HHS Public Access

Author manuscript

Chem Sci. Author manuscript; available in PMC 2019 May 16.

Published in final edited form as:

Chem Sci. 2011 September 1; 2(9): 1766–1771. doi:10.1039/c1sc00230a.

Nickel-catalyzed amination of aryl carbamates and sequential site-selective cross-couplings†

Tehetena Mesganaw, **Amanda L. Silberstein**, **Stephen D. Ramgren**, **Noah F. Fine Nathel**, **Xin Hong**, **Peng Liu**, and **Neil K. Garg***

Department of Chemistry and Biochemistry, University of California, 607 Charles Young Drive East, Box 951569, Los Angeles, CA, 90095, USA.

Abstract

We report the amination of aryl carbamates using nickel-catalysis. The methodology is broad in scope with respect to both coupling partners and delivers aminated products in synthetically useful yields. Computational studies provide the full catalytic cycle of this transformation, and suggest that reductive elimination is the rate-determining step. Given that carbamates are easy to prepare, robust, inert to Pd-catalysis, and useful for arene functionalization, these substrates are particularly attractive partners for use in synthesis. The sequential use of carbamate functionalization/site-selective cross-coupling processes highlights the utility of this methodology.

Introduction

The discovery of methods for the assembly of carbon-nitrogen bonds continues to be an active area of research. Among the numerous tactics available for C–N bond formation, transition metal-catalyzed processes, led by Buchwald and Hartwig, have become some of the most widely used methods in chemical synthesis.[1] Recent efforts have focused on the catalytic amination of phenol derivatives,[2–5] as phenols are readily available, with certain analogs being ideally poised for the synthesis of poly-substituted arenes.[6]

One particularly attractive class of electrophilies is the *N*,*N*-dialkyl aryl *O*-carbamate (**1**, Fig. 1). Features of these substrates include their ease of preparation,[7] pronounced stability, and low reactivity toward Pd(0). Furthermore, aryl carbamates can be used for arene functionalization[8] prior to a cross-coupling event, using either electrophilic aromatic substitution,[9] directed *o*-metallation,[10] or recently described Pd- or Ir-catalyzed methods.[11]

Although aryl carbamates have been employed in C–C bond forming processes (Fig. 1, **1** → **2**),[12,13] their use in amination reactions (**1** → **3**), has been less explored. Specifically, during the course of our own studies, only a single example of carbamate amination was reported using the *N*,*N*-diethylcarbamate derivative of phenol.[4] Considering the importance of transition metal-catalyzed amination reactions in modern synthetic chemistry,[1] coupled with the salient features of carbamate electrophiles, we sought to develop a general method for

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c1sc00230a

* neilgarg@chem.ucla.edu.

carbamate amination. In this manuscript, we report the broad scope of carbamate amination methodology, as well as a computational study of the full catalytic cycle. In addition, we demonstrate the value of these reaction partners for the synthesis of polysubstituted aryl amines using sequential carbamate functionalization/site-selective cross-coupling methodologies.

Results and discussion

Optimization and substrate scope

To initiate studies, we attempted the amination of diethylnaphthylcarbamates with morpholine under a variety of reaction conditions. Although Ni/PCy_3-based conditions have been useful for achieving C–C bond formation, it was not possible to achieve amination using related procedures.[14] After conducting an extensive survey of reaction parameters *(e.g.,* nickel catalysts, ligands, solvents, bases, temperature, *etc.*) it was observed that combinations of Ni catalysts and *N*-heterocyclic carbene ligands promoted the desired amination. Our laboratory and Chatani's have previously noted analogous findings in couplings of sulfa- mates and pivalates, respectively.[4,5]

We identified the use of catalytic $Ni(cod)_2$, SIPr HCl (**4**),[15] and NaO*t*Bu, in dioxane at 80 °C as optimal reaction conditions for amination and investigated the carbamate substrate scope (Table 1).[16,17] Naphthyl carbamates, which typically function well in the Suzuki-Miyaura coupling, were excellent substrates for the amination (entries 1 and 2). Non-fused aromatics were also tolerated by the methodology (entries 3–7). The electron-donating methoxy group (entry 4) and the electron-withdrawing trifluoromethyl group (entry 5) were suitable substrates. Methyl substituents at the *para* and *meta* positions were tolerated as well (entries 6 and 7).

The feasibility of coupling *o*-substituted carbamates, in addition to heterocyclic substrates, was examined (Table 2).[17] Of note, *o*-substituted aryl carbamates are readily accessible by functionalization of the parent carbamate (using directed metallation[10] or transition metal-catalyzed processes[11]), but have proven to be exceptionally challenging substrates in the recently discovered nickel-catalyzed Suzuki–Miyaura coupling.[12] We were delighted to find that a range of *o*-substituted phenylcarbamates could be employed in our amination methodology.[18] Carbon substituents were well-tolerated (entries 1 and 2), as were heteroatoms (entries 3–5). Furthermore, heterocyclic substrates containing indole or pyridine underwent coupling with morpholine under nickel catalysis (entries 6 and 7).

As shown in Table 3, a variety of amines can be employed in the carbamate amination.[17,19] Both cyclic and acyclic secondary amines were tolerated (entries 1–3), in addition to anilines (entries 4–6). Of note, use of the sterically congested 2, 6-dimethylaniline delivered the corresponding aminated product in 92% yield (entry 6). The methodology also allows for the coupling of amines with appended heterocycles (entries 7 and 8).

