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Nickel-Catalyzed Synthesis of Diarylamines via Oxidatively Induced C–N Bond Formation at Room Temperature

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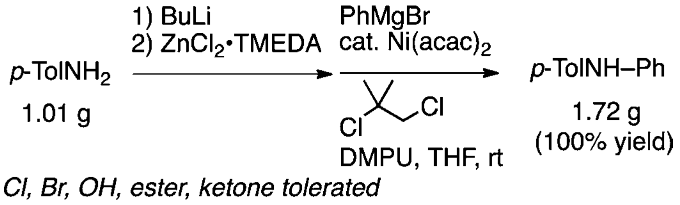
ABSTRACT



A nickel-catalyzed oxidative coupling of zinc amides with organomagnesium compounds selectively produces diarylamines under mild reaction conditions, with tolerance for chloride, bromide, hydroxyl, ester, and ketone groups. A diamine is bis-monoarylated. A bromoaniline undergoes *N*-arylation followed by Kumada–Tamao–Corriu coupling in one pot. The reaction may proceed via oxidatively induced reductive elimination of a nickel species.

Diarylamines form the core of many commercially available drugs,[1] and their synthesis,[2] such as transition-metal-catalyzed cross-coupling of amines with aryl halides, has received much attention.[3] There have also been reports on a different retrosynthetic strategy, where a metal amide is coupled with an organometallic reagent in the presence of an oxidant under mild reaction conditions, typically in the presence of a stoichiometric[4,5] or catalytic amount[6] of copper. We have recently demonstrated[7] that an iron catalyst can effect the oxidative reaction of zinc amides with diarylzinc reagents; however, the reaction requires a large amount of organometallic reagent and catalyst and a high reaction temperature, and the substrate scope is limited. We report here that a catalytic amount (5 mol %) of a nickel salt effects the coupling of zinc amides with organomagnesium reagents (1.2–3 equiv) at rt in the presence of an organic dihalide as a mild oxidant to produce diarylamines with high yields and with tolerance of chloride, bromide, hydroxyl, ester, and ketone groups. This reaction is a rare example of nickel-catalyzed oxidatively induced carbon–nitrogen bond formation.[8–10]

As depicted in Scheme 1, a large amount of organometallic reagent is necessary for amination under oxidative conditions because of fast decomposition of the organometallic species

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[1] Lawrence, S. A. *Amines: Synthesis, Properties and Applications*; Cambridge University Press: Cambridge, U.K., 2004.

[2] *Catalyzed Carbon-Heteroatom Bond Formation*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2011.

[3] For example: (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534–1544. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361. (c) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50.

[4] (a) Yamamoto, H.; Maruoka, K. *J. Org. Chem.* **1980**, *45*, 2739–2740. (b) del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7838–7842. (c) Kienle, M.; Dubbaka, S. R.; del Amo, V.; Knochel, P. *Synthesis* **2007**, *8*, 1272–1278. (d) Kienle, M.; Dunst, C.; Knochel, P. *Org. Lett.* **2009**, *11*, 5158–5161. (e) Alberti, A.; Cane, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677–1681.

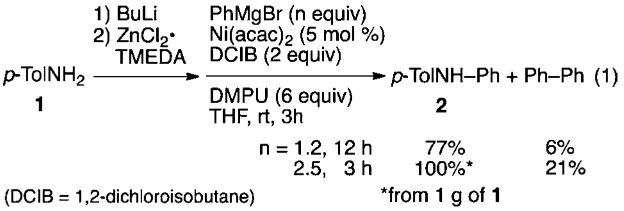
[5] For example: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449 and references therein. (b) Chan, D. M. T.; Monaca, K. L.; Wanag, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936. (c) Cundy, D. J.; Forsyth, S. A. *Tetrahedron Lett.* **1998**, *39*, 7979–7982. (d) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600–7601. (f) Lam, P. Y. S.; Clark, C. G.; Subern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, *5*, 674–676. (g) Elliott, G. I.; Konopelski, J. P. *Org. Lett.* **2000**, *20*, 3055–3057. (h) Sorenson, R. J. *J. Org. Chem.* **2000**, *65*, 7747–7749.

