ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, **55**, 13709

Received 26th August 2019,
Accepted 18th October 2019

DOI: 10.1039/c9cc06638a

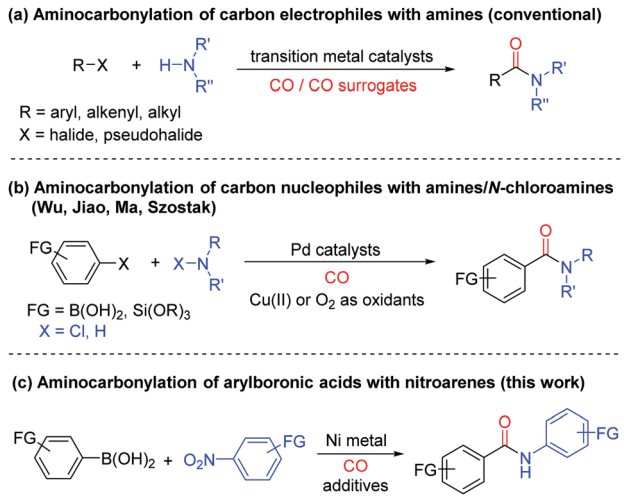
rsc.li/chemcomm

Direct amide synthesis *via* Ni-mediated aminocarbonylation of arylboronic acids with CO and nitroarenes†

Ni Shen,[ab] Chi Wai Cheung *[ab] and Jun-An Ma*[ab]

Herein we describe an alternative and unconventional approach of an aminocarbonylation reaction to access aryl amides from readily available and low-cost arylboronic acids and nitroarenes. Nickel metal can serve as both reductant and catalyst in this direct aminocarbonylation. This protocol exhibits a good functional group compatibility and allows a variety of aryl amides to be synthesized, including several drug-like molecules.

Amides are among the most important compounds in pharmaceutical, agrochemical, and materials chemistry.[1,2] The amidation of carboxylic acids with amines in the presence of coupling reagents has long been the traditional method to synthesize amides.[3] Meanwhile, the aminocarbonylation reaction represents an alternative attractive protocol for amide synthesis.[4] As a result, a myriad of amides could be easily accessed by simply assembling the readily available carbon monoxide (CO) or its surrogates, carbon electrophiles, and amine substrates in the presence of transition metal catalysts (Scheme 1a). To further extend the scope and utility in amide synthesis, various aminocarbonylation reactions using unconventional coupling substrates, such as carbon nucleophiles or nitrogen electrophiles, have also been explored (Scheme 1b).[4f,5] For example, Wu and co-workers first described the Pd-catalyzed aminocarbonylation of nucleophilic arylboronic acids using *N*-chloroamines as electrophilic nitrogen substrates.[6] Soon after, the groups of Jiao[7] and Ma[8] reported the Pd-catalyzed aminocarbonylation of arylboronic acids with amines using Cu(II) salts or oxygen as oxidants. Most recently, Szostak and co-workers disclosed the analogous oxidative Pd-catalyzed aminocarbonylation of arylsilanes with amines.[9] On the other hand, the C–N bond forming reactions using electrophilic nitroarenes as arylamine



Scheme 1 Various modes of aminocarbonylation for amide synthesis.

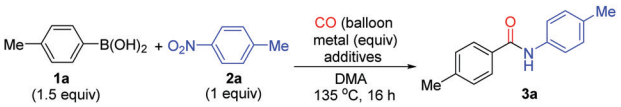
surrogates have emerged as an appealing research area due to the low cost, high stability, and high accessibility of nitroarenes.[10–15] In particular, aminocarbonylation with nitroarenes is among the most commonly studied approaches towards amide synthesis in recent years. Among them, the Beller,[10] Driver,[11] Hu,[12] and Wu groups[13] presented seminal aminocarbonylation methods *via* the three-component reactions with nitroarenes, CO or its surrogates, and a diverse set of carbon coupling partners such as arenes,[11] alkenes,[10,13] and aryl halides.[12] Strikingly, the aminocarbonylation reaction of nitroarenes with arylboronic acids remains underdeveloped, even though arylboronic acids have been extensively utilized in the C–C and C-heteroatom cross-coupling reactions.

