nature chemistry

ARTICLES

PUBLISHED ONLINE: 9 NOVEMBER 2015 | DOI: 10.1038/NCHEM.2388

Nickel-catalysed Suzuki–Miyaura coupling of amides

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The Suzuki–Miyaura coupling has become one of the most important and prevalent methods for the construction of C–C bonds. Although palladium catalysis has historically dominated the field, the use of nickel catalysis has become increasingly widespread because of its unique ability to cleave carbon–heteroatom bonds that are unreactive towards other transition metals. We report the first nickel-catalysed Suzuki–Miyaura coupling of amides, which proceeds by an uncommon cleavage of the amide C–N bond after *N*-*tert*-butoxycarbonyl activation. The methodology is mild, functional-group tolerant and can be strategically employed in sequential transition-metal-catalysed cross-coupling sequences to unite heterocyclic fragments. These studies demonstrate that amides, despite classically considered inert substrates, can be harnessed as synthons for use in reactions that form C–C bonds through cleavage of the C–N bond using non-precious metal catalysis.

Cross-coupling reactions catalysed by transition metals have become an indispensable tool for the construction of C–C bonds[1]. Although palladium catalysis has dominated the field and was the topic of the 2010 Nobel Prize in Chemistry, there has been much interest in the development of complementary nickel-catalysed processes[2–4]. Much of the excitement that surrounds nickel-catalysed cross-couplings stems from nickel being more abundant and therefore less expensive compared with palladium[2,3]. However, the most striking feature of nickel catalysis is the opportunity to uncover new reactivity. To this end, nickel-catalysed processes to cleave C–O bonds have led to the cross-coupling of unconventional phenol-based electrophiles[4], such as aryl pivalates and ethers, and reactions to break C–N bonds have allowed for the cross-coupling of aniline derivatives[5–7].

Recently, we discovered that Ni/SIPr (SIPr, 1,3-bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazol-2-ylidine) could facilitate the conversion of amides into esters (**1**→**2**, Fig. 1)[8–10]. With the hypothesis that this transformation occurred by the metal-catalysed activation of the amide C–N bond, which typically is considered stable and unreactive[11], we postulated that the putative oxidative addition intermediate **4** could be intercepted by carbon-based nucleophiles, ultimately to forge C–C bonds (**1**→**3**). Direct acyl couplings of this type have been achieved using acid chlorides, thioesters[12], carboxylic anhydrides[13], arylated mixed imides[14] and geometrically distorted cyclic imides[15]. A nickel-catalysed process to build acyl C–C bonds from amides would provide a powerful new synthetic tool for ketone synthesis, which would also complement Weinreb's widespread methodology[16,17], but without the need for strongly basic and pyrophoric organometallic reagents. In this article, we report the first method for building C–C bonds from *N*-*tert*-butoxycarbonyl (*N*-Boc)-activated secondary amides using non-precious metal catalysis.

Results and discussion

Discovery and optimization of the nickel-catalysed Suzuki–Miyaura coupling of amides. In considering possible amide cross-coupling partners for C–C bond formation, we elected to pursue the use of boron-based partners. Countless boron-coupling partners, including heterocycles that serve as building blocks to medicines and natural products, are commercially available and used pervasively in Suzuki–Miyaura cross-couplings[18,19]. Thus, we examined the coupling of amides **5** with phenylboronic acid (**6a**) or boronic ester **6b** with several of our key results involving Ni/SIPr, K_3PO_4 and toluene (Table 1). The use of anilide **5a**, which was an excellent coupling partner in our amide-to-ester conversion[8], only led to low yields of ketone product **7** (Table 1, entry 1). We also evaluated the use of *N*-Bn-*N*-Boc-derivative **5b**. Although the coupling of **5b** with boronic acid **6a** gave higher yields of the desired ketone, yields were inconsistent (Table 1, entry 2) and led us to consider the corresponding boronic ester. In turn, the use of pinacolatoboronate **6b** gave only trace amounts of the desired product **7** (Table 1, entry 3). As we, and others, have seen similar inconsistencies in nickel-catalysed Suzuki–Miyaura couplings, which were attributed to variations in water content[20–23], we tested the use of boronic ester