[6] (a) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233–1236. (b) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528–1531. (c) Lam, Y. S. P.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418. (d) Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077–2079. (e) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397–4400.

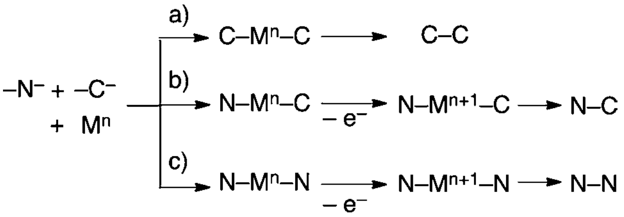
[7] Nakamura, Y.; Ilies, L.; Nakamura, E. *Org. Lett.* **2011**, *13*, 5998–6001.

10.1021/ol302688u

to give undesired homocoupling products (path a). The decomposition of organoiron species is especially fast,[11] and this pathway was dominant in our previous studies. We hypothesized that a nickel catalyst could be more efficient, because organonickel species are more stable,[12] and the oxidation of organonickel amides to generate a C–N bond is known to proceed smoothly.[8] Indeed, we found that the reaction of a zinc amide generated in situ from *p*-toluidine (**1**, 1 g) with PhMgBr (2.5 equiv) in the presence of Ni(acac)$_2$ (5 mol %), 1,2-dichloroisobutane (DCIB) as an oxidant,[11] and DMPU as an additive[13] in THF at rt gives *N*-phenyl-*p*-toluidine (**2**) in 100% yield (eq 1). Only a small amount of the homocoupling product (i.e., biphenyl, 21% based on PhMgBr) was observed. Notably, the reaction also proceeded with a nearly stoichiometric (1.2 equiv) amount of PhMgBr, when the amount of biphenyl was reduced to 6%, but the reaction became much slower and the yield decreased to 77% isolated yield (from 0.5 mmol of **1**, recovery of **1** in 23%). No overarylated product (*N*,*N*-diphenyl-*p*-toluidine) was observed.



Scheme 1. Competition between C–N and C–C Bond Formation under Oxidative Catalysis



We examined a variety of catalysts and reaction conditions; the results are summarized in Table 1. The reaction conditions using an iron catalyst that we previously reported[7] resulted in exclusive C–C bond formation and recovery of the starting amine **1** (entry 2). In the absence of a catalyst, neither C–N nor C–C bond formation proceeded (entry 3). Under the standard reaction conditions, other metal catalysts such as Co(acac)$_3$, CuCl$_2$, and PdCl$_2$(PPh$_3$)$_2$ (entry 4) did not give any of the C–N product **2**, and C–C bond formation and recovery of substrate **1** was observed, with the exception of the Cu catalyst, where homocoupling also hardly proceeded (3%). Without oxidant, **2** was not obtained at all, and homocoupling proceeded stoichiometrically (entry 5), suggesting that the oxidant promotes the reductive elimination step, rather than just reoxidizing the nickel species (see also eq 3). A polar additive such as DMPU had a beneficial effect and retarded homocoupling (entries 1 and 6); however, the reason is unclear.[13] A lithium amide prepared from **1** and BuLi did not react at all, and **1** was mostly recovered, together with the formation of biphenyl (entry 7).

Table 1. Effect of Several Key Parameters on the Ni-Catalyzed Oxidative Reaction of *p*-Tolylamidozinc Chloride with PhMgBr

entry	conditions	**2** (%)[b]	**1** (%)[b]	Ph–Ph (%)[c]
1	Cat. Ni(acac)$_2$, DCIB, DMPU[a]	100	0	21
2	Fe(acac)$_3$	0	96	44
3	No Ni(acac)$_2$	0	89	trace
4	Co(acac)$_3$, CuCl$_2$, PdCl$_2$(PPh$_3$)$_2$	0	84–94	3–66
5	without DCIB	0	96	9
6	without DMPU	68	27	53
7	without ZnCl$_2$·TMEDA	0	100	42

[a] The zinc amide was generated from **1** (0.50 mmol), *n*-BuLi in hexane (1.0 equiv), and ZnCl$_2$·TMEDA (1.0 equiv), and then it was reacted with PhMgBr (2.5 equiv) in the presence of Ni(acac)$_2$ (10 mol %) and DCIB (2.0 equiv) in THF at rt for 3 h. [b] Yield determined by ^{1}H NMR. [c] Based on PhMgBr.

