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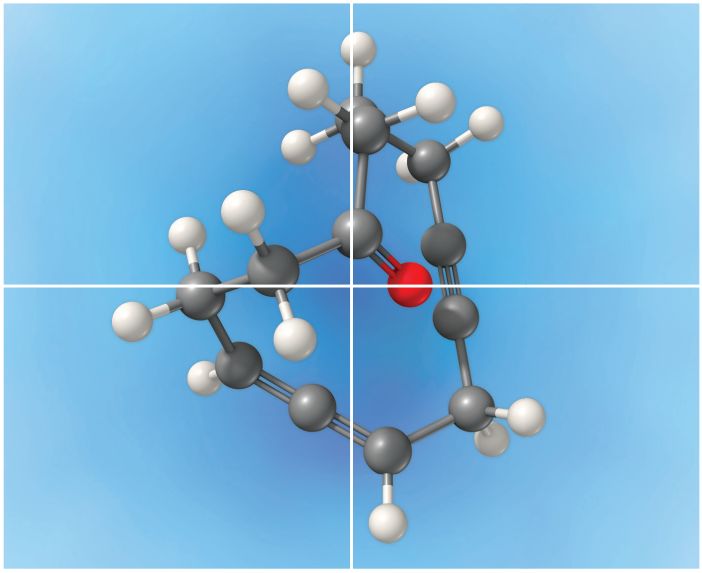

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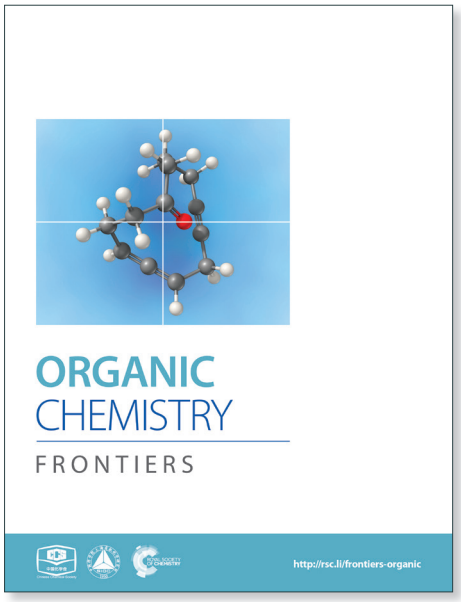

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ARTICLE

Acenaphthoimidazolium Chloride Enabled Nickel Catalyzed Amination of Bulky Aryl Tosylates†‡

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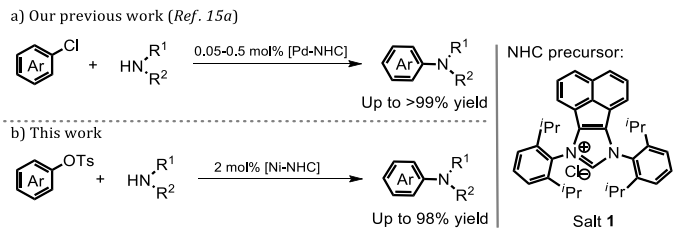
A robust catalyst derived from $NiCl_2$•(DME) and acenaphthoimidazolium chloride exhibited high activity towards challenging amination of bulky and heterocyclic aryl tosylates with secondary amines under mild reaction conditions at 2 mol% catalyst loading within 3 hours. Besides, a wide range of primary amines were also successfully mono-aminated by our new developed protocol.

