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Nickel/Briphos-Catalyzed Direct Transamidation of Unactivated Secondary Amides Using Trimethylsilyl Chloride

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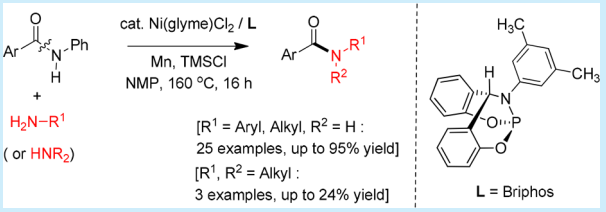
Supporting Information

ABSTRACT: Direct transamidation of secondary amides was developed via nickel catalysis. In the presence of trimethylsilyl chloride and manganese, Ni(diglyme)Cl_2 with a Briphos ligand efficiently promoted the transamidation of *N*-aryl benzamide derivatives with primary amines to afford the corresponding secondary amides in moderate to good yields. Primary amines bearing electron-donating groups gave higher yields of the transamidation products.

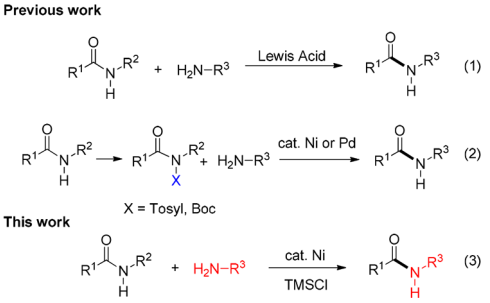


The amide functionality is one of the key structural motifs found in biological compounds such as peptides, proteins, and alkaloids. It is also widely used to prepare agrochemicals, pharmaceuticals, polymers, and materials.[1] Therefore, a number of synthetic routes to amides have been reported.[2] The conventional methods are based on (1) acyl substitution reactions with carboxylic acid derivatives and amines and (2) coupling reactions with organo halides and primary amides.[3] However, these methods have limitations, such as narrow substrate scope and the need for harsh reaction conditions and activating reagents. Transamidation has emerged as a topic of interest because it is an efficient, green, and direct method for the synthesis of amides.[4] However, direct transamidation is quite challenging because of the higher resonance stability of the amide as compared to that of other carbonyl compounds.[5]

A promising strategy to activate amides is transition-metal-catalyzed C−N bond activation. In the past decade, a variety of strategies for the conversion of amides to other amides, as well as esters and ketones, have been developed.[6] However, most of the efficient methods in this regard have been developed using tertiary amides, while the focus on secondary amides is limited. When a secondary amide reacts with a primary amine, the transamidation product is in equilibrium with the starting amide. Accordingly, Stahl suggested that transamidation reactions between tertiary amides and secondary amines are better than those between secondary amides and primary amines.[7]

Several modifications to the existing methods have been made in order to realize the transamidation of secondary amides (Scheme 1). While transamidation of secondary amides was initially carried out with the assistance of Lewis acids such as Al, Sc, Ti, and Zr, the reaction had a limited substrate scope and afforded a mixture of the substrates and product amides (Scheme 1, eq 1).[8] Two-step approaches have recently been developed, where the secondary amide was first converted to an activated tertiary amide with tosyl or *tert*-butyloxycarbonyl (Boc) groups using tosyl chloride or di-*tert*-butyl carbonate (Boc_2O), respectively. The *N*-functionalized amides were then allowed to react with amines to provide the corresponding secondary amides in good yields (Scheme 1, eq 2).[9] Garg and Szostak's groups developed catalytic systems with nickel and palladium, respectively. Hu's group developed another method to prepare *N*-Boc-activated amides by nickel-catalyzed reductive transamidation, using nitroarenes as amine surrogates.[10] Because two-step approaches still require a preparation step for introducing the activating group, it is highly desirable to develop a direct transamidation of secondary amides. Herein, we report the direct nickel-catalyzed transamidation of secondary amides in the presence of our π-acidic Briphos ligand[11] and trimethylsilyl chloride (TMSCl).[12]