Computational studies

Although the mechanism of palladium-based aminations has been studied computationally,[20–22] no theoretical studies of nickel-catalyzed aminations have been reported. Furthermore,

computational studies involving unconventional phenol-based electrophiles (e.g., esters, carbamates, sulfamates) are rare and have only been examined in the context of C–C bond formation.[23]Accordingly, we conducted a DFT study of the nickel-catalyzed carbamate amination, using *N*,*N*-dimethylphenylcarbamate and dimethylamine as substrates.[24]

The results of this computational study are shown in Fig. 2 in the form of a Gibbs free energy diagram, which in turn, provides the full catalytic cycle for carbamate amination. Analogous to Pd-catalyzed amination, three fundamental steps occur: oxidative addition, deprotonation, and reductive elimination.[25] Previous mechanistic and theoretical studies on similar Pd- and Ni-catalyzed reactions suggested that the oxidative addition initiates *via* monoligated η^2 complex **5**.[21,26,27] The oxidative addition occurs through five-centered transition state **TS6**, in which the carbonyl oxygen in the carbamate is coordinated with Ni.[28] The electron-rich NHC ligand facilitates the oxidative addition, which requires only 5.7 kcal mol^{-1} with respect to the η^2 complex **5**.[29] Similar oxidative additions with phosphine ligands require much higher activation energies ($\Delta G^{\ddagger}$ = 13.5 kcal mol^{-1} when PCy_3 ligand is used).[23b]

The oxidative addition leads to a stable intermediate (phenyl) nickel(II) carbamate intermediate **7** (–32.5 kcal mol^{-1}). Complex **7** undergoes ligand exchange with dimethylamine and *tert*-butoxide to liberate carbamate anion and form intermediate **8** (–18.4 kcal mol^{-1}). This ligand exchange process is endergonic, mainly due to entropic effects. The proton transfer from the coordinated amine to *tert*-butoxide (**TS9**) requires only 3.7 kcal mol^{-1} activation energy from complex **8**.[30] Subsequent dissociation of *tert*-butanol gives the (phenyl)(amino)nickel(II) complex **11** (–36.2 kcal mol^{-1}). Reductive elimination then occurs through **TS12** (–13.1 kcal mol^{-1}), which affords the product complex **13** (–26.2 kcal mol^{-1}). The reductive elimination from 11 to **TS12** requires 23.1 kcal mol^{-1} and is the rate-limiting step in the catalytic cycle. Thus, the overall energy span[31] of the catalytic cycle is 23.1 kcal mol^{-1}, in agreement with the experimental observations that the amination reaction readily occurs under slightly elevated temperatures. The barrier for reductive elimination with the Ni(NHC) catalyst is much higher compared to that of Pd-phosphine catalysts.[20b,22e] Following the reductive elimination, the reactant complex **5** can be regenerated by ligand exchange from the product complex **13** to initiate another catalytic cycle. The whole catalytic cycle is exergonic by 19.4 kcal mol^{-1}.[32]

Site-selective cross-couplings and synthetic applications

Fig. 3 highlights a series of experiments that were undertaken to explore carbamate directing group ability and the low reactivity of these substrates to conventional catalytic transformations. The key substrate for our studies, dihydroquinone derivative **14**, was selected with the aim of simultaneously probing the reactivity of aryl sulfamates, which have also proven to be extremely useful electrophiles in nickel-catalyzed couplings. Lithiation/bromination of substrate **14** provided trisubstituted arene **15**. In accord with literature precedent by Snieckus,[13f] the lithiation proceeded selectively adjacent to the carbamate. Bromoarene **15** was subsequently employed in a series of C–C and C–heteroatom bond constructions. Pd-catalyzed arylation (**15** → **17**), alkylation (**15** → **18**), and amination (**15**

→ **19**) proceeded smoothly, as did Cu-catalyzed C–N bond formation (**15** → **16**). In all cases, the sulfamate and carbamate were not disturbed.

Having demonstrated the robust nature of carbamates and sulfamates to a variety of conditions, we examined the subsequent cross-couplings of these functional groups (Fig. 4). *o*-Methylated derivative **18**, prepared by either *o*-bromination/Stille coupling (see Fig. 3) or direct *o*-methylation of **14**, was used in this study. We have found that the sulfamate of **18** is more reactive compared to the carbamate, and that high degrees of selectivity can be obtained in arylation.[33] Suzuki–Miyaura coupling of **18** furnished carbamate **20** in 52% yield. Subsequently, carbamate **20** was employed in our nickel-catalyzed amination to furnish polysubstituted aryl amine **21**. We expect that the ability to consecutively cross-couple bromides, sulfamates, and carbamates will be useful in the synthesis of complex molecules.