1. Introduction

The carbon-nitrogen bonds exist in numerous bio-active, conductive and fluorescent compounds, which have found broad applications in pharmaceutical and material sciences.[1] It is generally accepted that transition metal-catalyzed amination reactions have been recognized as one of the most powerful and practical approaches to construct C-N bonds,[2,3] as represented by the Buchwald-Hartwig amination of aryl halides[4] and triflates.[5] Along with these significant contributions and ever-growing developments, however, more and more attention, currently, have been focused especially on the amination of sluggish phenolic derivatives in the presence of inexpensive metal catalysts.[6] Among the family of phenolic derivatives, aryl tosylates are very attractive and promising partners in amination reactions due to their ready accessibility, pronounced stability and low toxicity.[7] On the other hand, the low activity of aryl tosylates renders the amination of aryl tosylates elusive, probably because of the difficulty in the selective oxidative addition of C_{aryl}-O bond instead of $S_{sulfonyl}$-O bond.[8] According to these previous findings, the use of electron rich and bulky σ-donor ligands may facilitate the oxidative addition of inert electrophiles. Therefore, alkylphosphines with electronic rich and bulky σ-donor functional groups[9] were considered as efficient ligands in the cross-coupling reactions of inactive electrophiles, including aryl tosylates. However, such amination reactions by using inexpensive nickel catalysts always suffered from low yields, even when high catalyst loadings, elevated reaction temperature and extended reaction time were employed.[10] Therefore, one of particular emphases in organic synthesis is putting on addressing the limitation of aryl tosylates as substrates in the amination reactions.

As we know, *N*-heterocyclic compounds (NHC) have been well-accepted as the ligands with strong σ-electron donor and week π-acceptor properties,[11] and many NHC-enabled coupling reactions are developed so far.[13] For example, the first nickel-catalyzed amination of aryl tosylates was initiated by Yang and co-workers by using *trans*-arylbis(triphenylphosphine)nickel(II) as a precatalyst and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr•HCl, a NHC carbine precursor) as an additional ligand.[12] The control experiments indicated that the catalytic system devoid of NHCs did not work well for the above amination reactions. By switching the precatalyst to air sensitive styrene-coordinated Ni(0) complex derived from IPr•HCl, Nicasio and co-workers realized the amination of aryl tosylates without any reductant addition.[14] Despite these advances in the nickel-catalyzed amination for C-N bond formation in recent years, the known methodologies are still suffered: 1) the air-sensitivity of the precatalysts; 2) relatively high catalyst loading (at least 5 mol% catalyst was required); and 3) limited substrates scope. Electron rich, bulky and heterocyclic aryl tosylates were unfavorable for the transformation. As a consequence, we conceived the amination of aryl tosylates could be realized efficiently with a broad functional groups tolerance in the presence of nickel and π-extended NHC catalyst.



Scheme 1 Represented examples of imidazolium salts enabled amination reactions with different transition metals.

Recently our group accomplished the amination of inactive (hetero)-aryl chlorides with diverse secondary and primary amines by using robust Pd-NHC complex derived from imidazolium salt **1** as the precatalyst. The reactions proceeded smoothly to offer the desired amination products in good to excellent yields. Particularly, the steric hindered and heterocyclic substrates were well tolerated

even in the presence of 0.5 mol% catalyst loading (Scheme 1).[15] Inspired by what mentioned above and our continuous interest in the synthesis, characterization and applications of novel NHC-based transition metal complexes in catalysis and soft matters,[15-17] we would like to further explore the feasibility of the amination of bulky (hetero)-aryl tosylates with diverse amines by using the nickel and imidazolium salt **1** directly.

Table 1 Optimization of amination conditions [a]

2 3

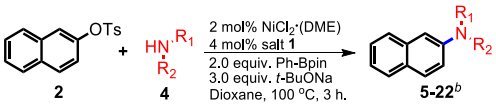
Entry	Solvent	Base (equiv.)	Yield (%)[b]
1	Dioxane	*t*-BuOK (3.0)	68
2	Dioxane	*t*-BuONa (3.0)	92
3	Dioxane	*t*-BuOLi (3.0)	41
4	Dioxane	K_3PO_4 (3.0)	18
5	Dioxane	*t*-BuONa (3.0)	82[c]
6	Dioxane	*t*-BuONa (1.6)	51
7	Toluene	*t*-BuONa (3.0)	78
8	*m*-Xylene	*t*-BuONa (3.0)	86
9	THF	*t*-BuONa (3.0)	72
10	DME	*t*-BuONa (3.0)	59
11	Dioxane/Toluene	*t*-BuONa (3.0)	91[d]
12	Dioxane	*t*-BuONa (3.0)	51[e]
13	Dioxane	*t*-BuONa (3.0)	13[f]

