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Efficient Nickel-Mediated Intramolecular Amination of Aryl Chlorides

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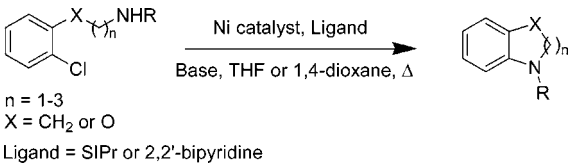
ABSTRACT



The use of an in situ generated Ni(0) catalyst associated with 2,2′-bipyridine or *N*,*N*′-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene (SIPr) as a ligand and NaO-*t*-Bu as the base for the intramolecular coupling of aryl chlorides with amines is described. The procedure has been applied to the formation of five-, six-, and seven-membered rings.

As a result of the important pharmacological activity of nitrogen heterocycles, general and efficient methods for their preparation are continually being developed. Among them, transition-metal-promoted processes have gained in popularity in recent years.[1]

One significant area of improvement is that of metal-catalyzed cross-coupling methods. Palladium-catalyzed amination, first introduced by Buchwald and Hartwig, has proven to be a valuable synthetic method for aryl carbon−nitrogen bond formation and has been intensively examined for the preparation of a wide range of arylamines.[2] This method has gained popularity as a mild alternative for the synthesis of amino derivatives, inaccessible through other routes.

An intramolecular variant of this reaction has first been utilized to construct indoline, tetrahydroquinoline, benzazepine, oxindole, and carboline derivatives.[3−11] A few extensions for the synthesis of *N*-aryl-indazoles[12] and benzimidazoles[13] have also been reported.

Despite significant improvements in the cyclization of aryl bromides with secondary amines and carbamates with bisphosphines such as DPEphos (bis(2-diphenylphosphinophenyl)ether) or Xantphos (9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene) or with the monophosphine MOP ligand (2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl),[8] no optimization study has been undertaken with aryl

(1) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Pergamon: Amsterdam, 2000.

(2) Reviews: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (d) Muci, A. R.; Buchwald, S. L. Practical Palladium Catalysts for C−N and C−O Bond Formation. In *Cross-Coupling Reaction: A Practical Guide*: Miyaura, N., Ed.; Topics in Current Chemistry Ser. 219; Springer-Verlag: New York, 2002; pp 131−209.

(3) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546.

(4) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028−1030.

(5) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458.

(6) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417−6418.

(7) Abouabdellah, A.; Dodd, R. H. *Tetrahedron Lett.* **1998**, *39*, 2119−2122.

(8) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37.

(9) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501−2504.

(10) Brown, J. A. *Tetrahedron Lett.* **2000**, *41*, 1623−1626.

(11) Margolis, B. J.; Swidorski, J. J.; Rogers, B. N. *J. Org. Chem.* **2003**, *68*, 644−647.

(12) (a) Song, J. J.; Yee, N. K. *Org. Lett.* **2000**, *2*, 519−521. (b) Song, J. J.; Yee, N. K. *Tetrahedron Lett.* **2001**, *42*, 2937−2940.

(13) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133−136.

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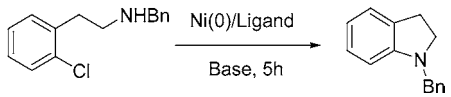
chlorides with pendant simple amines. Moreover, the high cost of palladium invites less expensive alternatives.

We initially reported the use of 2,2′-bipyridine (bpy)-bound Ni(0) clusters, generated in situ by reduction of a nickel(II) salt with alkoxide-activated sodium hydride, to mediate the coupling of aryl chlorides with secondary cyclic and acyclic amines.[14] The use of a Pd(0)/*N*-heterocyclic carbene[15] (NHC) catalyst system for the amination of aryl chlorides was first described by Hartwig[16] and Nolan.[17] Following up on this work, we have recently reported the use of a Ni(0) catalyst associated with a strong electron-donating and sterically hindered NHC (*N*,*N*′-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene, SIPr) to allow mild amination of aryl chlorides with several classes of amines.[18] Motivated by the extension of this method and by increased understanding of Ni-catalyzed amination reactions, we report herein an alternative synthesis of nitrogen heterocycles from aryl chlorides with pendant amino groups by intramolecular Ni(0)-catalyzed *N*-arylation reactions.

