Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal

Published on 09 June 2015. Downloaded by Dalhousie University on 25/06/2015 03:00:11.

Rhenium-catalyzed C–H aminocarbonylation of azobenzenes with isocyanates†

Xiaoyu Geng and Congyang Wang*

Cite this: DOI: 10.1039/c5ob01121c

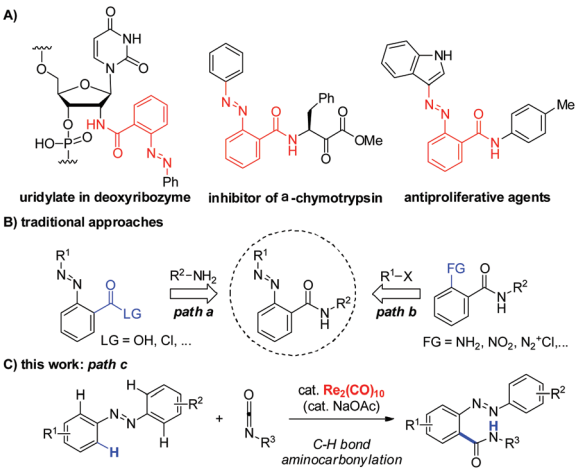
Received 4th June 2015,
Accepted 5th June 2015

DOI: 10.1039/c5ob01121c

www.rsc.org/obc

The first C–H aminocarbonylation of azobenzenes with isocyanates is achieved by using rhenium-catalysis, which provides an expedient and atom-economical access to varied *o*-azobenzamides from readily available starting materials. The reaction efficiency can be enhanced by the catalytic use of sodium acetate *via* accelerated C–H bond activation.

Because of the unique azo motif and conjugated characteristics, aromatic azo compounds find wide applications in industries as dyes and pigments.[1] Also, the light-driven reversible isomerization between the *cis* and *trans* forms renders them extremely suitable for supermolecular recognition, photochemical molecular switches, light-driven molecular motors, biosensors, pharmaceuticals, and so on.[2] Specifically, the *o*-azobenzamide skeleton is often found as a key structural unit in biologically active molecules such as photomodulated deoxyribozymes for RNA cleavage, photoswitchable peptidomimetic inhibitors of α-chymotrypsin, and antiproliferative agents (Scheme 1A).[3] In general, the *o*-azobenzamide core is constructed either through the amide bond formation by traditional condensation reactions of *o*-azobenzoic acid derivatives with amines (path a, Scheme 1B), or through the azo bond formation by manipulation of *o*-nitro/-aminobenzamides (path b).[3,4] Of note, both these approaches require 1,2-bisfunctionalized arenes as starting materials and often result in the formation of undesired waste byproducts. In principle, a more atom-economical way to build this unit is the direct *ortho*-C–H bond addition of azobenzenes to isocyanates (path c, Scheme 1C). However, as far as we are aware, this direct C–H bond aminocarbonylation process is unprecedented for azobenzenes though other types of C–H bond transformations of azobenzenes have been reported recently.[5] As our continuous interest in rhenium-catalysis,[6,7] herein we report the first C–H aminocarbonylation of azobenzenes with isocyanates by using rhenium-catalysis (Scheme 1C).[8] Thus, varied *o*-azobenzamides are accessed from readily available starting materials in an expedient and atom-economical manner. Importantly, only mono-C–H functionalized products are formed through a regioselective C–C bond formation, which circumvents the homocoupling issue in the synthesis of unsymmetrical azoarenes with traditional methods.[4]



Scheme 1 Bioactive *o*-azobenzamides and their synthetic approaches.

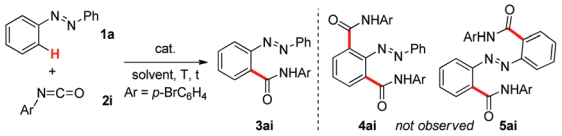
At the outset, we examined the model reaction of azobenzene **1a** with *p*-bromophenyl isocyanate **2i** (Table 1).[9] No products were observed in the absence of catalysts (entry 1). To our delight, with 5 mol% of $Re_2(CO)_{10}$ the C–H aminocarbonylated product **3ai** was obtained in 60% NMR yield (entry 2). Variations on solvents showed that toluene was the best (entries 3–6).[9] Further tuning of the ratio of the starting materials and reaction temperature demonstrated that higher yield of **3ai** could be achieved at 130 °C with excess of **1a** (entries 7–11). A slightly higher concentration and longer reaction time led to the best results among the conditions tested

Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China. E-mail: wangcy@iccas.ac.cn

†Electronic supplementary information (ESI) available: Experimental details, characterization data and NMR spectra for all new compounds, and X-ray data. CCDC 1055707 for **3an**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob01121c

Published on 09 June 2015. Downloaded by Dalhousie University on 25/06/2015 03:00:11.