Scheme 1. Transamidation of Secondary Amides



The reaction of *N*-phenylbenzamide **1a** with *p*-toluidine **2a** in the presence of TMSCl was adopted as the model reaction. First, we tested a variety of nickel sources using 1,10-

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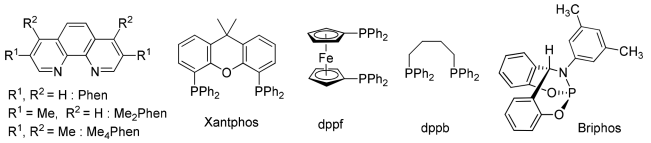
phenanthroline as a ligand, which was previously shown to be compatible with nickel catalysis.[10] All the tested nickel sources afforded the transamidated product **3aa** in moderate yields of 28% to 42% (Table 1, entries 1–6). Ni(glyme)Cl_2 was found to be the best source, although only a moderate product yield of 42% was observed (Table 1, entry 6). With the selected nickel source, *N*,*N*-chelating ligands were tested. The use of Me_2Phen increased the product yield to 59% (Table 1, entry 7). When using Me_4Phen and TMEDA, the product yields were 38% and 30%, respectively (Table 1, entries 8 and 9). P,P-Chelating phosphines such as Xantphos, dppf, and dppb afforded **3aa** in 55%, 52%, and 42% yields, respectively (Table 1, entries 10–12). Monophosphine ligands PPh_3 and PCy_3 gave the product **3aa** in 60% and 58% yields, respectively (Table 1, entries 13 and 14). When Briphos, which has been used with rhodium and palladium catalysts,[11] was employed, the product was formed in 69% yield (Table 1, entry 15). However, π-acidic phosphites such as $P(OPh)_3$ and $P(OEt)_3$ were found to be inefficient in this reaction (Table 1, entries 16 and 17).

Table 1. Optimal Conditions for Nickel-Catalyzed Transamidation of *N*-Phenyl Benzamide in the Presence of TMSCl[a]

entry	catalyst	ligand[h]	solvent	yield (%)[b] **3aa**
1	$NiCl_2$	Phen	NMP	28
2	NiI_2	Phen	NMP	30
3	$Ni(OAc)_2$	Phen	NMP	33
4	$Ni(PPh_3)_2Cl_2$	Phen	NMP	32
5	$Ni(OTf)_2$	Phen	NMP	31
6	Ni(glyme)Cl_2	Phen	NMP	42
7	Ni(glyme)Cl_2	Me_2Phen	NMP	59
8	Ni(glyme)Cl_2	Me_4Phen	NMP	38
9	Ni(glyme)Cl_2	TMEDA	NMP	30
10	Ni(glyme)Cl_2	Xantphos	NMP	55
11	Ni(glyme)Cl_2	dppf	NMP	52
12	Ni(glyme)Cl_2	dppb	NMP	42
13	Ni(glyme)Cl_2	PPh_3	NMP	60
14	Ni(glyme)Cl_2	PCy_3	NMP	58
15	Ni(glyme)Cl_2	Briphos	NMP	69
16	Ni(glyme)Cl_2	$P(OPh)_3$	NMP	12
17	Ni(glyme)Cl_2	$P(OEt)_3$	NMP	45
18	Ni(glyme)Cl_2	Briphos	DMF	trace
19	Ni(glyme)Cl_2	Briphos	Diglyme	61
20	Ni(glyme)Cl_2	Briphos	*o*-Xylene	45
21	Ni(glyme)Cl_2	Briphos	1,2-$Cl_2C_6H_4$	12
22[c]	Ni(glyme)Cl_2	Briphos	NMP	42
23[d]	Ni(glyme)Cl_2	Briphos	NMP	9
24[e]	Ni(glyme)Cl_2	Briphos	NMP	0
25[f]	Ni(glyme)Cl_2	Briphos	NMP	0
26[g]	Ni(glyme)Cl_2	Briphos	NMP	0