The cyclization of *N*-benzyl-*N*-(2-chlorophenethyl)amine into *N*-benzylindoline was first studied to establish the most effective conditions (Table 1).

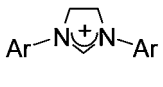
Table 1. Optimization of Conditions[a]



entry	mol % Ni	conditions	ligand	solvent	yield[b] (%)
1	10	B	SIPr	THF	77
2	10	B	SIPr	dioxane	97
3	5	B	SIPr	dioxane	94
4	2	B	SIPr	dioxane	95
5	10	A	bpy	THF	84
6	5	A	bpy	THF	84
7	2	A	bpy	THF	52
8	2	A	bpy	dioxane	47
9	10	B	SIMes	dioxane	13
10	10	B	SITol	dioxane	9
11	10	B	phen	dioxane	4
12	10	B	dppf	dioxane	55
13	-	A	bpy	THF	8
14	-	B	SIPr	dioxane	9

[a] Reaction conditions A: 10.0 mmol of *N*-benzyl-*N*-(2-chlorophenetyl)-amine, L/Ni = 3/1, 1.0 mmol of NaO-*t*-Bu, 9.5 mmol of NaH, 0.5 mmol of styrene, 15 mL of solvent, reflux, 5 h. Reaction conditions B: 10 mmol of *N*-benzyl-*N*-(2-chlorophenethyl)amine, L/Ni = 1/1, 15 mmol of NaO-*t*-Bu, 15 mL of solvent, reflux, 5 h. [b] Isolated yield; average of two runs.

Besides SIPr and bpy (which were typically used in our previous reports of intermolecular arylation of amines), other NHCs, 1,10-phenanthroline (phen), and dppf (1,1′-bis-(diphenylphosphino)ferrocene) used by Buchwald[19] and Lipshutz[20] in aryl aminations catalyzed by Ni(cod)$_2$ were tested as ligands. With SIPr or bpy as ligand, the reaction went smoothly to completion without any formation of undesired byproducts (Table 1, entries 4 and 6). With the Ni/SIPr catalyst, reactions were best performed with 2 mol



SIPr: Ar = 2,6-*i*-Pr$_2$C$_6$H$_3$
SIMes: Ar = 2,4,6-Me$_3$C$_6$H$_2$
SITol : Ar = 4-MeC$_6$H$_4$

Figure 1. NHC precursors used for the nickel-catalyzed amination reaction.

% Ni in dioxane, whereas with bpy as ligand, reactions required 5 mol % Ni and better results were obtained in THF compared to dioxane. During our optimization efforts, the influence of the nickel/ligand ratio was also investigated. We have found that with SIPr as supporting ligand, a 1:1 nickel−ligand ratio afforded optimum reaction rates, whereas with bpy, a 1:3 nickel−ligand ratio was found to be the most effective. We have subsequently verified in control experiments containing all of the reagents, except Ni(0) and ligand, that without catalyst, only traces amounts of indoline were obtained (entries 13 and 14).

Using SIMes or SITol as ligand gave poor results. Even with 10 mol % Ni, the reaction reached only 13% and 9% yield, respectively (Table 1, entries 9 and 10), showing that SIPr is a much better ligand for this Ni-catalyzed C−N bond-forming reaction and that the steric hindrance of the ligand is responsible for the improved catalytic performances. The use of phen (Table 1, entry 11) led to complex mixtures where 53% of the starting material, 43% dechlorinated *N*-benzyl-*N*-(2-chlorophenethyl)amine, and only 4% *N*-benzylindoline were observed. A catalyst based on the dppf ligand also possesses lower activity than Ni/SIPr or Ni/bpy for intramolecular Ni-catalyzed C−N bond forming reactions (Table 1, entry 12).