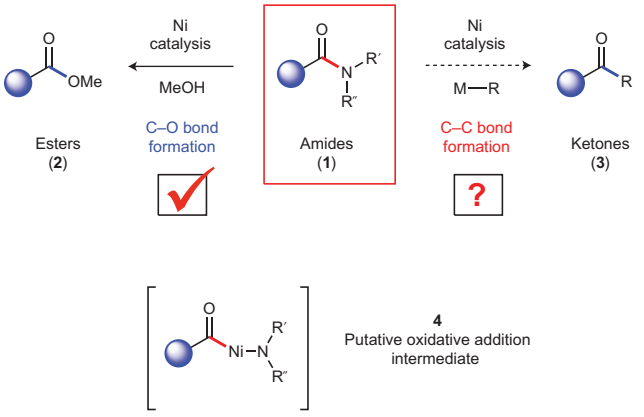

Figure 1 | Development of Ni-catalysed coupling of amides with carbon nucleophiles. After the discovery of nickel-catalysed conversion of amides (**1**) into esters (**2**), this study sought to intercept putative oxidative addition intermediate **4** with carbon-based nucleophiles to uncover a new methodology for the synthesis of ketones (**3**) from amides (**1**). The development of the reaction indicated by the dashed arrow supports the intermediacy of **4** and provides a new and mild method for the synthesis of ketones—complementary to the Weinreb ketone synthesis.

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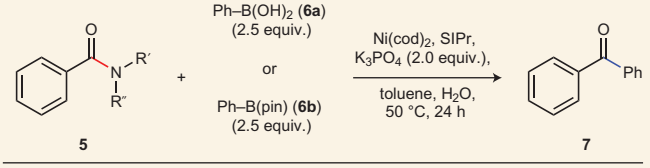
Table 1 | Reaction discovery and optimization.



Entry		Boron source	$Ni(cod)_2$ (mol%)	SIPr (mol%)	H_2O (equiv.)	Yield*
1	**5a**	**6a**	10	10	—	12%
2	**5b**	**6a**	10	10	—	42–89%
3	**5b**	**6b**	10	10	—	7%
4	**5b**	**6b**	10	10	2.0	>99%
5	**5b**	**6b**	5	5	2.0	>99%

Conditions: $Ni(cod)_2$ (5 or 10 mol%), SIPr (5 or 10 mol%), substrate 5a or 5b (1.0 equiv.), boron source **6a** or **6b** (2.5 equiv.), K_3PO_4 (2.0 equiv.), toluene (1.0 M) and H_2O (if applicable, 2.0 equiv.) at 50 °C for 24 hours. *Yields of 7 were determined by ^1H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

6b with added water. We were delighted to find that the coupling proceeded smoothly to give a quantitative yield of ketone 7 when 2.0 equiv. water was used (Table 1, entry 4). Further optimization allowed us to lower the catalyst and ligand loadings to 5 mol% without any loss in yield (Table 1, entry 5). No evidence of decarbonylation was observed. This is significant as Yamamoto's group and, more recently, Itami and co-workers reported decarbonylation in processes to cleave acyl C–O bonds[24–26]. The coupling required $Ni(cod)_2$, (cod, cyclooctadiene), SIPr and K_3PO_4 to proceed, as demonstrated by control experiments. Specifically, in the absence of any of these components, conversion into the desired ketone product was not observed. Control experiments are described in the Supplementary Information (see Supplementary Table 2).

Scope of methodology. Having identified suitable reaction conditions, we assessed the scope of the methodology. Table 2 showcases isolated yields for a variety of substrates and boronic esters. Beyond the parent coupling to give 7 in 96% isolated yield (Table 2, entry 1), *para*-, *meta*- and *ortho*-substitutions were tolerated, as shown by the formation of ketones 8–10, respectively (entries 2–4). Additionally, electron-rich substrates that possess methoxy or amino substituents underwent the desired coupling to give products 11–13 (entries 5–7). Substrates with electron-withdrawing substituents, such as –F, $–CF_3$, $–CO_2Me$ and –C(O)Me, were also suitable and gave adducts 14–17 in synthetically useful yields (entries 8–11). It is notable that ketones and esters are compatible with this methodology (as are tertiary alcohols, nitriles, secondary amides, carboxylic acids, epoxides and the free NHs of indoles; see Supplementary Table 4 for the robustness screen results), as these functional groups often pose challenges for Weinreb amide chemistry[13]. Finally, an extended aromatic system was evaluated, which gave naphthylphenyl ketone 18 in 70% yield (entry 12).