With the optimized conditions in hand, we next investigated the scope of this reaction (Tables 2 and 3). Compared with the previously reported reaction using iron catalysis,[7] the reaction scope was expanded to include sterically hindered anilines, hydroxyl-, ester-, and ketone-possessing substrates, diamine, indolylamine, benzamide, and protected aminoarylmagnesium reagents. As shown in Table 2, various anilines, including electron-rich (entries 2, 10, and 11) and electron-deficient (entries 3–5 and 7) anilines reacted well. Sterically demanding amines (entries 11 and 12), which gave poor results under iron catalysis,[7] reacted smoothly under the present conditions. We did not observe any overarylated product (i.e., triarylamine) in any cases; however, the reaction of diarylamine **2** (entry 9) gave a small amount of triarylamine. A diamine (*m*-phenylenediamine, entry 10) was monoarylated at both amine sites

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(8) Stoichiometric reactions: (a) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421–4423. (b) Koo, K.; Hillhouse, G. L. *Organometallics* **1996**, *15*, 2669–2671. (c) Mindiola, D. J.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2001**, *123*, 4623–4624. (d) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890–2891.

(9) Muñiz, K.; Streuff, J.; Hövelmann, C. H.; Núñez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125–7127.

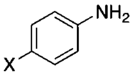
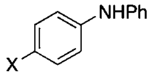
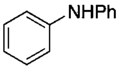
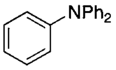
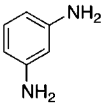
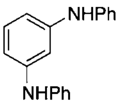
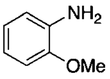
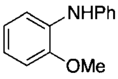
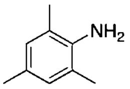
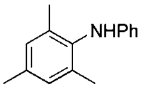
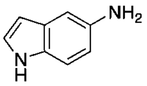
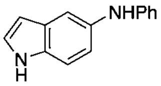
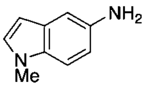
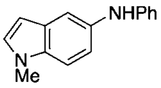
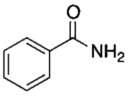
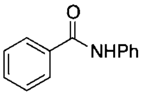
(10) While this manuscript was in preparation, a reaction of boronic acids with amines catalyzed by 20 mol % of nickel, presumably under oxidative conditions, was reported: Raghuvanshi, D. S.; Gupta, A. K.; Singh, K. N. *Org. Lett.* **2012**, *14*, 4326–4329.

(11) (a) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859. (b) Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 2925–2928. (c) Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 6557–6559. (d) Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 7672–7675. (e) Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem.—Asian J.* **2011**, *6*, 3059–3065. (f) Ilies, L.; Kobayashi, M.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2012**, *354*, 593–596.

(12) *Modern Organonickel Chemistry*; Tamaru, A., Ed.; Wiley-VCH: Weinheim, Germany, 2005.

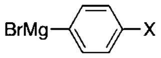
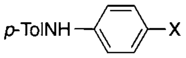
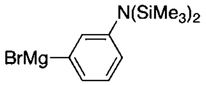
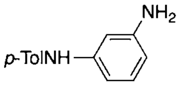
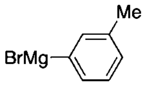
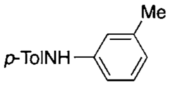
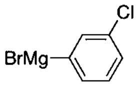
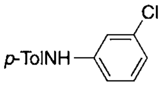
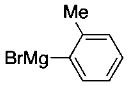
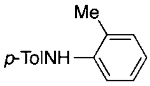
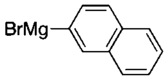
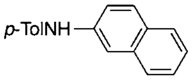
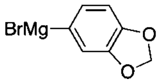
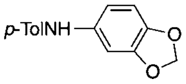
(13) (a) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428–429. (b) Ilies, L.; Chen, Q.; Zeng, S.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221–5223. (c) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232–3234.