Conclusions

In summary, we have found that aryl carbamates are excellent substrates for the nickel-catalyzed amination reaction. The scope of the methodology is broad with respect to both coupling partners, and includes the coupling of electron-rich, heterocyclic, and sterically congested carbamates. DFT calculations reveal the full catalytic cycle of the nickel-catalyzed carbamate amination and suggest that reductive elimination (23.1 kcal mol^{-1} barrier) is the rate-determining step. Moreover, we have demonstrated that aryl carbamates are outstanding precursors for the synthesis of polysubstituted aryl amines using sequential carbamate functionalization/site-selective coupling processes. The use of this methodology in natural product synthesis will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors are grateful to Boehringer Ingelheim, Bristol-Myers Squibb (T.M.), DuPont, Eli Lilly, Amgen, NOBCChE/GlaxoSmithKline (T.M.), the University of California, Los Angeles, and the Chemistry-Biology Interface training program (A.L.S., USPHS National Research Service Award GM08496) for financial support. We thank the Garcia-Garibay laboratory (UCLA) for access to instrumentation, Dr. John Greaves (UC Irvine) for mass spectra, K. N. Houk for helpful discussions, and Materia Inc. for chemicals.

Notes and references

1. (a) Wolfe JP, Wagaw S, Marcoux J-F and Buchwald SL, Acc. Chem. Res, 1998, 31, 805–818;(b) Hartwig JF, Angew. Chem., Int. Ed, 1998, 37, 2046–2067;(c) Muci AR and Buchwald SL, Practical Palladium Catalysts for C–N and C–O Bond Formation, in Topics in Current Chemistry, Vol. 219 (Ed: Miyaura N), Springer–Verlag, Berlin, 2001, p 131;(d) Kienle M, Dubbaka SR, Brade K and Knochel P, Eur. J. Org. Chem, 2007, 4166–4176;(e) Hartwig JF, Nature, 2008, 455, 314–322; [PubMed: 18800130] (f) Surry DS and Buchwald SL, Chem. Sci, 2011, 2, 27–50. [PubMed: 22432049]

2. For examples of tosylate and mesylate amination, see:(a) Hamann BC and Hartwig JF, J. Am. Chem. Soc, 1998, 120, 7369–7370;(b) Roy AH and Hartwig JF, J. Am. Chem. Soc, 2003, 125, 8704–8705; [PubMed: 12862447] (c) Ogata T and Hartwig JF, J. Am. Chem. Soc, 2008, 130, 13848–13849; [PubMed: 18811161] (d) Gao C-Y and Yang L-M, J. Org. Chem, 2008, 73, 1624–1627; [PubMed:

18198889] (e) Fors BP, Watson DA, Biscoe MR and Buchwald SL, J. Am. Chem. Soc, 2008, 130, 13552–13554; [PubMed: 18798626] (f) So CM, Zhou Z, Lau CP and Kwong FY, Angew. Chem., Int. Ed, 2008, 47, 6402–6406.

3. The amination of aryl methyl ethers is largely limited to the coupling of 2-methoxynaphthalene with cyclic secondary amines. Deviation from these substrates leads to significantly lower yields (ca. 30–50%). Tobisu M, Shimasaki T and Chatani N, Chem. Lett, 2009, 38, 710–711.
4. For the amination of aryl pivalates, see: Shimasaki T, Tobisu M and Chatani N, Angew. Chem., Int. Ed, 2010, 49, 2929–2932.
5. For sulfamate amination, see:(a) Ramgren SD, Silberstein AL, Yang Y and Garg NK, Angew. Chem., Int. Ed, 2011, 50, 2171–2173;(b) Ackermann L, Sandmann R and Song W, Org. Lett, 2011, 13, 1784–1786. [PubMed: 21351758]
6. For recent reviews andhighlights regarding the cross-coupling of phenolic derivatives, see:(a) Rosen BM, Quasdorf KW, Wilson DA, Zhang N, Resmerita A-M, Garg NK and Percec V, Chem. Rev, 2011, 111, 1346–1416; [PubMed: 21133429] (b) Li B-J, Yu D-G, Sun C-L and Shi Z-J, Chem.-Eur. J, 2011, 17, 1728–1759; [PubMed: 21274921] (c) Yu D-G, Li B-J and Shi Z-J, Acc. Chem. Res, 2010, 43, 1486–1495; [PubMed: 20849101] (d) Knappke CEI and Jacobi von Wangelin A, Angew. Chem. Int. Ed, 2010, 49, 3568–3570;(e) Goossen LJ, Goossen K and Stanciu C, Angew. Chem., Int. Ed, 2009, 48, 3569–3571.
7. Aryl N,N-diethylcarbamates are readily prepared from aryl alcohols and commercially available N,N-diethylcarbamoyl chloride The latter reagent costs approximately $20–25 per mol ($0.15–$0.20 per gram) from common chemical suppliers, such as Alfa Aesar and Aldrich Chemical Co., Inc.
8. Other phenol-based amination partners cannot be used effectively for directed metallation/functionalization. Specifically, aryl sulfonates and pivalates are not suitable substrates, whereas aryl methyl ethers are poor metalation substrates. Aryl sulfamates can be used in ortho-lithiation, but the sulfamate directing group ability is approximately 20x less compared to carbamates; see ref. 13f
9. Smith MB and March J, in March's Advanced Organic Chemistry, 6th ed., John Wiley & Sons, Inc., New Jersey, 2007, p 670.
10. (a) Snieckus V, Chem.Rev, 1990, 90, 879–933;(b) Hartung CG and Snieckus V, in Modern Arene Chemistry (Ed.: Astruc D), Wiley-VCH, New York, 2002, pp 330–367;(c) Macklin T and Snieckus V, in Handbook of C-H Transformations (Ed.: Dyker G), Wiley-VCH, New York, 2005, pp 106–119.
11. (a) Bedford RB, Webster RL and Mitchell CJ, Org. Biomol. Chem, 2009, 7, 4853–4857; [PubMed: 19907774] (b) Zhao X, Yeung CS and Dong VM, J. Am. Chem. Soc, 2010, 132, 5837–5844; [PubMed: 20359220] (c) Nishikata T, Abela AR, Huang S and Lipshutz BH, J. Am. Chem. Soc, 2010, 132, 4978–4979; [PubMed: 20307066] (d) Yamazaki K, Kawamorita S, Ohmiya H and Sawamura M, Org. Lett, 2010, 12, 3978–3981. [PubMed: 20731364]
12. For the use of aryl carbamates in C–C bond forming processes, see:(a) Quasdorf KW, Riener M, Petrova KV and Garg NK, J. Am. Chem. Soc, 2009, 131, 1774–17749;(b) Antoft-Finch A, Blackburn T and Snieckus V, J. Am. Chem. Soc, 2009, 131, 17750–17752; [PubMed: 19928763] (c) Xi L, Li B-J, Wu Z-H, Lu X-Y, Guan B-T, Wang B-Q, Zhao K-Q and Shi Z-J, Org. Lett, 2010, 12, 884–887. [PubMed: 20099867]
13. For C–C bond formingprocesses involving aryl pivalates, methylethers, or sulfamates, see:(a) Quasdorf KW, Tian X and Garg NK, J. Am. Chem. Soc, 2008, 130, 14422–14423; [PubMed: 18839946] (b) Guan B-T, Wang Y, Li B-J, Yu D-G and Shi Z-J, J. Am. Chem. Soc, 2008, 130, 14468–14470; [PubMed: 18847272] (c) Li B-J, Li Y-Z, Lu X-Y, Liu J, Guan B-T and Shi Z-J, Angew. Chem., Int. Ed, 2008, 47, 10124–10127;(d) Tobisu M, Shimasaki T and Chatani N, Angew. Chem., Int. Ed, 2008, 47, 4866–4869;(e) Dankwardt JW, Angew. Chem., Int. Ed, 2004, 43, 2428–2432;(f) Macklin TK and Snieckus V, Org. Lett, 2005, 7, 2519–2522; [PubMed: 15957880] (g) Wehn PM and Du Bois J, Org. Lett, 2005, 7, 4685–4688. [PubMed: 16209510]
14. This finding is likely not surprising since C–N and C–C bond forming processes would proceed through fairly different mechanistic pathways (although the initial oxidative addition step would be common to both processes).
15. SIPr HCl (4), is commercially available (CAS# 258278–25-0).