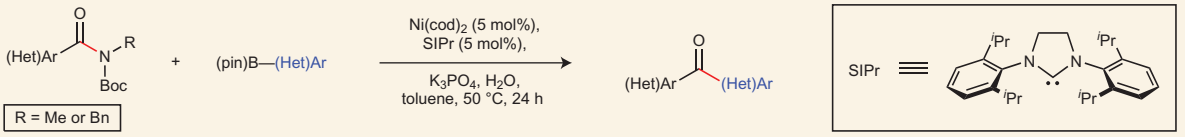
The scope with regard to the boronic ester coupling partner, in addition to the tolerance of the methodology towards heterocycles, was also examined (entries 13–25). The use of methyl-substituted boronic esters smoothly provided tolyl ketones 8–10 (Table 2, entries 13–15), whereas the use of the *para*-methoxy-substituted boronic ester gave 19 in 95% yield (entry 16). The fluoro- and trifluoromethyl substituents were also tolerated to give 14 and 20, respectively (entries 17 and 18). Moreover, a naphthylboronic ester could be employed to provide 18 (entry 19). As shown by the formation of 21–26, furan, thiophene, indole, pyrrole and pyrazole heterocycles were all tolerated (entries 20–25), which thus demonstrates the potential utility of this methodology for the synthesis of medicinally relevant scaffolds[27]. Indeed, diaryl or hetaryl ketone frameworks are seen in several currently marketed drugs or compounds under clinical evaluation[28].

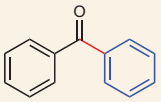
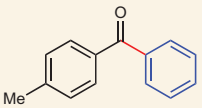
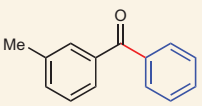
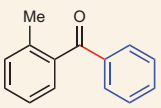
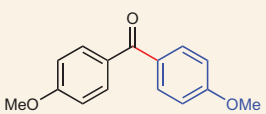
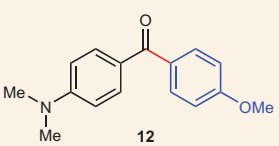
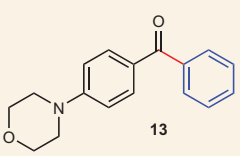
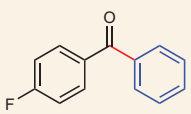
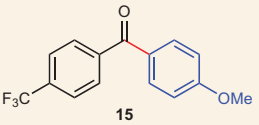
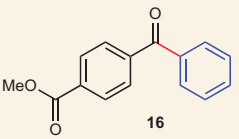
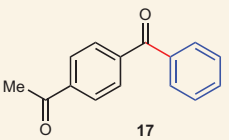
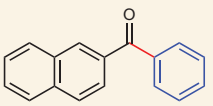
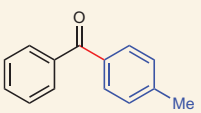
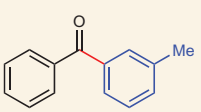
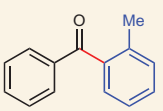
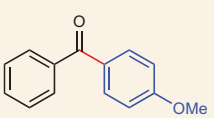
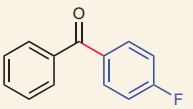
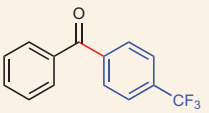
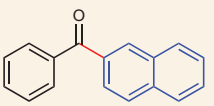
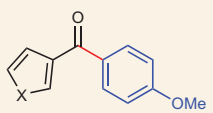
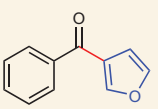
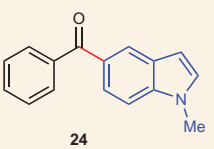
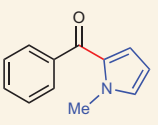
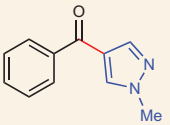
Synthetic applications that involve amide Suzuki–Miyaura coupling methodology. Several synthetic applications were undertaken to assess further the utility of the amide Suzuki–Miyaura couplings. In the first of these, we performed the gram-scale coupling of amide 27 with indolylboronic ester 28 (Fig. 2a). This smoothly delivered ketone 29, a nanomolar tubulin-binding agent[29], in 83% yield. Next, the potential to carry out sequential palladium- and nickel-catalysed Suzuki–Miyaura couplings of heterocycles was tested (Fig. 2b). Furanylboronic acid (30) was first cross-coupled with aryl chloride 31 using palladium catalysis[30]. This facilitated the aryl–aryl coupling to furnish 32 in 71% yield, without disturbing the amide. Next, amide 32 underwent nickel-catalysed aryl–acyl coupling with pyrazolylboronic ester 33 to furnish 34. The ability to unite heterocyclic fragments using such sequences should prove useful in the synthesis of drug candidates, new materials and natural products.