Table 2. Nickel-Catalyzed Oxidative Monoarylation of Various Amines with PhMgBr[a]

entry	amine	product	yield (%)[b]
1[c]			100 (X = H)
2[c,d]		**2**	100 (X = Me)
3			83 (X = F)
4			87 (X = Cl)
5			77 (X = Br)
6			75 (X = OH)
7			99 (X = CO_2-*t*-Bu)
8			44[e] (X = $COCH_3$)
9			8[e]
10[f]			48
11			100
12			81
13			29
14			93
15			62
16	*n*-$C_8H_{17}NH_2$	*n*-$C_8H_{17}NHPh$	20[e]

[a] Reaction conditions: the zinc amide was generated from the corresponding amine (0.50 mmol), *n*-BuLi in hexane (1.0 equiv), and $ZnCl_2 \cdot$TMEDA (1.0 equiv), and then it was reacted with PhMgBr (3.0 equiv) in the presence of Ni(acac)$_2$ (10 mol %) and DCIB (2.0 equiv) in THF at rt. See the Supporting Information for details. [b] Isolated yield. The homocoupling product was observed in 5–20% yield (based on the starting PhMgBr), except when the yield was low. [c] Reaction performed with 2.5 equiv of PhMgBr and 5 mol % of Ni(acac)$_2$. [d] Reaction performed with 1 g of substrate. [e] Yield determined by GC in the presence of tridecane as an internal standard. [f] 5 equiv of PhMgBr, 12 equiv of DMPU, and 4 equiv of DCIB were used.

Table 3. Nickel-Catalyzed Oxidative Monoarylation of *p*-Toluidine with Various Grignard Reagents[a]

entry	ArMgBr	product	yield (%)[b]
1			93 (X = F)
2			53 (X = OMe)
3			95 (X = *n*-Bu)
4			69 (X = NMe_2)
5			98[c]
6			96
7			72
8			0
9			70
10			59

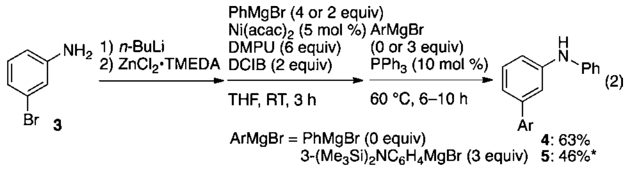
[a] Reaction conditions: the zinc amide was generated from **1** (0.50 mmol), *n*-BuLi in hexane (1.0 equiv), and $ZnCl_2 \cdot$TMEDA (1.0 equiv), and then it was reacted with ArMgBr (3.0 equiv) in the presence of Ni(acac)$_2$ (10 mol %) and DCIB (2.0 equiv) in THF at rt. See the Supporting Information for details. [b] Isolated yield. The homocoupling product was observed in 5–20% yield (based on the starting ArMgBr); a larger amount was observed when electron-rich ArMgBr was used. [c] The $SiMe_3$ groups were removed under acidic conditions.

with complete selectivity. The mild reaction conditions allowed the tolerance of chloride (entry 4 and Table 3, entry 7), bromide (entry 5), ester (entry 7), and ketone (entry 8). *p*-Hydroxyaniline (entry 6) could be reacted without the need to protect the hydroxyl group, and despite using only 1 equiv of BuLi/ZnCl$_2$, the aniline reacted chemoselectively over the phenol. Unprotected 5-aminoindole (entry 13) reacted with selectivity at the primary amine but with low yield; protection of the heteroaromatic nitrogen greatly improved the yield (entry 14), suggesting unproductive coordination of the indole's nitrogen to the active nickel species. Other heteroaromatic amines did not react under the present conditions. Benzamide could also be used as a substrate (entry 15) to produce benzanilide. An aliphatic amine could also be used (entry 16), albeit with low yield.