16. Although these conditions are broadly useful, aminations of certain substrates proceed even at ambient temperature. For example, N,N- diethylphenylcarbamate undergoes coupling with morpholine in 24 h at 23 °C using 5 mol% catalyst (~90% conversion based on ^{1}H NMR analysis with internal standard).[1]

17. For certain substrates, the use of standard reaction conditions led to slow conversion to aminated product. In these cases, higher catalyst, ligand, and/or amine loadings could be used to expedite reaction progress as indicated in Tables 1–3. The formation of undesired byproducts is not typically observed.

18. The carbamate derived from 2,6-dimethylphenol fails to undergo amination under our reaction conditions.

19. Attempts to effect the amination of primary aliphatic amines, such as benzyl amine and n-butylamine, led to the recovery of starting material, albeit with some non-specific decomposition.

20. (a) For a pertinent review, see:Xue L and Lin Z, Chem. Soc. Rev, 2010, 39, 1692–1705; [PubMed: 20419215] (b) For a theoretical study on the Pd-catalyzed amination of bromobenzenes, see:Harvey JN, Fey N and McMullin CL, J. Mol. Catal. A: Chem, 2010, 324, 48–55.

21. For theoretical studies on Pd-mediated oxidative addition, see:(a) Ahlquist M, Fristrup P, Tanner D and Norrby PO, Organometallics, 2006, 25, 2066–2073;(b) Ahlquist M and Norrby PO, Organometallics, 2007, 26, 550–553;(c) Li Z, Fu Y, Guo QX and Liu L, Organometallics, 2008, 27, 4043–4049;(d) Harvey JN, Fey N and Jover J, J. Mol. Catal. A: Chem, 2010, 324, 39–47;(e) McMullin CL, Jover J, Harvey JN and Fey N, Dalton Trans, 2010, 39, 10833–10836. [PubMed: 20963224]

22. For theoretical studies on Pd-mediated reductive elimination, see:(a) Ananikov VP, Musaev DG and Morokuma K, J. Am. Chem. Soc, 2002, 124, 2839–2852; [PubMed: 11890836] (b) Ananikov VP, Musaev DG and Morokuma K, Organometallics, 2005, 24, 715–723;(c) Zuidema E, van Leeuwen PWNM and Bo C, Organometallics, 2005, 24, 3703–3710;(d) Ananikov VP, Musaev DG and Morokuma K, Eur. J. Inorg. Chem, 2007, 5390–5399;(e) Barder TE and Buchwald SL, J. Am. Chem. Soc, 2007, 129, 12003–12010; [PubMed: 17850080] (f) Koizumi T, Yamazaki A and Yamamoto T, Dalton Trans, 2008, 3949–3952; [PubMed: 18648696] (g) Ariafard A and Yates BF, J. Organomet. Chem, 2009, 694, 2075–2084.