The recently discovered nickel-catalysed esterification of amides, paired with the Suzuki–Miyaura coupling of amides, provides opportunities to construct acyl C–C and acyl C–O bonds sequentially, as demonstrated in Fig. 2c. In one scenario, bis(amide) 35 was coupled with furanylboronic ester 36 to furnish furanyl ketone 37, without disturbing the secondary amide. Subsequent Boc activation and Ni-catalysed esterification[8] of 37 furnished menthol ester 39. The coupling sequence can also be reversed. Esterification of bis(amide) 35 with (–)-menthol (38)[8] provided amidoester 40. Boc activation and Suzuki–Miyaura coupling of 40 with furanyl boronic ester 36 delivered ketoester 39. The ester of 40 withstood the base-mediated reaction conditions and was also not disrupted by the nickel catalyst.

In summary, we have developed the first nickel-catalysed method for the construction of C–C bonds from amides. Our approach relies on the use of nickel catalysis to activate the amide C–N bond. *In situ* coupling of the putative oxidative addition intermediate **4** with boronic esters furnishes the products of Suzuki–Miyaura cross-coupling. The methodology is mild and tolerant of a variety of functional groups, which include ketones and amines, in addition to several heterocycles and functional groups that bear acidic protons. With the future design and testing of new catalysts, we expect that the scope of nickel-catalysed amide couplings will be broadened further. Nonetheless, we show here that the present methodology can be used to prepare bioactive molecules (Fig. 2a), and can be employed strategically in sequential cross-couplings that involve palladium or nickel catalysis to unite heterocyclic fragments in controlled ways (Fig. 2b,c). Taken together, these studies demonstrate that amides, despite classically being considered inert substrates, can actually be harnessed as synthons for use in reactions that form C–C bonds with non-precious metal catalysis.

Table 2 | Scope of nickel-catalysed Suzuki–Miyaura coupling of amides.



Entry	Ketone product	Yield*
1	 **7**	96%
2	 **8**	92%
3	 **9**	91%
4	 **10**	51%†,‡
5	 **11**	78%
6	 **12**	59%
7	 **13**	81%
8	 **14**	90%
9	 **15**	85%
10	 **16**	77%‡
11	 **17**	72%†
12	 **18**	70%
13	 **8**	73%
14	 **9**	80%†
15	 **10**	66%†
16	 **19**	95%
17	 **14**	88%
18	 **20**	81%
19	 **18**	94%
20 21	 **21** (X = O) **22** (X = S)	64%† 66%†
22	 **23**	86%†
23	 **24**	80%
24	 **25**	96%
25	 **26**	82%†

Conditions unless otherwise stated: $Ni(cod)_2$ (5 mol%), SIPr (5 mol%), substrate (1.0 equiv.; R = Me or Bn as specified in the Supplementary Information), boron source (1.2–2.5 equiv.), K_3PO_4 (2.0 equiv.), toluene (1.0 M) and H_2O (2.0 equiv.) at 50 °C for 24 hours; The yields shown reflect the average of two isolation experiments. *Yields determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. †$Ni(cod)_2$ (10 mol%) and SIPr (10 mol%) were used.