Table 1 Optimization of reaction conditions[a]



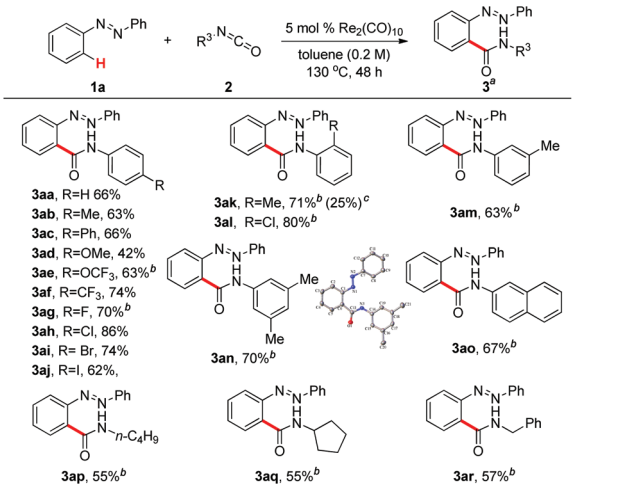
Entry	Cat. (5 mol%)	**1a**/**2i**	Solvent	*T* (°C)	Yield of **3ai**[b] (%)
1	—[c]	1/2.5	Toluene	150	0
2	$Re_2(CO)_{10}$	1/2.5	Toluene	150	60
3	$Re_2(CO)_{10}$	1/2.5	DCE	150	46
4	$Re_2(CO)_{10}$	1/2.5	CCl_4	150	0
5	$Re_2(CO)_{10}$	1/2.5	CH_3CN	150	0
6	$Re_2(CO)_{10}$	1/2.5	1,4-Dioxane	150	55
7	$Re_2(CO)_{10}$	1/1	Toluene	150	32
8	$Re_2(CO)_{10}$	2.5/1	Toluene	150	54
9	$Re_2(CO)_{10}$	2.5/1	Toluene	140	69
10	$Re_2(CO)_{10}$	2.5/1	Toluene	130	72
11	$Re_2(CO)_{10}$	2.5/1	Toluene	120	0
12[d]	**$Re_2(CO)_{10}$**	**2.5/1**	**Toluene**	**130**	77 (75)[e]
13[d]	$ReBr(CO)_5$	2.5/1	Toluene	130	0
14[d]	$Mn_2(CO)_{10}$	2.5/1	Toluene	130	0
15[d]	$Ru_3(CO)_{12}$	2.5/1	Toluene	130	7
16[d]	$Rh(PPh_3)_3Cl$	2.5/1	Toluene	130	0
17[d]	$Pd(OAc)_2$	2.5/1	Toluene	130	0

[a] Reaction conditions unless otherwise noted: **1a** (0.2 mmol), **2i** (0.5 mmol), catalyst (0.01 mmol), solvent (2 mL), 24 h. [b] Yields determined by ^1H NMR analysis. [c] No catalyst. [d] Toluene (0.2 M), 48 h. [e] Isolated yield on 0.5 mmol scale, **1a** was recovered in 70% isolated yield. DCE = 1,2-dichloroethane.

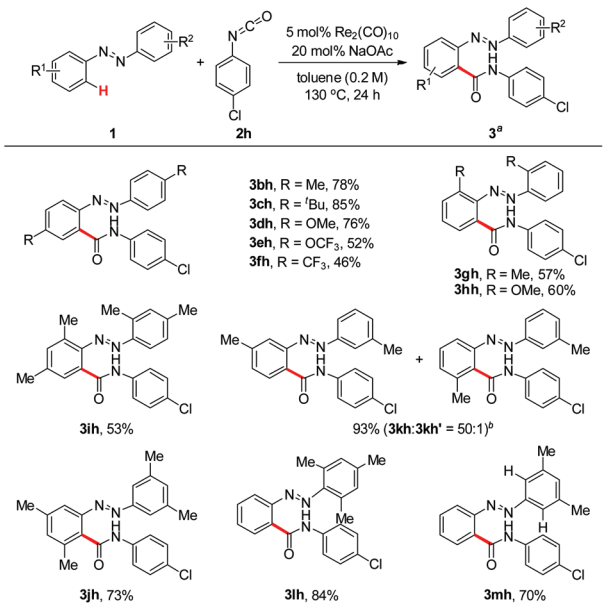
and **3ai** was obtained in 75% isolated yield (entry 12). Rhenium, manganese, and ruthenium carbonyls and other transition metal catalysts displayed very low reactivity, if any at all (entries 13–17).[9] Of note, no bis-C–H functionalized products such as **4ai** and **5ai** were detected during the entire screening process, which showcased the excellent chemoselectivity in this reaction.