The intramolecular aryl amination was applied to various aryl chlorides using the two sets of optimized conditions, method A for Ni/bpy (Table 1, entry 6) and method B for Ni/SIPr (Table 1, entry 4) catalysis. Note that method A is not effective for the arylation of primary amines.[18b]

Treatment of amino aryl chlorides with a nickel catalyst and a base in THF for Ni/bpy catalyst or 1,4-dioxane for

(14) (a) Brenner, E.; Fort, Y. *Tetrahedron Lett*. **1998**, *39*, 5359−5362. (b) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829−12842. (c) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2000**, *41*, 2875−2879. (d) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2000**, *41*, 2881−2884. (e) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2001**, *42*, 247−250. (f) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron* **2001**, *57*, 7657−7664. (g) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **2002**, *58*, 6913−6924. (h) Desmarets, C.; Schneider, R.; Fort, Y.; Walcarius, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1844−1849.

(15) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309.

(16) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett*. **2000**, *2*, 1423−1426.

(17) For recent reports, see: (a) Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett*. **2003**, *5*, 1479−1482. (b) Viciu, M. S.; Kissling, R. M.; Stevens, E. D.; Nolan, S. P. *Org. Lett*. **2002**, *4*, 2229−2231. (c) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem*. **2001**, *66*, 7729−7737.

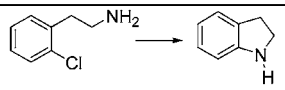
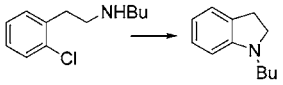
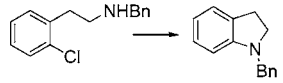
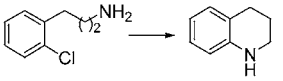
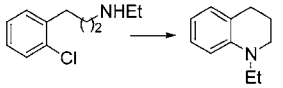
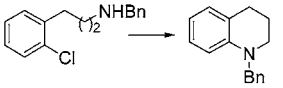
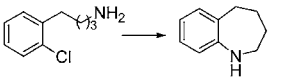
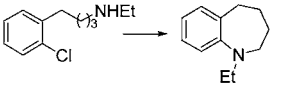
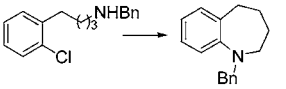
(18) (a) Gradel, B.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett*. **2001**, *42*, 5689−5692. (b) Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem*. **2002**, *67*, 3029−3036.

(19) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 6054−6058.

(20) (a) Lipshutz, B. H.; Ueda, H. *Angew. Chem., Int. Ed*. **2000**, *39*, 4492−4494. (b) Lipshutz, B. H.; Tasler, S.; Chrisman, W.; Spliethoff, B.; Tesche, B. *J. Org. Chem*. **2003**, *68*, 1177−1189. (c) Tasler, S.; Lipshutz, B. H. *J. Org. Chem*. **2003**, *68*, 1190−1199.

Ni/SIPr catalyst promoted the cyclization into the corresponding heterocycles (Table 2). At reflux temperature, the

Table 2. Ni(0)-Catalyzed Intramolecular *N*-Arylation[a]

entry	transformation	cond.	*t*/h	yield (%)[b]
1		B	3	98[d]
2		A	6	82[d]
3		B	7	87[d]
4		A	7	84[d]
5		B	9	95[d]
6		B	4	96
7		A	7	83
8		B	7	82
9		A	7	95
10		B	9	93
11		B	11	81
12		A	13	70
13		B	15	73
14		A	14	72
15		B	17	78

