

Funding Open access funding provided by University of KwaZulu-Natal. Rajshekhar Karpoormath would like to thank the National Research Foundation-South Africa (NRF-SA) for funding this project (Grant No. 129247).

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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