23. (a) Li Z, Zhang S-L, Fu Y, Guo Q-X and Liu L, J. Am. Chem. Soc, 2009, 131, 8815–8823; [PubMed: 19505075] (b) Quasdorf KW, Antoft-Finch A, Liu P, Silberstein AL, Komaromi A, Blackburn T, Ramgren SD, Houk KN, Snieckus V and Garg NK, J. Am. Chem. Soc, 2011, 133, 6352–6363. [PubMed: 21456551]

24. All geometries were optimized using the B3LYP functional and a mixed basis set of SDD for Ni and 631G(d) for other atoms. A larger base set, SDD for Ni and 6–311 + G(2d, p) for other atoms was used for single point energy calculations and solvation energy corrections using the CPCM model. Single point calculations using the B3P86 and B3PW91 functionals were also performed and give comparable results to the B3LYP calculations (see ESI† for details) The isopropyl groups on the SIPr ligand were replaced with methyls in the calculations to reduce computational cost. All calculations were performed using Gaussian 09. Gaussian 09, revision B.01, M. J. Frisch et al. Gaussian, Inc., Wallingford CT, 2010.

25. The Ni-catalyzed amination of aryl carbamates is not inhibited in the presence of galvinoxyl radical or BHT; thus, we propose that a Ni(I)/Ni (III) catalyticcycle is likely not operative. For examples where additives such as galvinoxyl radical or BHT are used to probe the presence of Ni(I) intermediates, see:(a) Tsou TT and Kochi JK, J. Am. Chem. Soc, 1979, 101, 6319–6332;(b) Tsou TT and Kochi JK, J. Am. Chem. Soc, 1979, 101, 7547–7560;(c) Kochi J, Pure Appl. Chem, 1980, 52, 571–605;(d) Lipshutz BH, Sclafani JA and Blomgren PA, Tetrahedron, 2000, 56, 2139–2144;(e) Kamigaito M, Ando T and Sawamoto M, Chem. Rev, 2001, 101, 3689–3745; [PubMed: 11740919] (f) Zhou J, Ph.D. Thesis, Massachusetts Institute of Technology, 2005;(g) Phapale VB, Guisan-Ceinos M, Bunuel E and Cardenas DJ, Chem.-Eur. J, 2009, 15, 12681–12688. [PubMed: 19847828] For recent examples of catalytic reactions that proceed via Ni(I)/Ni(III) cycles, see:(h) Zhang K, Conda-Sheridan M, Cooke SR and Louie J, Organometallics, 2011, 30, 2546–2552; [PubMed: 21572533] (i) Miyazaki S, Koga Y, Matsumoto T and Matsubara K, Chem. Commun, 2010, 46, 1932–1934.

26. The monoligated oxidative addition is suggested as a preferred pathway in most Pd- and Ni-catalyzed oxidative additions with phosphine and NHC ligands:(a) Stambuli JP, Kuwano R and

Hartwig JF, Angew. Chem., Int. Ed, 2002, 41, 4746–4748;(b) Stambuli JP, Buehl M and Hartwig JF, J. Am. Chem. Soc, 2002, 124, 9346–9347; [PubMed: 12167009] (c) Stambuli JP, Incarvito CD, Buehl M and Hartwig JF, J. Am. Chem. Soc, 2004, 126, 1184–1194; [PubMed: 14746489] (d) Yamashita M and Hartwig JF, J. Am. Chem. Soc, 2004, 126, 5344–5345; [PubMed: 15113190] (e) Green JC and Herbert BJ, J. Organomet. Chem, 2005, 690, 6054–6067;(f) Goossen LJ, Koley D, Hermann HL and Thiel W, Organometallics, 2006, 25, 54–67;(g) Sergeev AG, Zapf A, Spannenberg A and Beller M, Organometallics, 2008, 27, 297–300;(h) Barrios-Landeros F, Carrow BP and Hartwig JF, J. Am. Chem. Soc, 2009, 131, 8141–8154; [PubMed: 19469511] (i) Böhm VPW, Gstöttmayr CWK, Weskamp T and Herrmann WA, Angew. Chem., Int. Ed, 2001, 40, 3387–3389.

27. We calculate that Ni(NHC)2 is 22.6 kcal mol^{-1}more stable in solution compared to 5. However, increasing the concentration of the NHC liganddoes not suppress the amination reaction (see ESI†), suggesting that Ni(NHC)2 is not the catalyst resting state. Although not presently well-understood, it is likely that the dissociation of one NHC ligand from Ni(NHC)2 is facilitated by other species in the reaction mixture. For similar hypotheses involving NHC dissociation from Ni(NHC)2 complexes, see:$^{-1}$(a) Zimmerman PM, Paul A, Zhang Z and Musgrave CB, Angew. Chem., Int. Ed, 2009, 48, 2201–2205;(b) Zimmerman PM, Paul A and Musgrave CB, Inorg. Chem, 2009, 48, 5418–5433. [PubMed: 19456138]
28. An alternative pathway involving three-centered oxidative addition transition state requires much higher activation energy than the five- centered pathway via TS6. Similar effects are observed in oxidative additions of carbamates and sulfamates with $Ni(PR_3)$; see ref. 23b.$_3$
29. Similar effects of ligands have been reported previously:(a) Corbet JP and Mignani G, Chem. Rev, 2006, 106, 2651–2710; [PubMed: 16836296] (b) Ahlquist M and Norrby P, Organometallics, 2007, 26, 550–553;(c) Marion N and Nolan SP, Acc. Chem. Res, 2008, 41, 1440–1449; [PubMed: 18774825] (d) Shen Q, Ogata T and Hartwig JF, J. Am. Chem. Soc, 2008, 130, 6586–6596. [PubMed: 18444639]
30. Since the mechanism involves charged species, the energetics of the deprotonation step is expected to be strongly affected by solvation effects. We have tested a number of DFT methods and basis sets with the CPCM solvation model. These results (provided in the ESI†) all indicate that deprotonation is not the rate-limiting step.
31. Kozuch S and Shaik S, Acc. Chem. Res, 2011, 44, 101–110. [PubMed: 21067215]
32. The energy difference (–19.4 kcal mol^{-1}) between complex 5 at the beginning and end of the plot represents the energy released in the catalytic cycle. ref. 31.$^{-1}$
33. Competition experiments between phenol-derived carbamates and sulfamates indicate that sulfamates are inherently more reactive than carbamates in both the nickel-catalyzed Suzuki-Miyaura coupling and amination. The preference for sulfamate coupling seen in the conversion of 18 → 20 is likely heightened because of the carbamate's ortho substituent.