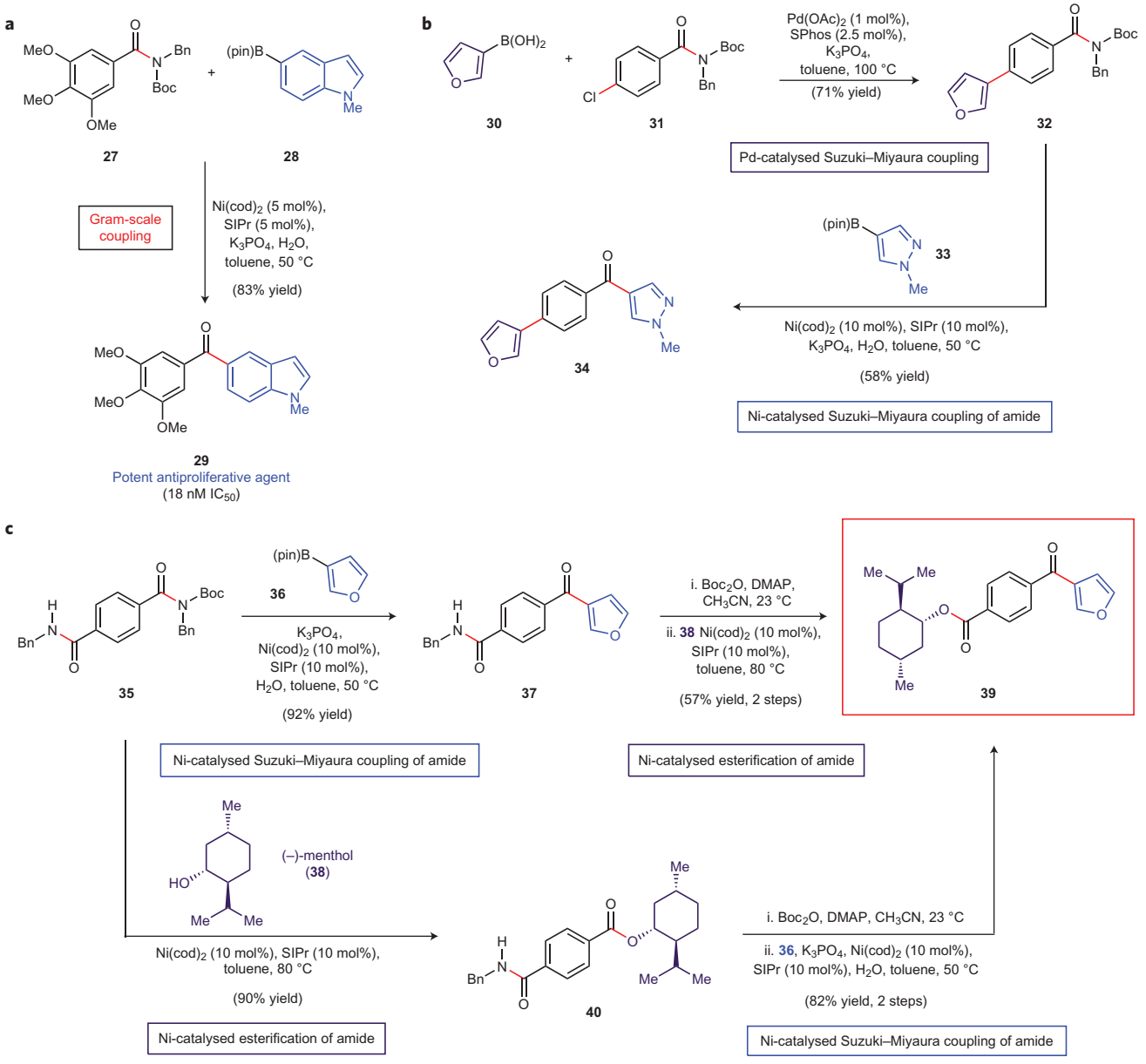


Figure 2 | Several applications of the Suzuki–Miyaura coupling of amides were carried out to assess the synthetic utility of the methodology. **a**, The gram-scale coupling of trimethoxy amide **27** and heterocyclic fragment **28** was conducted to furnish tubulin-binding agent **29**, a potent antiproliferative diaryl ketone. **b**, A sequence of Suzuki–Miyaura couplings was performed to access **34**, using palladium and nickel catalysis, and thus highlight the capacity of this method to unite heterocyclic frameworks. **c**, Sequential Ni-catalysed esterification and Suzuki–Miyaura couplings of amides were carried out to illustrate the ability of amides to be used in multistep synthesis through controlled activation–coupling sequences. DMAP, 4-dimethylaminopyridine; pin, pinacolato; SPhos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

Received 18 July 2015; accepted 29 September 2015; published online 9 November 2015

References

1. Muci, A. R. & Buchwald, S. L. in *Cross-Coupling Reactions: A Practical Guide* (ed. Miyaura, N.) 131–209 (Topics in Current Chemistry 219, Springer, 2002).
2. Tasker, S. Z., Standley, E. A. & Jamison, T. F. Recent advances in homogeneous nickel catalysis. *Nature* **509,** 299–309 (2014).
3. Mesganaw, T. & Garg, N. K. Ni- and Fe-catalyzed cross-coupling reactions of phenol derivatives. *Org. Process. Res. Dev.* **17,** 29–39 (2013).