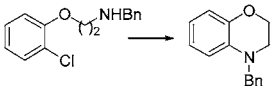
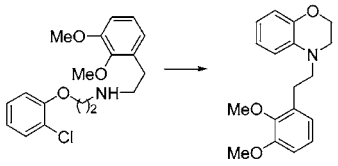
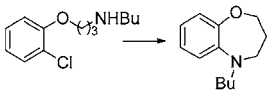
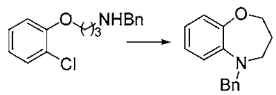
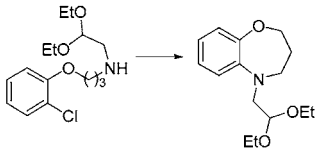
[a] Reactions conditions A: 10.0 mmol of amino aryl chloride, 5 mol % Ni(0), 15 mol % bpy, 1 mmol of NaO-*t*-Bu, 9.5 mmol of NaH, 5 mol % styrene, THF (15 mL), 65 °C. Reactions conditions B: 10 mmol of amino aryl chloride, 2 mol % Ni(0), 2 mol % SIPr, 15.0 mmol of NaO-*t*-Bu, dioxane (15 mL), 100 °C. [b] Isolated yields. [d] Isolated as a 9:1 mixture with the corresponding indole.

synthesis of indolines (entries 1−5) and tetrahydroquinolines (entries 6−10) proceeded quickly (3−9 h) and in excellent yields. It is worth noting that indolines (entries 1−5) were isolated as 90:10 mixtures with side products identified as the corresponding indoles, arising from a classical oxidation, which were separable by column chromatography. Dehalogenation of the starting aryl chloride was only a minor side reaction (<1%) and no side products were isolated from any of the other intramolecular aryl amination.

The reaction gave better results in the formation of five- and six-membered rings. The cyclization into 2,3,4,5-tetrahydro-1*H*-1-benzazepines required longer reaction times (11−17 h) (the conversion being incomplete even after heating for 24 h) and gave slightly lower yields (entries 11−15).

A series of ether-linked substrates, shown in Table 3, were next subjected to these cross-coupling conditions to explore the reaction scope further.

Table 3. Ni(0)-Catalyzed Synthesis of Benzoxazines and Benzoxazepines[a]

entry	transformation	cond.	*t*/h	yield (%)[b]
1		A	13	51
2		B	15	47
3		A		46
4		B		44
5		A	13	50
6		B	16	-[c]
7		A	14	49
8		B	20	-[c]
9		A	15	53
10		B	24	-[c]

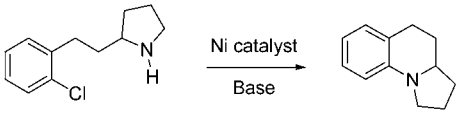
[a] Reactions conditions A: 10.0 mmol of amino aryl chloride, 5 mol % Ni(0), 15 mol % bpy, 1 mmol of NaO-*t*-Bu, 9.5 mmol of NaH, 5 mol % styrene, THF (15 mL), 65 °C. Reactions conditions B: 10 mmol of amino aryl chloride, 2 mol % Ni(0), 2 mol % SIPr, 15.0 mmol of NaO-*t*-Bu, dioxane (15 mL), 100 °C. [b] Isolated yields of pure material. [c] No conversion of the starting material.

Examples 1−4 of Table 3 clearly indicate that the cyclization into benzoxazines worked under conditions A and B but provided the oxygenated heterocycles in decreased yields compared to their carbon analogues. These results are not surprising and follow the electronic trends expected for these electron-rich aryl chlorides. Finally, the synthesis of benzoxazepines (entries 5−10, Table 3) could be achieved with the Ni/bpy catalyst, but the presence of an ortho oxygen completely inhibited the Ni/SIPr-catalyzed cyclizations. The superiority of bpy relative to SIPr for the preparation of seven-membered benzoxazine rings might result from a coordination of the SIPr-bound nickel center at the oxygen atom of the starting 3-(2-chlorophenoxy)-1-propanamine, as previously observed with *o*-chloro- or fluoroanisoles in amination[18b] and defluorination[21] reactions mediated by our Ni(0)/NHC complexes. This coordination seems not to take

place in the putative Ni(II) oxidative addition complex yielding benzoxazines (entries 2 and 4, Table 3).