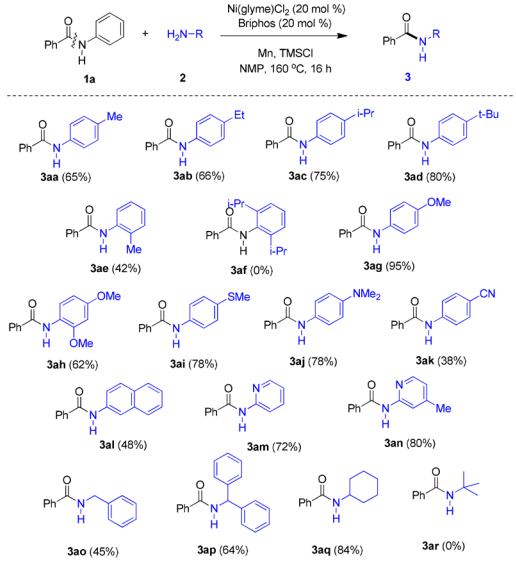
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), Ni (0.06 mmol), ligand (0.06 mmol), Mn (1.5 mmol), and TMSCl (0.6 mmol) were reacted in the solvent (1.2 mL) at 160 °C for 16 h. [b]Determined by gas chromatography and ^{1}H NMR with internal standard. [c]Reaction temperature = 140 °C. [d]Reaction temperature = 100 °C. [e]No TMSCl. [f]No Mn. [g]*N*-Methyl benzanilide was used instead of **1a**. [h]Ligand structure.



With Briphos as the ligand, we next investigated the solvent effect. The reaction in DMF gave trace amounts of the product (Table 1, entry 18). The reactions with diglyme, *o*-xylene, and 1,2-dichlorobenzene afforded the transamidation product in 61%, 45%, and 12% yields, respectively (Table 1, entries 19–21). Thus, NMP was found to be the best among the solvents tested. When the reaction temperature decreased to 140 and 100 °C, the yields were reduced to 42% and 9%, respectively (Table 1, entries 22 and 23). When the reaction was carried out in the absence of TMSCl or Mn, no product was formed (Table 1, entries 24 and 25). However, when *N*-methylbenzamide was employed instead of **1a**, no product was found (Table 1, entry 26). Next, we evaluated other silane sources such as TMSI, $ClSiHMe_2$, TBSOTf, and PMHS, but they all gave low yields or no products (see the Supporting Information).[13] Based on these observations, the optimized reaction conditions were as follows: reaction of the secondary amide and amine at 160 °C for 16 h in NMP using Ni(glyme)Cl_2/Briphos in the presence of Mn powder and TMSCl.

With the optimized reaction conditions in hand, we then evaluated the utility of this nickel-catalyzed transamidation protocol (Scheme 2). First, a variety of amines were allowed to react with *N*-phenyl benzamide under the optimal conditions. *p*-Toluidine provided the desired product **3aa** in 65% isolated yield. 4-Ethyl-, 4-isopropyl-, and 4-*tert*-butyl anilines provided the corresponding transamidated products **3ab**, **3ac**, and **3ad** in 66%, 75%, and 80% yields, respectively. However, 2-methylaniline gave **3ae** with a somewhat lower yield of 42%,

Scheme 2. Transamidation of *N*-Phenyl Benzamide with Primary Amines[a]



[a]Reaction conditions: **1a** (2.0 mmol), **2** (4.0 mmol), Ni(glyme)Cl_2 (0.4 mmol), Briphos (0.4 mmol), Mn (10.0 mmol), and TMSCl (4.0 mmol) were allowed to react in NMP at 160 °C for 16 h.