Herein we report our efforts in developing an alternative direct aminocarbonylation based on arylboronic acids and CO by using nitroarenes as nitrogen electrophiles (Scheme 1c). Most recently, Wu and co-workers described the Pd-catalyzed aminocarbonylation of arylboronic acids with nitroarenes using $Mo(CO)_6$ as a CO surrogate and K_2CO_3 as a base.[16] Our complementary method highlights the use of more sustainable

[a] *Department of Chemistry, Tianjin Key Laboratory of Molecular Optoelectronic Sciences, and Tianjin Collaborative Innovation Center of Chemical Science & Engineering, Tianjin University, Tianjin 300072, People's Republic of China. E-mail: zhiwei.zhang@tju.edu.cn, majun_an68@tju.edu.cn*
[b] *Joint School of NUS & TJU, International Campus of Tianjin University, Fuzhou 350207, People's Republic of China*

† Electronic supplementary information (ESI) available: Experimental and spectral data. See DOI: 10.1039/c9cc06638a

Table 1 The optimization of aminocarbonylation[a]



Entry	Metal (equiv.)	Additives (equiv.)	Yield[b] (%)
1	Ni (4)	TMSCl (3), PPh_3 (1.5)	62
2	Ni (4)	TMSBr (3), PPh_3 (1.5)	33
3	Ni (4)	TMSI (3), PPh_3 (1.5)	52
4	Mn (4)	TMSCl (3), PPh_3 (1.5)	20
5	Co, Mg, or Zn (4)	TMSCl (3), PPh_3 (1.5)	0–5
6	Ni (4)	TMSCl (3), dppp (1)	60
7	Ni (3)	TMSCl (3), PPh_3 (1)	63
8	Ni (3)	TMSCl (3), PPh_3 (1), NaI (2)	85
9	Ni (3)	TMSCl (3), PPh_3 (1), NaBr (2)	62
10	Ni (3)	TMSCl (3), PPh_3 (1), NaI (1)	76
11	Ni (3)	TMSCl (3), PPh_3 (1), NaI (2)	72[c]
12	Ni (3)	TMSCl (3), PPh_3 (1), NaI (2)	81[d]
13	Ni (3)	TMSCl (3), PPh_3 (1), NaI (2)	0[e]
14	Ni (3)	TMSCl (3), PPh_3 (1), NaI (2)	46[f]
15	Ni (3)	TMSCl (3), PPh_3 (1), NaI (2), $CoCl_2$ (10 mol%)	66
16	Ni (3)	TMSCl (3), PPh_3 (1), NaI (2), $CuCl_2$ (10 mol%)	61
17	Ni (3)	TMSCl (3), PPh_3 (1), NaI (2), $PdCl_2$ (10 mol%)	48

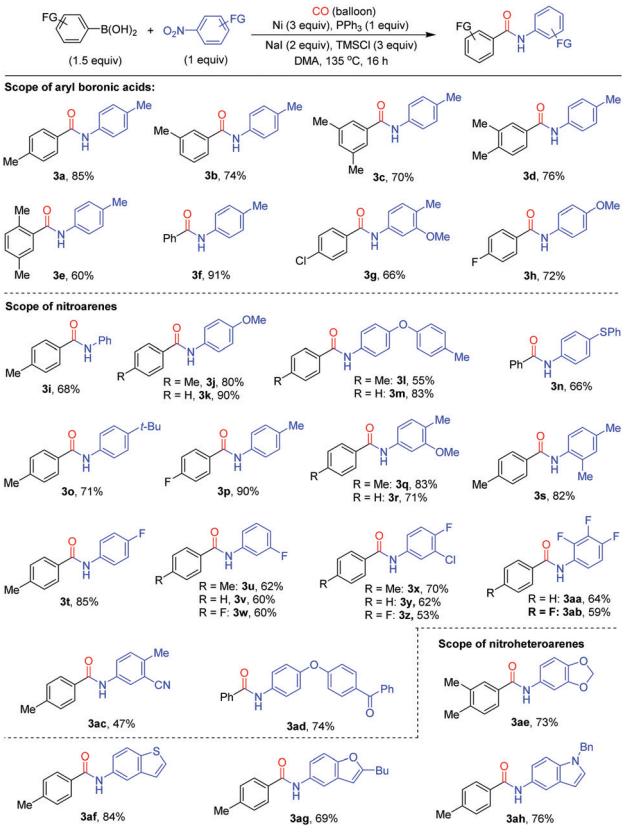
[a] General procedure: **1a** (0.75 mmol), **2a** (0.5 mmol), CO (balloon), metal powder, additives (ligand, halotrimethylsilane, metal salt), DMA (1.5 mL), 135 °C, 16 h. [b] Isolated yield. [c] Dimethylformamide was used instead of DMA. [d] *N*-Methylpyrrolidine was used instead of DMA. [e] $Mo(CO)_6$ (2 equiv.) was used instead of CO. [f] $Co_2(CO)_8$ (2 equiv.) was used instead of CO.