The application of our Ni-catalyzed cyclization protocols to couplings involving secondary cyclic amines was also briefly explored. The synthesis of benzo[*e*]indolizidine (Scheme 1) under Pd-catalysis was first explored by Buch-

Scheme 1. Ni-Catalyzed Synthesis of Benzo[*e*]indolizidine



Method A (Ni/bpy catalyst) : 85% (5 h)
Method B (Ni/SIPr catalyst) : 81% (6 h)

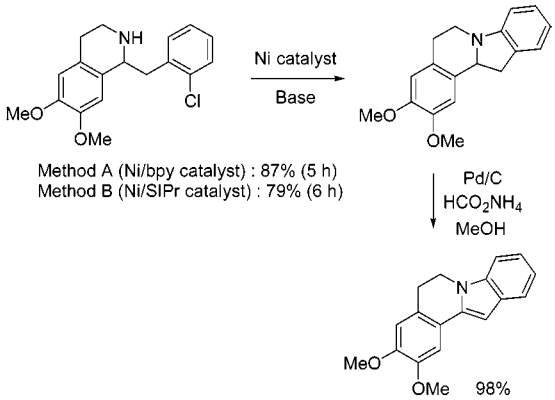
wald, and the reported conditions did not efficiently provide access to the desired ring system ($Pd(PPh_3)_4$ (10 mol %), NaO-*t*-Bu, toluene, 100 °C, 55%).[3]

We applied the conditions described in Table 2 to this intramolecular cycloamination and were pleased to find out that both Ni catalysts were quite equally effective and allowed the transformation in good yields and short reaction times.

We finally evaluated the efficiency of our Ni(0) catalysts for the synthesis of indolo[2,1-*a*]isoquinoline. Recent studies have demonstrated that nucleophilic addition of the isoquinoline nitrogen to an aryl bromide is the more general route to the desired tetracyclic structure, but the reaction required rather harsh conditions and long reaction times (K_2CO_3, DMF, reflux, 2−3 days).[22]

Under Ni catalysis, the cyclization of the readily accessible 1-(2-chlorobenzyl)tetrahydroisoquinoline[22a] proceeded ef-

Scheme 2. Ni-Catalyzed Synthesis of 5,6-Dihydroindolo[2,1-*a*]isoquinoline



Method A (Ni/bpy catalyst) : 87% (5 h)
Method B (Ni/SIPr catalyst) : 79% (6 h)

ficiently within 7 h (Scheme 2). The 5,6,12,12a-tetrahydroindolo[2,1-*a*]isoquinoline could, however, not be characterized because of its instability and was converted to the corresponding 5,6-dihydro[2,1-*a*]isoquinoline by treatment with HCO_2NH_4 in the presence of Pd/C.[23]

In summary, we report alternative methods for intramolecular coupling of aryl chlorides with amines using Ni/bpy or Ni/SIPr catalysts. The complexes show good catalytic activity for the synthesis of indoles, quinolines, benzazepines, benzoxazines, and benzoxazepines. We have also disclosed promising results in the Ni-catalyzed intramolecular arylation of cyclic amines. Work is currently underway to optimize and extend the scope of these Ni-catalyzed aminations.

Supporting Information Available: Experimental details and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Kuhl, S.; Schneider, R.; Fort, Y. *Adv. Synth. Catal.* **2003**, *345*, 341−344.

(22) (a) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Sugimone, H. *J. Org. Chem.* **1999**, *64*, 6583−6596. (b) Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. *Org. Lett.* **2000**, *2*, 1799−1801.

(23) Kiguchi, T.; Kuninobu, N.; Yukiyo, Y.; Naito, T.; Ninomiya, I. *Synthesis* **1989**, 778−781.