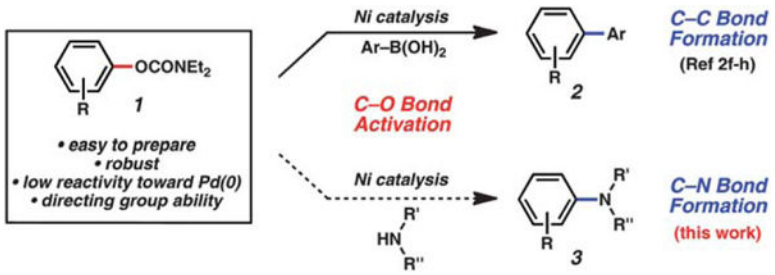


Fig. 1.

Known C–C and proposed C–N bond formation reactions using aryl carbamates as substrates.

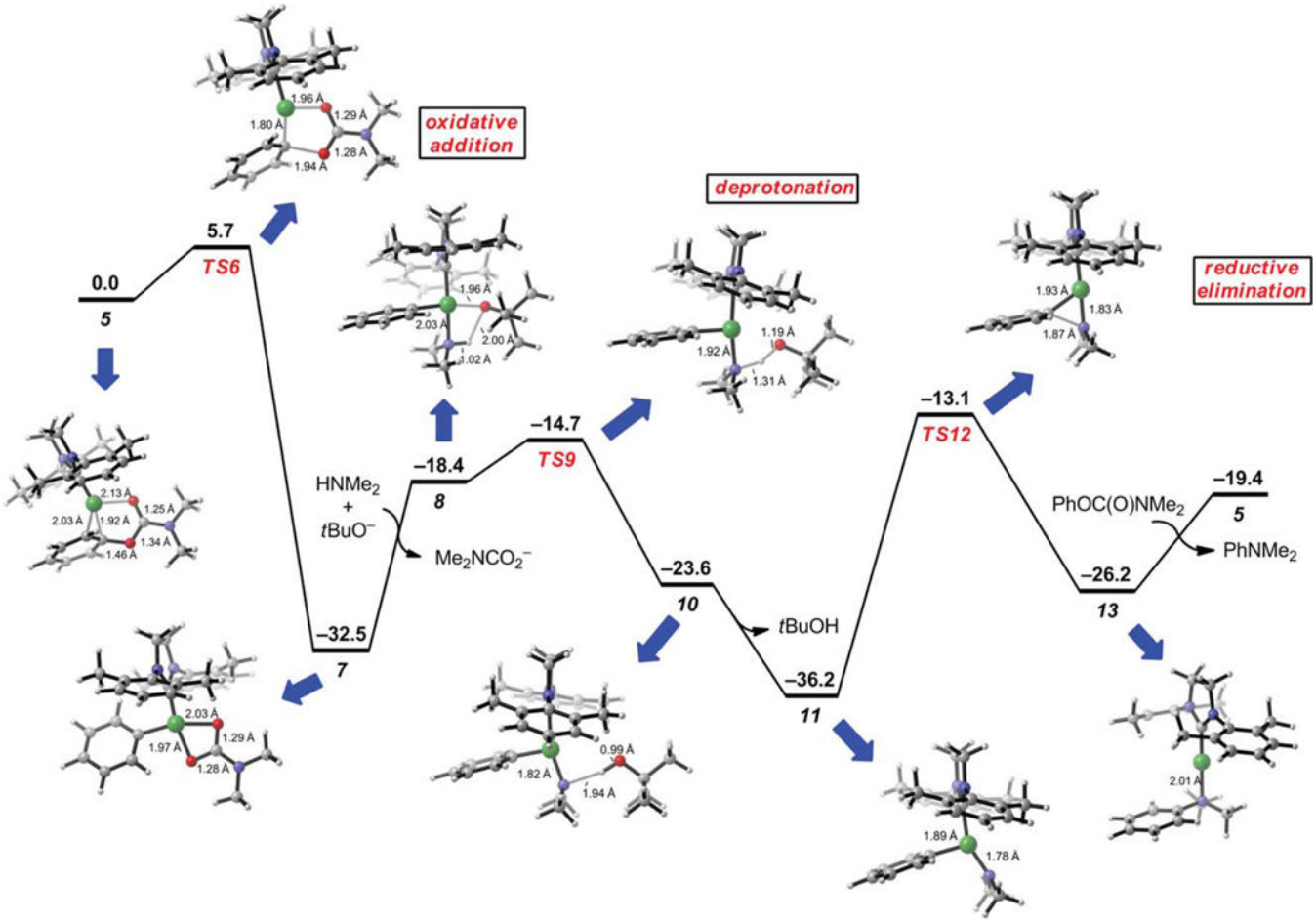


Fig. 2.