and inexpensive CO and Ni metal as the carbonyl source and reductant, respectively. Additional base is not required in this protocol, thus allowing the synthesis of a broader range of aryl amides, including several drug-like amide molecules.

We commenced our study on aminocarbonylation using 4-tolylboronic acid (**1a**) and 4-nitrotoluene (**2a**) as the model substrates (Table 1). In the presence of CO, Ni metal powder (4 equiv.), chlorotrimethylsilane (TMSCl, 3 equiv.), and triphenylphosphine (PPh_3, 1 equiv.), **1a** (1.5 equiv.) and **2a** (1 equiv.) reacted in dimethylacetamide (DMA) solvent at 135 °C to deliver the desired amide **3a** in 62% yield (entry 1). In this context, Ni powder likely reacted as both reductant and mediator, PPh_3 likely acts as the ligand for Ni-mediated reaction, and TMSCl served as the deoxygenating reagent of nitroarene.[12,14] The use of bromotrimethylsilane (TMSBr) or iodotrimethylsilane (TMSI) in place of TMSCl only gave **3a** in 33% and 52% yields, respectively (entries 2 and 3). In addition, when Mn metal was used as a reductant in lieu of Ni, **3a** was formed in 20% yield (entry 4), while the use of Co, Mg, or Zn metal did not induce the reaction at all (entry 5), suggesting the indispensable role of nickel in the reaction. Moreover, the use of bidentate ligand, 1,3-bis(diphenylphosphino)propane (dppp, 1 equiv.), gave **3a** in 60% yield (entry 6). By lowering the loadings of Ni and PPh_3 to 3 equiv. and 1 equiv., respectively, **3a** was still formed in 63% yield (entry 7). Interestingly, by adding 2 equivalents of NaI as additive, the yield of amide improved significantly to 85% (entry 8). In stark contrast, when NaBr was used instead of NaI or when 1 equivalent of NaI was used, the yields dropped accordingly (entries 9 and 10). DMA was a superior solvent to other polar aprotic solvents such as dimethylformamide and *N*-methylpyrrolidine (entries 11 and 12). Moreover, CO was a more effective carbonyl source than $Mo(CO)_6$ and $Co_2(CO)_8$ (entries 13 and 14). In the presence of catalytic amounts of metal salts such as Co, Cu, and Pd, **3a** was formed in moderate yields (48–66%, entries 15–17), indicating that the trace metals possibly present in Ni metal are unlikely the catalysts for aminocarbonylation.