[a] 0.5 mmol reaction scale, with 2 mol% $NiCl_2$• (DME) and imidazolium salt **1** at 100 °C for 3 hours. [b] Isolated yield. [c] With 1 mol% $NiCl_2$• (DME) and imidazolium salt **1**. [d] Dioxane and Toluene in 1:1 ratio. [e] IPr•HCl was used. [f] IMes•HCl was used.

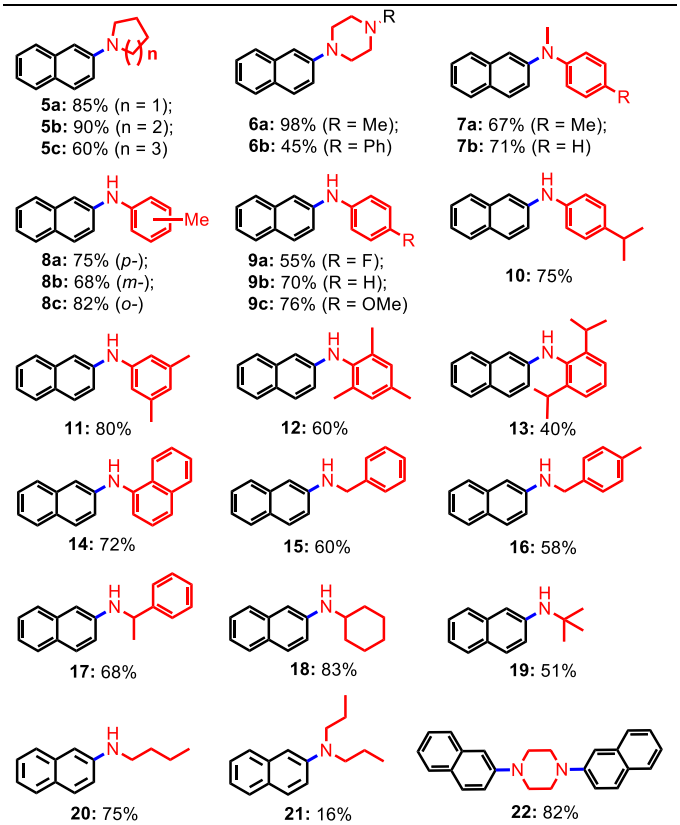
2. Results and discussion

Initially, the model reaction of bulky β-naphthyltosylate **2** and morpholine was carried out under 2 mol% $NiCl_2$•(DME), 4 mol% imidazolium salt **1**, 2.0 equiv. Ph-Bpin, and 3.0 equiv. *t*-BuOK in dioxane at 100°C. As expected, it was pleased to find that the amination product **3** was provided in a 68% isolated yield. Other inorganic salts were also evaluated accordingly. From the screening results, it seemed that *t*-BuONa was the best choice (Table 1, Entry 2). When relatively week base like K_3PO_4 was employed, only an 18% isolated yield was obtained (Table 1, Entry 4). The control experiment of bases suggested the base was still critical for the transformation.[15b] More details on the evaluation of bases were illustrated in supporting information (see ESI‡). Decrease of the catalyst loading to 1 mol% or the base amount to 1.6 equiv. were unfavorable for the amination, and the desired amine **3** was produced in the yields of 82% and 51%, respectively (Table 1, Entries 5-6). Other result-affecting factors such as solvents and temperature were also optimized. The yields of reactions decreased when toluene (78% yield) and *m*-xylene (86% yield) were used as the solvent (Table 1, Entries 7-8). Ether solvents like THF and DME afforded worse outcomes than that of dioxane (72 % and 59% *vs.* 92%, Table 1, Entries 9-10 *vs.* 2). In order to improve the amination efficiency, the mixture solvents were also involved in the optimization, however, no better results were found. When dioxane and toluene were mixed in 1:1 ratio, an excellent yield was found, which was similar to that obtained from dioxane (91%, Table 1, entry 11). Furthermore, other classical NHC precursors, such as IPr•HCl and IMes•HCl were also involved the optimization, however, only inferior yields were observed (51% and 13%, Table 1, Entries 12-13), which is also consisted with previous reports.[12]