Gibbs free energy diagram of Ni-catalyzed amination of *N,N*-dimethylphenylcarbamate and dimethylamine. Energies are given in kcal mol^{-1}.

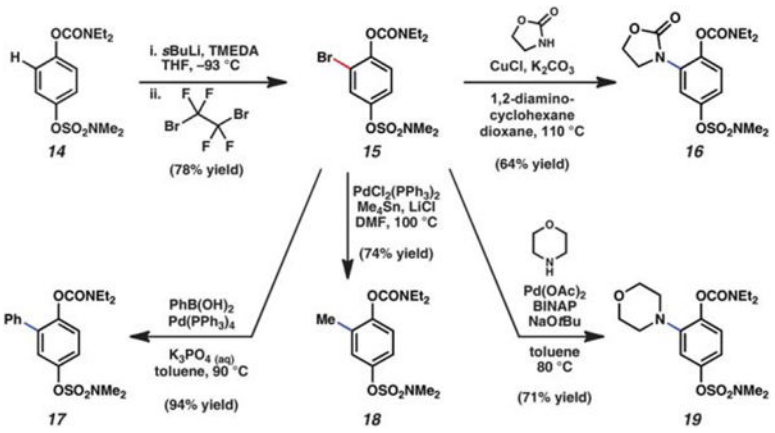


Fig. 3.

Carbamate functionalization and low reactivity of carbamates and sulfamates toward conventional Pd- and Cu-catalyzed couplings.

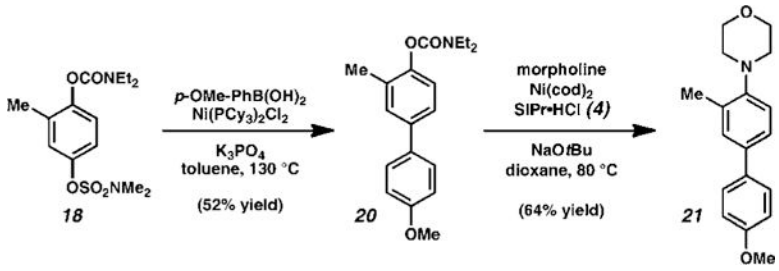
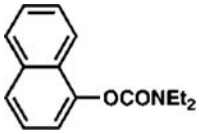
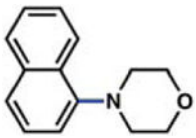
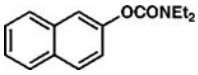
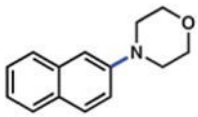
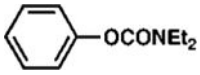
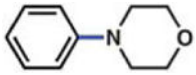
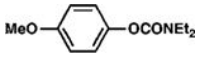
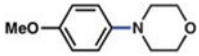
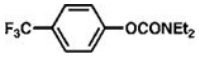
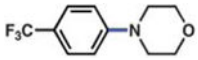
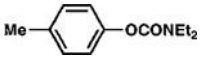
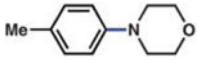
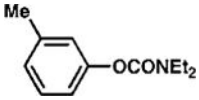
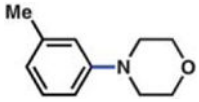


Fig. 4.

Synthesis of polysubstituted arenes using sequential sulfamate/ carbamate couplings.

Table 1

Amination of aryl carbamates with morpholine.[a]

Entry	Ar-OCONEt$_2$	Product	Yield[b]
1			91%
2			92%
3			90%
4[c]			74%
5			90%
6[d]			77%
7			80%

[a] Conditions unless otherwise stated: Ni(cod)$_2$ (5 mol%), **4** (10 mol%), carbamate substrate (1 equiv), morpholine (1.2 equiv), NaO*t*Bu (1.4 equiv), 3 h.

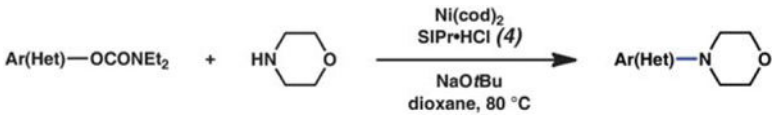
[b] Isolated yields.

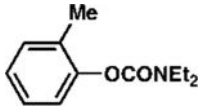
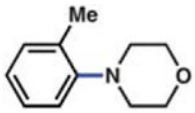
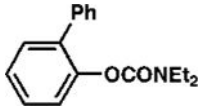
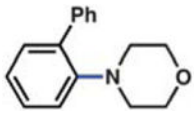
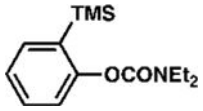
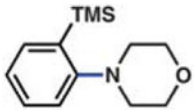
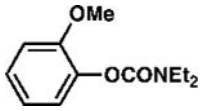
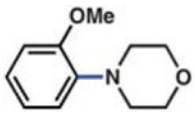
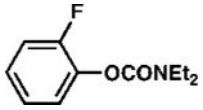
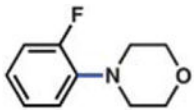
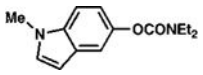
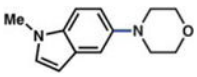
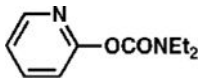
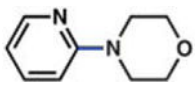
[c] Ni(cod)$_2$ (15 mol%), **4** (30 mol%), morpholine (1.8 equiv), NaO*t*Bu (2.2 equiv).