We applied the optimized reaction conditions (Table 1, entry 8) to study the scope of the aminocarbonylation of arylboronic acids and CO with nitroarenes (Scheme 2). Electron-rich (**3a–3e**), electron-neutral (**3f**), and electron-deficient arylboronic acids (**3g**, **3h**) all reacted to form the corresponding aryl amides in good to high yields (60–91%). In this context, the amide **3e** derived from sterically hindered 2,5-dimethylphenylboronic acid could be synthesized without significant diminishment of yield. In addition, a wide range of nitroarenes were tolerated in this protocol. Electron-neutral (**3i**), electron-rich (**3j–3s**), and electron-deficient nitroarenes (**3t–3ad**) were suitable reaction partners. While the electron-neutral and electron-rich nitroarenes reacted to give the amide products in generally high to excellent yields (~70–90%), the reactions with electron-deficient nitroarenes usually afforded the amides in good to high yields (~50–70%). Nevertheless, mono-, di- and tri-substituted nitroarenes all reacted smoothly. Notably, the aminocarbonylation with sterically bulky 2,4-dimethyl-1-nitrobenene delivered the corresponding amide in 82% yield (**3s**). Moreover, various nitroheteroarenes could be incorporated in the amides, including benzodioxole (**3ae**), benzothiophene (**3af**), benzofuran (**3ag**), and *N*-benzyl indole (**3ah**). Furthermore, a variety of functional groups were tolerated on both arylboronic acid and nitroarene substrates, such as thioether (**3n**), chloro (**3g**, **3x–3z**), flouro (**3h**, **3t–3ab**), cyano (**3ac**), and keto groups (**3ad**). Notably, this protocol allowed for the synthesis of various types of fluorine-containing aryl amides, which are ubiquitous structural motifs in medicinal and agrochemical chemistry.

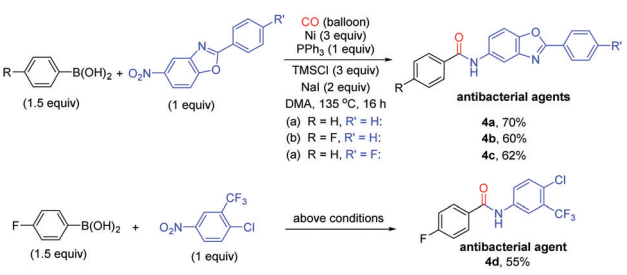
The application of this aminocarbonylation protocol was demonstrated by the synthesis of several drug-like amide molecules.



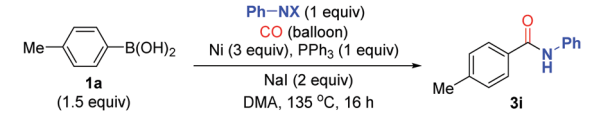
Scheme 2 The scope of aminocarbonylation. Isolated yields are shown.

Under this protocol, three benzoxazole-based antibacterial agents **4a**,[17] **4b**,[17] and **4c**,[18] as well as a fluoro-containing antibacterial agent **4d**,[19] could be synthesized using the commercially available or readily available arylboronic acids and nitro(hetero)arenes (Scheme 3).

During the reaction, Ni metal acts as a reductant to reduce nitroarenes to various nitrogen-containing species, including nitrosoarene, *N*-aryl hydroxylamine, azoxyarene, azoarene, and 1,2-diaryl hydrazine,[20] whilst Ni is oxidized to Ni(II) species. To probe their roles in aminocarbonylation, the reactions of these nitrogen-based species with 4-tolylboronic acid **1a** and CO under otherwise identical conditions were examined (Scheme 4). Nitrosobenzene (**5a**), *N*-phenyl hydroxylamine (**5b**), azoxybenzene (**5c**), azobenzene (**5d**), and 1,2-diphenyl hydrazine (**5e**) all reacted to give the amide **3i** in moderate to good yields (48–77%). Most likely, nitrobenzene is reduced successively by Ni in the course of



Scheme 3 Applications in medicinal chemistry.



nitrogen-based species (Ph-NX)	yield of **3i** [a]	nitrogen-based species (Ph-NX)	yield of **3i** [a]
Ph–NO (**5a**)	48%	1/2 Ph–N=N–Ph (**5d**)	77%
Ph–NHOH (**5b**)	68%		
1/2 Ph(O⊖)–N=N⊕–Ph (**5c**)	56%	1/2 Ph–HN–NH–Ph (**5e**)	71%

[a] Isolated yield.