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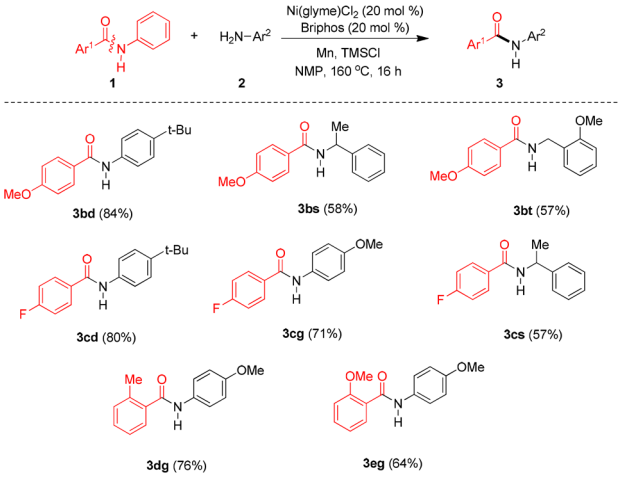
and 2,6-diisopropylaniline did not provide the desired product due to the steric effect of the *ortho*-substituent. The reaction with 4-methoxyaniline proceeded to completion to provide **3ag** in 95% yield. 2,4-Dimethoxy aniline afforded **3ah** in 62% yield. 4-Methylthio- and 4-dimethylamino anilines furnished **3ai** and **3aj** in good yields, but 4-aminobenzonitrile provided the transamidated **3ak** in only 38% yield. 2-Aminonaphthalene, 2-aminopyridine, and 2-amino-4-methylpyridine participating in the transamidation furnished the corresponding products in 48%, 72%, and 80% yields, respectively. Benzylamine and benzhydrylamine provided **3ao** and **3ap** in 45% and 64% yields, respectively. Alkylamines such as cyclohexylamine gave good product yields in the transamidation, but *tert*-butylamine did not give the transamidated product.

Next, we evaluated the substrate scope of *N*-phenyl benzamide in the transformation. 4-Methoxy-, 4-fluoro, 2-methyl, and 2-methoxyl-*N*-phenylbenzamides (**1b**, **1c**, **1d**, and **1e**) were employed in the transamidation with primary amines. In most cases, the desired products were obtained in good yields (57%−84%), as summarized in Scheme 3. In particular,

Scheme 3. Transamidation of *N*-Aryl Benzamide Derivatives with Aniline Derivatives[a]



[a]Reaction conditions: **1** (2.0 mmol), **2** (4.0 mmol), Ni(glyme)Cl_2 (0.4 mmol), Briphos (0.4 mmol), Mn (10.0 mmol), and TMSCl (4.0 mmol) were allowed to react in NMP at 160 °C for 16 h.

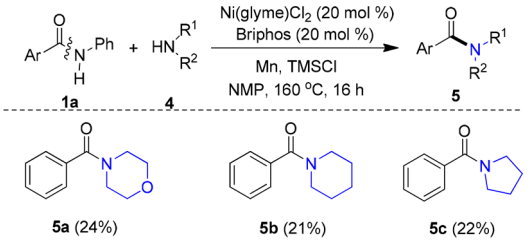
the reactions with 4-*tert*-butylaniline gave more than 80% product yields. In addition, 2-methyl- or 2-methoxy-substituted *N*-phenylbenzamide was allowed to react with 4-methoxyaniline to provide **3dg** and **3eg** in 76% and 64% yields, respectively.

Our attempts to extend this methodology to transamination with secondary amines was not successful (Scheme 4). The reactions between *N*-phenylbenzamide and secondary amines such as morpholine, piperidine, and pyrrolidine afforded the transamidation products **5a**, **5b**, and **5c** in only 24%, 21%, and 22% yields, respectively. However, when *N*-methylaniline was employed, no product was formed.

Next, alkyl amides such as *N*-phenyl cyclohexanecarboxamide **6** were also employed in this transamidation. As shown in Scheme 5, alkyl amide **6** reacted with **2g** to afford **7** in 85% yield.

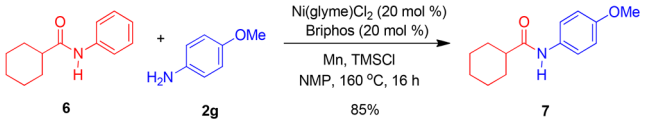
Competition experiments were conducted to understand the reactivity of the Ni-catalyzed transamination. When 4-*tert*-butylaniline and 4-cyanoaniline were allowed to react with **1a**,

Scheme 4. Transamidation of *N*-Phenyl Benzamide with Secondary Amines[a]



[a]Reaction conditions: **1a** (2.0 mmol), **4** (4.0 mmol), Ni(glyme)Cl_2 (0.4 mmol), Briphos (0.4 mmol), Mn (10.0 mmol) and TMSCl (4.0 mmol) were allowed to react in NMP at 160 °C for 16 h.