4. Rosen, B. M. *et al.* Nickel-catalyzed cross-couplings involving carbon–oxygen bonds. *Chem. Rev.* **111,** 1346–1416 (2011).
5. Blakey, S. B. & MacMillan, D. W. C. The first Suzuki cross-couplings of aryltrimethylammonium salts. *J. Am. Chem. Soc.* **125,** 6046–6047 (2003).
6. Zhang, X.-Q. & Wang, Z.-X. Nickel-catalyzed cross-coupling of aryltrimethylammonium triflates and amines. *Org. Biomol. Chem.* **12,** 1448–1453 (2014).
7. Tobisu, M., Nakamura, K. & Chatani, N. Nickel-catalyzed reductive and borylative cleavage of aromatic carbon–nitrogen bonds in *N*-aryl amides and carbamates. *J. Am. Chem. Soc.* **136,** 5587–5590 (2014).
8. Hie, L. *et al.* Conversion of amides to esters by the nickel-catalyzed activation of amide C–N bonds. *Nature* **524,** 79–83 (2015).
9. Louie, J. in *N-Heterocyclic Carbenes in Synthesis* (ed. Nolan, S. P.) 163–182 (Wiley, 2006).
10. Hoshimoto, Y., Hayashi, Y., Suzuki, H., Ohashi, M. & Ogoshi, S. One-pot, single-step, and gram-scale synthesis of mononuclear [(η^6-arene)Ni(*N*-heterocyclic carbene)] complexes: useful precursors of the Ni^0-NHC unit. *Organometallics* **33,** 1276–1282 (2014).
11. Greenberg, A., Breneman, C. M. & Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science* (Wiley, 2002).
12. Blangetti, M., Rosso, H., Prandi, C., Deagostino, A. & Venturello, P. Suzuki–Miyaura cross-coupling in acylation reactions, scope and recent developments. *Molecules* **18,** 1188–1213 (2013).