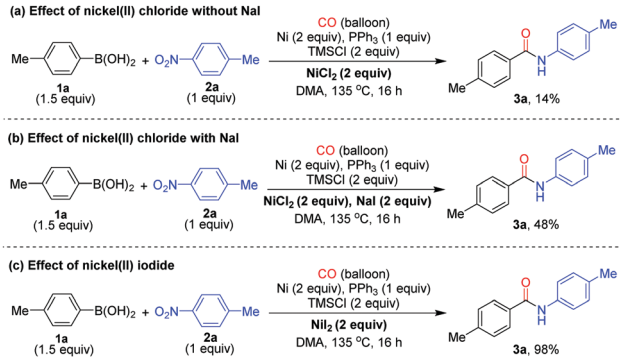
Scheme 4 Probing nitrogen-based species for aminocarbonylation.

reaction to less reduced nitrogen-based species (**5a**, **5b**), followed by intermediately-reduced species (**5c**, **5d**), and eventually to the more reduced species (**5e**).[14a,20] **5e** is most likely the ultimate nitrogen-containing species for reaction. **5e** reacted to give the amide in slightly lower yields than **5d**, presumably due to the lower stability of **5d** than **5e** at the high reaction temperature.

The addition of NaI was found to promote the efficiency of aminocarbonylation and significantly enhance the yield of amide (Table 1, entries 7 and 8). A possible role of NaI is to generate I_2, which can also induce the formation of iodoarene, such that both I_2 and iodoarene could promote the aminocarbonylation [Scheme S1, (i), ESI†]. Iodide could coordinate to Ni(II) species to form $Ni^{II}I_2$, which liberates I_2 under high temperature.[21] Arylboronic acid then reacts with I_2 to form iodoarene,[22] which further reacts with Ni metal and nitroarene to give amide.[12] However, when I_2 was used instead of KI, the reaction was less efficient, giving the amide product in much less yield [Scheme S1, (ii), ESI†]. Moreover, no iodoarene was formed in the Ni(II)-mediated reaction between arylboronic acid and I_2 [Scheme S1, (iii), ESI†]. These results suggested that the *in situ* formation of iodine or iodoarene does not take place to trigger aminocarbonylation.

Next, we switched our attention to the halogen effect of nickel(II) halides on aminocarbonylation. $Ni^{II}Cl_2$ could be formed *via* the reduction of nitroarene with Ni metal and TMSCl. $Ni^{II}Cl_2$ could then undergo halide substitution with NaI to form $Ni^{II}I_2$. Several control experiments based on these Ni(II) salts were studied. In the absence of NaI, $Ni^{II}Cl_2$ mediated the reaction under otherwise identical conditions to deliver the amide in 14% yield (Scheme 5(a)). The addition of NaI promoted the $Ni^{II}Cl_2$-mediated reaction to afford the amide in 48% yield (Scheme 5(b)). Furthermore, the direct use of $Ni^{II}I_2$ even significantly enhanced the reaction to generate the amide quantitatively (Scheme 5(c)). The results strongly indicated that NaI facilitates the *in situ* formation of $Ni^{II}I_2$ to mediate the aminocarbonylation much more efficiently.

Based on the above results, we proposed a plausible mechanism of this aminocarbonylation reaction (Scheme S2, ESI†). Ni metal (Ni(0)) reduces nitroarene successively to 1,2-diaryl hydrazine[20] in the presence of TMSCl as a deoxygenating additive[12,14] [Scheme S2(a), ESI†]. Meanwhile, Ni(0) is oxidized to Ni(II) salts,



Scheme 5 The halide effect of Ni(II) salts on aminocarbonylation.

in which the counter anion could be chloride or O-centered ligands [trimethylsilanolate (TMS-O$^-$), hydroxide (OH$^-$)]] originated from the reduction process of nitroarene. Ni(II) salts then undergo ligand substitution with NaI to form $Ni^{II}I_2$, which further reacts with PPh_3 to form ligated $Ni^{II}I_2$ complexes **6** [Scheme S2(b), ESI†]. We speculated that the formation of complex **6** could prevent Ni precipitation with O-centered ligands.[23] The good leaving group ability of iodide[23] also enables rapid iodide dissociation from **6**, providing a vacant site to effect transmetalation of arylboronic acid *via* the activation with TMS-O$^-$ or OH$^-$, as well as to effect the subsequent CO insertion to form acyl-Ni^{II} intermediate **7** [Scheme S2(c), ESI†]. 1,2-Diaryl hydrazine bears a weak N–N bond (bond dissociation energy ~39 kcal mol^{-1})[24] and likely splits readily into amino radicals, which then react with **7** to give Ni^{III}(acyl)(amino) complex **8** [Scheme S2(d), ESI†]. Finally, **7** undergoes reductive elimination to afford the amide product, while the co-product Ni(I) species could disproportionate to regenerate $Ni^{II}I_2$ and Ni(0).[25] The detailed reaction mechanism will be subjected to a future dedicated study.