Table 2 Amination of β-naphthyl tosylate **2** with various amines[a]



2 4 5-22[b]



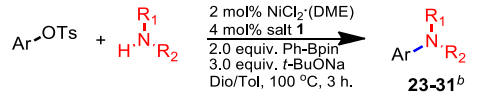
[a] 0.5 mmol scale for 1 hour at rt, then 3 hours at 100 °C, with 2 mol% $NiCl_2$• (DME). [b] Isolated yield.

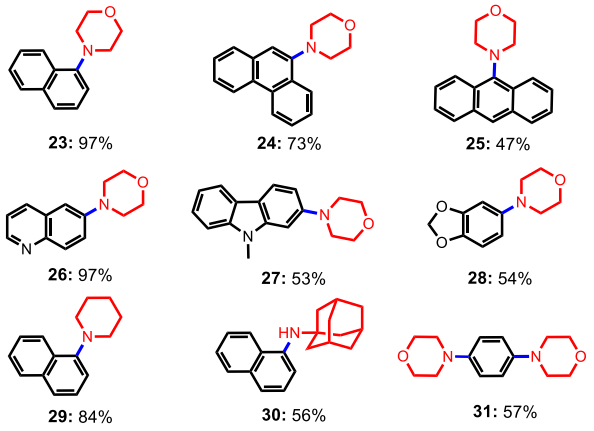
With the optimized reaction conditions in hand (2 mol% $NiCl_2$• (DME), 4 mol% imidazolium salt **1**, 2.0 equiv. Ph-Bpin, and 3.0 equiv. *t*-BuONa in dioxane at 100°C), the scope of reaction was then explored. As shown in Table 2, various primary and secondary amines were used to evaluate the protocol efficiency. In the case of secondary amines, whenever cyclic and linear amines were employed, the reaction worked well with the formation of the products **5-7** in moderate to excellent yields. The ring size of the cyclic amine slightly influenced the amination process, piperidine revealed the best outcome compared to pyrrolidine and azepane (**5b** *vs.* **5a** and **5c**, 90% *vs.* 85% and 60%). The amination using *N*-methylpiperazine as the substrate gave almost a quantitative yield (98%, **6a**), however, only a 45% isolated yield was

observed with the use of its phenyl analogue (**6b**) as the reaction partner. Acyclic *N*-methylanilines with various electron properties were also compatible for the amination, and similar results were obtained (67-71%, **7a-b**). To our delight, when a series of primary amines were utilized, the corresponding mono-amination products **8-20** were found in moderate to good isolated yields. The steric hindrance and electron effect of primary amines made slight impact on the transformations. The results compiled in Table 2 revealed that electron-rich groups were more favorable than electron-poor ones (75 % and 76% *vs.* 55%, **8a** and **9c** *vs.* **9a**). The reactions of *o*-substituted substrates gave rise to better outcomes than that of its *p*- and *m*- analogues (82 % *vs.* 75% and 68%, **8c** *vs.* **8a** and **8b**). Interestingly, more steric hindered substrates, such as 2,4,6-trimethylaniline, 2,6-diisopropyl-aniline and α-naphthylamine, were also investigated, still resulting in products **12**, **13** and **14** in 60%, 40% and 72% yields, respectively. Due to the potential tendency of β-hydride elimination of the resulting transition-metal amide complexes, acyclic aliphatic primary amines were considered as challenging substrates for the amination reactions.[18] Delightedly, our results indicated that they are also suitable substrates for the transformation (**15-20**). Again, steric hindrance was well tolerated, aliphatic primary amines with α-substituents were more favorable for the transformation, and better yields were afforded (83% and 68% *vs.* 60 %, **18** and **17** *vs.* **15**). As we expected, a 51% isolated yield was obtained when low-bowling point *t*-butyl amine was used as the substrate (**19**). When *n*-butyl amine, which has a higher boiling point, was involved in, the yield could be increased to 75% (**20**). However, only a 16% yields was obtained with *n*-alkylated secondary amine ((*n*-Pr)$_2$NH) was applied (**21**), which is absolutely unlike the cyclic cases (**5-6**). Diamination reactions were observed when *N*-free piperazine was involved. Diarylation product (**22**) was offered in an 82% yield under the standard conditions.