13. Chen, Q., Fan, X.-H., Zhang, L.-P. & Yang, L.-M. Nickel-catalyzed cross-coupling of carboxylic anhydrides with arylboronic acids. *RSC Adv.* **4,** 53885–53890 (2014).
14. Li, X. & Zou, G. Acylative Suzuki coupling of amides: acyl-nitrogen activation via synergy of independently modifiable activating groups. *Chem. Commun.* **51,** 5089–5092 (2015).
15. Meng, G. & Szostak, M. Sterically controlled Pd-catalyzed chemoselective ketone synthesis via N–C cleavage in twisted amides. *Org. Lett.* **17,** 4364–4367 (2015).
16. Nahm, S. & Weinreb, S. M. *N*-Methoxy-*N*-methylamides as effective acylating agents. *Tetrahedron Lett.* **22,** 3815–3818 (1981).
17. Balasubramaniam, S. & Aidhen, I. S. The growing synthetic utility of the Weinreb amide. *Synthesis* 3707–3738 (2008).
18. Lennox, J. J. A. & Lloyd-Jones, G. C. Selection of boron reagents for Suzuki–Miyaura coupling. *Chem. Soc. Rev.* **43,** 412–443 (2014).
19. Miyaura, N. & Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev.* **95,** 2457–2483 (1995).
20. Quasdorf, K. W. *et al.* Suzuki–Miyaura cross-coupling of aryl carbamates and sulfamates: experimental and computational studies. *J. Am. Chem. Soc.* **133,** 6352–6363 (2011).
21. Guan, B.-T., Wang, Y., Li, B.-J., Yu, D.-G. & Shi, Z.-J. Biaryl construction via Ni-catalyzed C–O activation of phenolic carboxylates. *J. Am. Chem. Soc.* **130,** 14468–14470 (2008).
22. Antoft-Finch, A., Blackburn, T. & Snieckus, V. *N,N*-Diethyl *O*-carbamate: directed metalation group and orthogonal Suzuki–Miyaura cross-partner. *J. Am. Chem. Soc.* **131,** 17750–17752 (2009).
23. Jezorek, R. L. *et al.* Coupling of aryl sulfamates with aryl neopentylglycolboronates at room temperature. *Org. Lett.* **16,** 6326–6329 (2014).
24. Yamamoto, T., Ishizu, J., Kohara, T., Komiya, S. & Yamamoto, A. Oxidative addition of aryl carboxylates to nickel(0) complexes involving cleavage of the acyl–oxygen bond. *J. Am. Chem. Soc.* **102,** 3758–3764 (1980).
25. Amaike, K., Muto, K., Yamaguchi, J. & Itami, K. Decarbonylative C–H coupling of azoles and aryl esters: unprecedented nickel catalysis and application to the synthesis of muscoride A. *J. Am. Chem. Soc.* **134,** 13573–13576 (2012).
26. Muto, K., Yamaguchi, J., Musaev, D. G. & Itami, K. Decarbonylative organoboron cross-coupling of esters by nickel catalysis. *Nature Commun.* **6,** 7508 (2015).
27. Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **57,** 10257–10274 (2014).
28. *DrugBank Version 4.3* (Wishart Research Group, Alberta).
29. Hu, L. *et al.* Novel potent antimitotic heterocyclic ketones: synthesis, antiproliferative activity, and structure–activity relationships. *Bioorg. Med. Chem. Lett.* **17,** 3613–3617 (2007).
30. Billingsley, K. & Buchwald, S. L. Highly efficient monophosphine-based catalyst for the palladium-catalyzed Suzuki–Miyaura reaction of heteroaryl halides and heteroaryl boronic acid and esters. *J. Am. Chem. Soc.* **129,** 3358–3366 (2007).

Acknowledgements

The authors are grateful to Boehringer Ingelheim, DuPont, Bristol-Myers Squibb, the Camille and Henry Dreyfus Foundation, the A. P. Sloan Foundation, the S. T. Li Foundation and the University of California, Los Angeles. S. Anthony (UCLA) is acknowledged for experimental assistance. We are grateful to the National Science Foundation (NSF) (N.A.W. and E.L.B., No. DGE-1144087) and the Foote Family (N.A.W.) for fellowship support. These studies were also supported by shared instrumentation grants from the NSF (No. CHE-1048804) and the National Center for Research Resources (No. S10RR025631).

Author contributions

N.A.W. and E.L.B. designed and performed the experiments and analysed the experimental data. N.K.G. directed the investigations and prepared the manuscript with contributions from all the authors; all the authors contributed to discussions.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to N.K.G.

Competing financial interests

The authors declare no competing financial interests.