[d] Ni(cod)$_2$ (10 mol%), **4** (20 mol%).

Table 2

Amination of *o*-substituted and heterocyclic carbamates.[a]



Entry	Ar-OCONEt$_2$	Product	Yield[b]
1[c]			65%
2[d]			53%
3[e]			61%
4[d]			55%
5[f]			84%
6[g]			55%
7			78%

[a] Conditions unless otherwise stated: Ni(cod)$_2$ (5 mol%), **4** (10 mol%), carbamate substrate (1 equiv), morpholine (1.2 equiv), NaO*t*Bu (1.4 equiv), 3 h.

[b] Isolated yields.

[c] Ni(cod)$_2$ (15 mol%), **4** (30 mol%), morpholine (1.8 equiv), NaO*t*Bu (2.2 equiv).

[d] Ni(cod)$_2$ (15 mol%), **4** (30 mol%), morpholine (2.4 equiv), NaO*t*Bu (2.2 equiv).

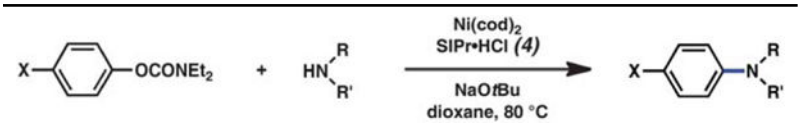
[e] Ni(cod)$_2$ (20 mol%), **4** (40 mol%), morpholine (1.2 equiv), NaO*t*Bu (1.7 equiv), 120 °C.

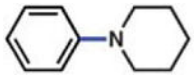
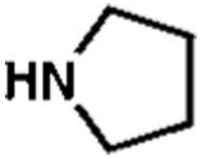
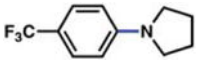
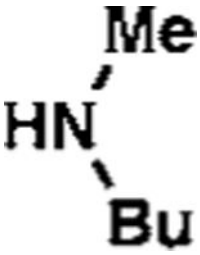
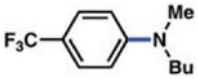
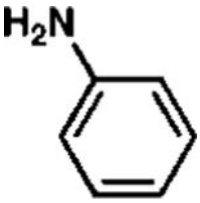
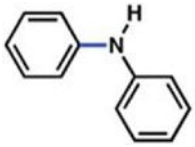
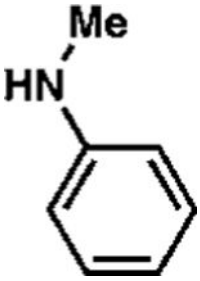
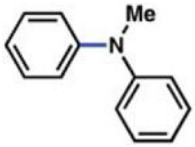
[f] Ni(cod)$_2$ (10 mol%), **4** (20 mol%).

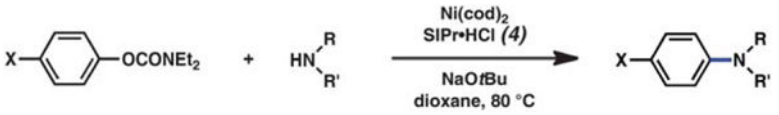
[g] $Ni(cod)_2$ (20 mol%), **4** (40 mol%), morpholine (1.8 equiv), NaO*t*Bu (2.2 equiv).

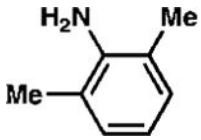
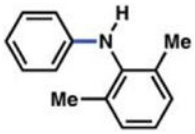
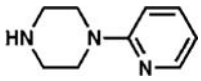
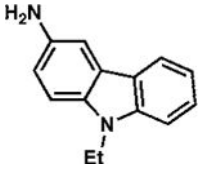
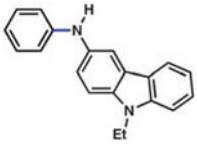
Table 3

Amination of aryl carbamates with various amines.[a]



Entry	Amine	Product	Yield[b]
1[c]			96%
2			91%
3			86%
4[d]			84%
5[d]			70%



Entry	Amine	Product	Yield[b]
6[e]			92%
7[c]			94%
8[c]			93%

[a]Conditions unless otherwise stated: $Ni(cod)_2$ (5 mol%), **4** (10 mol%), carbamate substrate (1 equiv), amine (1.2 equiv), NaO*t*Bu (1.4 equiv), 3 h.

[b]Isolated yields.

[c]$Ni(cod)_2$ (10 mol%), **4** (20 mol%).

[d]$Ni(cod)_2$ (15 mol%), **4** (30 mol%), amine (1.8 equiv), NaO*t*Bu (2.2 equiv).

[e]$Ni(cod)_2$ (15 mol%), **4** (30 mol%), amine (2.4 equiv), NaO*t*Bu (2.2 equiv).