The scope of the Grignard reagent is summarized in Table 3. Both electron-deficient (entries 1 and 7) and electron-rich (entries 2–6) reagents gave the desired diarylamines in good yields. A dimethylamino group was tolerated (entry 4), and a Grignard reagent possessing a bis(trimethylsilyl)amino group (entry 5) gave a mono-*N*-substituted phenylenediamine in quantitative yield after removing the trimethylsilyl group under acidic conditions. Although *para*- (entries 1–4) and *meta*-substituted (entries 5–7) arylmagnesium reagents reacted well, *ortho*-substitution (entry 8) completely shut off the reaction.

2-Naphthylmagnesium bromide (entry 9) and a heterocyclic Grignard (entry 10) reacted with moderate to good yield. Alkylmagnesium compounds did not react under these conditions.

The chemoselectivity of the amination reaction under oxidative conditions could be exploited for sequential oxidative phenylation of bromoaniline **3**, followed by one-pot Kumada–Tamao–Corriu coupling with PhMgBr or protected aminophenyl Grignard to give **4** and **5**, respectively (eq 2). The cross-coupling reaction proceeded upon simply adding a phosphine ligand and heating at 60 °C.



*Isolated as the free amine after acidic workup.

On the basis of reports from Hillhouse that Ni(III)–amide complexes undergo facile reductive elimination to form a C–N bond,[8] we speculate that a nickel arylamide species is oxidized by DCIB to a higher valent species that readily undergoes reductive elimination to give the diarylamine product. This conjuncture is supported by the complete shutoff of the C–N bond-forming reaction in the absence of an oxidant, even when a stoichiometric amount of nickel salt is used, while the homocoupling reaction proceeds regardless of the oxidant (eq 3). Heat-induced reductive elimination of the putative Ni(II) species did not produce the C–N bond,[14] and only homocoupling proceeded (eq 3), demonstrating the unique chemoselectivity of the oxidatively induced process. When a radical-trapping reagent such as TEMPO was added, the C–N bond-forming reaction was largely shut off, whereas the homocoupling reaction was unaffected (eq 4). This may suggest that the C–N bond-forming process involves radical species, possibly generated from DCIB by single-electron transfer[11] from Ni(II).

$$\underset{(1\text{ equiv})}{\mathrm{Ni(acac)_2}} + \underset{(2\text{ equiv})}{p\text{-}\mathrm{TolNHZnCl}} + \underset{(2\text{ equiv})}{\mathrm{PhMgBr}} \xrightarrow[\text{THF, rt, 3 h}]{\substack{\text{DCIB (n equiv)}\\ \text{DMPU (6 equiv)}}} p\text{-}\mathrm{TolNH{-}Ph} + \mathrm{Ph{-}Ph} \qquad (3)$$

	p-TolNH–Ph	Ph–Ph
n = 0	0%	58%
0, 80 °C	0%	54%
2	76%	27%

$$\underset{(1\text{ equiv})}{p\text{-}\mathrm{TolNHZnCl}} + \underset{(2\text{ equiv})}{\mathrm{PhMgBr}} \xrightarrow[\substack{\text{DMPU (6 equiv)}\\ \text{THF, rt, 3 h}}]{\substack{\mathrm{Ni(acac)_2}\text{ (5 mol \%)}\\ \text{DCIB (2 equiv)}\\ \text{TEMPO (2 equiv)}}} \underset{3\%}{p\text{-}\mathrm{TolNH{-}Ph}} + \underset{53\%}{\mathrm{Ph{-}Ph}} \qquad (4)$$

In conclusion, we have developed a nickel-catalyzed oxidative coupling of zinc amides with organomagnesium compounds under mild reaction conditions and without the need for an external ligand, to produce diarylamines selectively and with tolerance of chloride, bromide, hydroxyl, ester, and ketone groups. We have shown here that a new catalysis design can control the hetero ligand coupling over homocoupling that is often so problematic in oxidative coupling reactions. The new catalysis design resulted in higher yields, milder reaction conditions, and expanded scope and functional group tolerance as compared with previous iron catalysis.[7] This work suggests the potential of nickel catalysis for oxidatively induced carbon–heteroatom formation, a strategy that has often been exploited recently in palladium and copper catalysis.[15]

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

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The authors declare no competing financial interest.