In summary, we have disclosed an alternative aminocarbonylation method for amide synthesis using readily available carbon monoxide, arylboronic acids, and nitroarenes as reaction substrates. Nickel metal serves as both a reductant and mediator in this protocol. Diverse aryl amines could be synthesized, including several drug-like molecules. Further advancement of the reaction protocol, especially the endeavour to use safer carbon monoxide surrogates instead of the more toxic carbon monoxide, are underway in our laboratory.

We acknowledged the National Natural Science Foundation of China (No. 21532008, 21772142, 21901181, and 21971186) and Tianjin University for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) *The Chemistry of Amides* ed. J. Zabicky, Wiley-VCH, New York, 1970; (*b*) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science* ed. A. Greenberg, C. M. Breneman and J. F. Liebman, Wiley-VCH, New York, 2000.
2 For a recent review, see: (*a*) R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.*, 2013, 7453; (*b*) A. Ojeda-Porras and D. Gamba-Sánchez, *J. Org. Chem.*, 2016, **81**, 11548; (*c*) M. T. Sabatini, L. T. Boulton, H. F. Sneddon and T. D. Sheppard, *Nat. Catal.*, 2019, **2**, 10. Aryl amides are versatile building blocks in organic synthesis; for examples, see: (*d*) X. Wang, *Nat. Catal.*, 2019, **2**, 98; (*e*) L. Hie, N. F. Fine Nathel, T. K. Shah, E. L. Baker, X. Hong, Y.-F. Yang, P. Liu, K. N. Houk and N. K. Garg, *Nature*, 2015, **524**, 79; (*f*) L.-H. Li, Z.-J. Niu and Y.-M. Liang, *Chem. – Eur. J*, 2017, **23**, 15300; (*g*) Y.-H. Huang, S.-R. Wang, D.-P. Wu and P.-Q. Huang, *Org. Lett.*, 2019, **21**, 1681.
3 For recent reviews, see: (*a*) E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606; (*b*) A. El-Faham and F. Albericio, *Chem. Rev.*, 2011, **111**, 6557; (*c*) J. R. Dunetz, J. M. Javier Magano and G. A. Weisenburger, *Org. Process Res. Dev.*, 2016, **20**, 140; (*d*) R. M. de Figueiredo, J.-S. Suppo and J.-M. Campagne, *Chem. Rev.*, 2016, **116**, 12029.
4 For selected reviews, see: (*a*) C. F. J. Barnard, *Organometallics*, 2008, **27**, 5402; (*b*) A. Brennführer, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114; (*c*) S. Roy, S. Roy and G. W. Gribble, *Tetrahedron*, 2012, **68**, 9867; (*d*) S. Sumino, A. Fusano, T. Fukuyama and I. Ryu, *Acc. Chem. Res.*, 2014, **47**, 1563; (*e*) P. Gautam and B. M. Bhanage, *Catal. Sci. Technol.*, 2015, **5**, 4663; (*f*) J.-B. Peng, F.-P. Wu and X.-F. Wu, *Chem. Rev.*, 2019, **119**, 2090.
5 (*a*) C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405; (*b*) X.-F. Wu, H. Neumann and M. Beller, *ChemSusChem*, 2013, **6**, 229; (*c*) Y. Li, Y. Hu and X.-F. Wu, *Chem. Soc. Rev.*, 2018, **47**, 172.