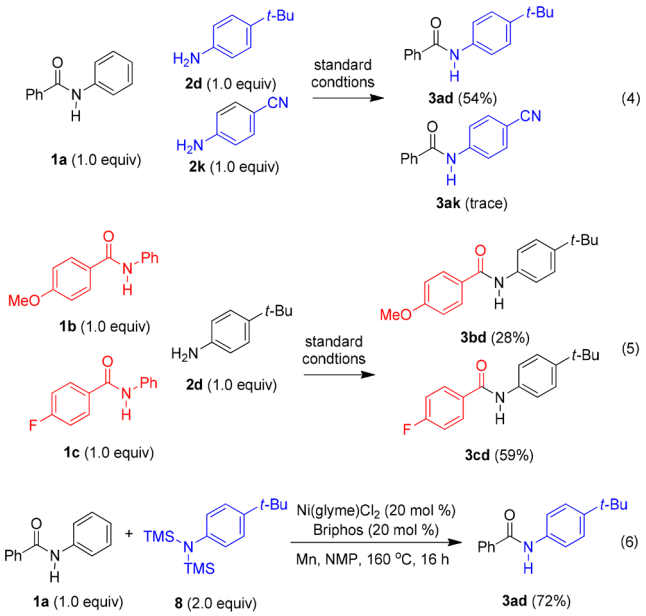
Scheme 5. Transamidation of Alkyl Amide 6[a]



[a]Reaction conditions: **6** (2.0 mmol), **2g** (4.0 mmol), Ni(glyme)Cl_2 (0.4 mmol), Briphos (0.4 mmol), Mn (10.0 mmol), and TMSCl (4.0 mmol) were allowed to react in NMP at 160 °C for 16 h.

only **3ad** was formed in 54% yield (Scheme 6, eq 4). When 4-methoxy- and 4-fluoro-*N*-phenylbenzamaide were allowed to

Scheme 6. Control Experiments



react with 4-*tert*-butylaniline, **3cd** was formed in higher yield than **3bd** (Scheme 6, eq 5). These results indicate that the transamination was promoted by the electron-donating amine and the electron-withdrawing benzamide. The role of TMSCl was also investigated. 4-*tert*-Butyl-*N*,*N*-bis(trimethylsilyl)-aniline **8**[14] reacted with **1a** to afford the product **3ad** in 72% yield, implying that TMSCl activates the primary amine to generate **8** *in situ* in the optimized reaction conditions (Scheme 6, eq 6). However, we were unable to detect any activated amides (TMS-attached amides) (see Scheme S3 in the Supporting Information).

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The mechanism and the role of TMSCl are not clear at this time. We propose that Ni(0) was generated by manganese and added to the C−N bond of amide through oxidative addition to give an acyl amino nickel(II) complex, followed by the coordination of a primary amine to the nickel complex to provide a transaminated nickel(II) complex. We suggest that TMSCl might accelerate oxidative addition and/or transamination steps. Finally, the reductive elimination provides the transamidated secondary amide and Ni(0) catalyst.

In summary, we developed a direct transamidation of secondary amides using a catalytic combination of nickel and a Briphos ligand. Preactivation of the secondary amide is not necessary because TMSCl activates the aniline derivatives via the formation of the corresponding bis(trimethylsilyl)anilines. The reaction of secondary amides and anilines proceeded efficiently to afford the transamidation products in moderate to good yields. Aniline derivatives having electron-donating groups showed higher yields than those having electron-withdrawing groups. Secondary amines participated in this reaction, but the product yields were low. Further studies on the reaction mechanism are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03304.

Experimental procedures, NMR spectroscopic and MS data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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