In consideration of our new developed protocol was applicable for steric bulky substrates for both amination partners; morpholine was selected to verify its feasibility for diverse steric bulky and heterocyclic tosylates (Table 3). By altering the solvent to co-solvent of dioxane and toluene, all selected bulky aryl tosylates were well tolerated in the amination process. For instance, the amination of bulky α-naphthyl tosylate resulted in a higher yield than that of its β-analogue (97% *vs.* 92%, **23** *vs.* **3** in Table 1, Entry 2). Tosylate derived from phenanthren-9-ol was more favorable for the amination than that of anthryl analogue, producing the corresponding products **24** and **25** in the yields of 73% and 47%, respectively. To our delight, bulky heterocyclic tosylates containing quinolone core, carbazole and benzodioxole rings were all tolerated and gave out moderate to excellent yields (up to 97%, **26-28**). When other amines such as piperidine and adamantan-1-amine were utilized in the amination of bulky α-naphthyltosylate, moderate to good yields were also obtained (84% yield and 56% yield, **29** and **30**). Furthermore, double amination of 1,4-phenylene-bis-tosylates with morpholine also proceeded well and provided a 57% isolated yield (**31**).

Table 3 Amination of steric hindered and heterocyclic aryl tosylates.[a]





[a] 0.5 mmol scale for 1 hour at rt, then 3 hours at 100°C, with 2 mol% $NiCl_2$•(DME). [b] Isolated yield.

Conclusions

In summary, we have discovered a robust catalyst derived from $NiCl_2$•(DME) and acenaphthoimidazolium chloride **1,** which exhibited high activity towards the amination of bulky and heterocyclic aryl tosylates with various secondary amines under mild reaction conditions at 2 mol% catalyst loading within 3 hours. Furthermore, a wide range of primary amines were also successfully mono-aminated. The protocol presented herein may provide a practical approach for the synthesis of disubstituted aryl amines. The reaction results mentioned above confirm that NHC-ligand derived from acenaphthoimidazolium chloride **1** does enhance the catalytic efficiency of the resulted Ni-NHC complex, enabling the challenging amination of inactive bulky and heterocyclic aryl tosylates. More detailed studies on the applications of acenaphthoimidazolium chloride in other challenging coupling reactions are under exploring in our laboratory, and the results will be reported in due course.

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Notes and references

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† Dedicated to Prof. Li-Xin Dai on the occasion of his 90th birthday.

‡ Electronic supplementary information (ESI) available: General experimental methods and the characterization data of compounds. See DOI: 10.1039/b000000x/

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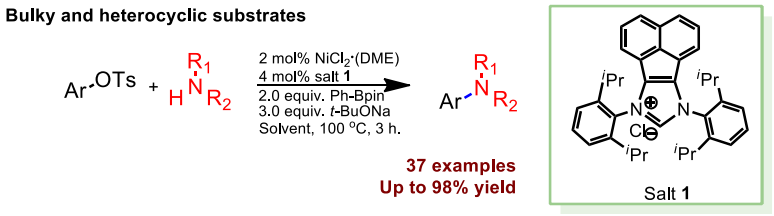

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