6 (*a*) W. Li and X.-F. Wu, *Chem. – Eur. J.*, 2015, **21**, 7374. For the subsequent related work, see: (*b*) Z. Yin, Z. Wang, W. Li and X.-F. Wu, *Eur. J. Org. Chem.*, 2017, 1769.
7 L. Ren, X. Li and N. Jiao, *Org. Lett.*, 2016, **18**, 5852.
8 J. Zhang, Y. Ma and Y. Ma, *Eur. J. Org. Chem.*, 2018, 1720.
9 J. Zhang, Y. Hou, Y. Ma and M. Szostak, *J. Org. Chem.*, 2019, **84**, 338.
10 X. Fang, R. Jackstell and M. Beller, *Angew. Chem., Int. Ed.*, 2013, **52**, 14089.
11 F. Zhou, D.-S. Wang, X. Guan and T. G. Driver, *Angew. Chem., Int. Ed.*, 2017, **56**, 4530.
12 C. W. Cheung, M. L. Ploeger and X. Hu, *Chem. Sci.*, 2018, **9**, 655.
13 J.-B. Peng, H.-Q. Geng, D. Li, X. Qi, J. Ying and X.-F. Wu, *Org. Lett.*, 2018, **20**, 4988.
14 For recent examples of direct amide synthesis *via* the amidation of carboxylic acid derivatives with nitroarenes, see: (*a*) C. W. Cheung, M. L. Ploeger and X. Hu, *Nat. Commun.*, 2017, **8**, 14878; (*b*) C. W. Cheung, M. L. Ploeger and X. Hu, *ACS Catal.*, 2017, **7**, 7092; (*c*) C. W. Cheung, J.-A. Ma and X. Hu, *J. Am. Chem. Soc.*, 2018, **140**, 6789; (*d*) C. W. Cheung, N. Shen, S.-P. Wang, A. Ullah, X. Hu and J.-A. Ma, *Org. Chem. Front.*, 2019, **6**, 756.
15 For selected examples of direct amine synthesis using nitroarenes as substrates, see: (*a*) C. W. Cheung and X. Hu, *Nat. Commun.*, 2016, **7**, 12494; (*b*) J. Xiao, Y. He, F. Ye and S. Zhu, *Chem*, 2018, **4**, 1645; (*c*) T. V. Nykaza, J. C. Cooper, G. Li, N. Mahieu, A. Ramirez, M. R. Luzung and A. T. Radosevich, *J. Am. Chem. Soc.*, 2018, **140**, 15200; (*d*) S. Suárez-Pantiga, R. Hernández-Ruiz, C. Virumbrales, M. R. Pedrosa and R. Sanz, *Angew. Chem., Int. Ed.*, 2019, **58**, 2129; (*e*) M. Rauser, R. Eckert, M. Gerbershagen and M. Niggemann, *Angew. Chem., Int. Ed.*, 2019, **58**, 6713.
16 J.-B. Peng, D. Li, H.-Q. Geng and X.-F. Wu, *Org. Lett.*, 2019, **21**, 4878.
17 E. A. Şener, Ö. T. Arpacı, İ. Yalçın and N. Altanlar, *IL Farmaco*, 2000, **55**, 397.
18 Ö. T. Arpacı, İ. Ören and N. Altanlar, *IL Farmaco*, 2002, **57**, 175.
19 M. G. Vigorita, G. Saporito, G. T. Previtera, F. C. Pizzimenti and G. Bisignano, *Farmaco Sci.*, 1986, **41**, 168.
20 (*a*) H.-U. Blaser, *Science*, 2006, **313**, 312; (*b*) H.-U. Blaser, H. Steiner and M. Studer, *ChemCatChem*, 2009, **1**, 210.
21 H. Nakajima, S. Shimizu, K. Onuki, Y. Ikezoe and S. Sato, *Nippon Kagaku Kaishi*, 1984, **8**, 1257.
22 R. H. Tale, G. K. Toradmal, V. B. Gopula, A. H. Rodge, R. P. Pawar and K. M. Patil, *Tetrahedron Lett.*, 2015, **56**, 2699.
23 P. M. Maitlis, A. Haynes, B. R. James, M. Catellanic and G. P. Chiusolic, *Dalton Trans.*, 2004, 3409.
24 Y.-R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, 2007.
25 A. A. Danopoulos, T. Simler and P. Braunstein, *Chem. Rev.*, 2019, **119**, 3730.