With the optimized conditions in hand, we first investigated the reaction scope with regard to isocyanates (Scheme 2). It turned out that both electron-donating and -withdrawing substituents on the aromatic ring of isocyanates were tolerated affording products **3aa–j** smoothly. Importantly, a wide range of functional groups such as OMe, OCF_3, CF_3, F, Cl, Br, and I remain intact under the reaction conditions allowing for further synthetic transformations. The *ortho*-substituted phenyl isocyanates showed rather sluggish reactivity upon the sole catalysis of $Re_2(CO)_{10}$. However, the addition of a catalytic amount of NaOAc dramatically accelerated the reaction giving *o*-azobenzamide **3ak–l** in good yields. *meta*-Substituted phenyl isocyanates as well as 2-naphthalenyl isocyanate were all amenable to these conditions leading to products **3am–o** without difficulty. The structure of **3an** was unambiguously confirmed by single-crystal X-ray diffraction analysis. Pleasingly, aliphatic isocyanates, no matter linear, cyclic or benzylic, also reacted well with **1a** to give the corresponding products **3ap–r** in synthetically useful yields.

Next, we examined the substrate scope of azobenzenes (Scheme 3). It was found that azobenzenes with *para* electron-



Scheme 2 Substrate scope for isocyanates. Reaction conditions: **1a** (1.25 mmol), **2** (0.5 mmol), $Re_2(CO)_{10}$ (0.025 mmol), toluene (2.5 mL), 130 °C, 48 h. [a] Isolated yields are shown. [b] NaOAc (20 mol%). [c] ^1H NMR yield without NaOAc.

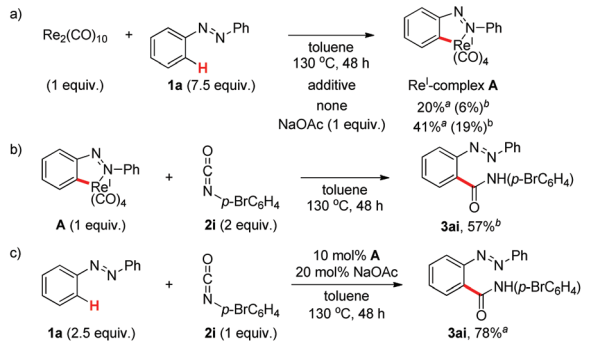


Scheme 3 Substrate scope for azobenzenes. Reaction conditions: **1** (1.25 mmol), **2h** (0.5 mmol), $Re_2(CO)_{10}$ (0.025 mmol), NaOAc (0.1 mmol), toluene (2.5 mL), 130 °C, 24 h. [a] Isolated yields are shown. [b] Ratio in the crude reaction mixture determined by GC-MS.

donating groups gave products in higher yields than those of azobenzenes bearing electron-withdrawing groups (**3bh–fh**). Meanwhile, *ortho*-methyl and -methoxyl azobenzenes were also suitable substrates despite the enhanced steric hindrance (**3gh–ih**). *meta*-Disubstituted azobenzene delivered product **3jh** in good yield. When *meta*-monosubstituted azobenzene was used, the sterically more accessible C–H bond was functionalized with excellent regioselectivity (**3kh**). Unsymmetrical azo-

This journal is © The Royal Society of Chemistry 2015

Published on 09 June 2015. Downloaded by Dalhousie University on 25/06/2015 03:00:11.



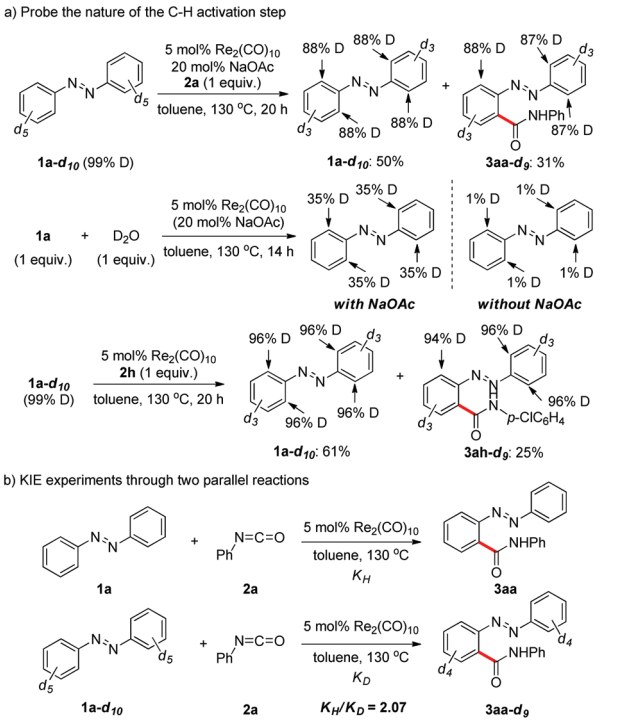
Scheme 4 Probe the possible reaction intermediate. [a] ^{1}H NMR yield. [b] Isolated yield.

benzene containing a bulky mesityl group on the N-atom showed high reactivity in the reaction (**3lh**). Again, the sterically less congested C–H bond in the unsymmetrical azobenzene was regio-specifically amino-carbonylated affording a single product (**3mh**).

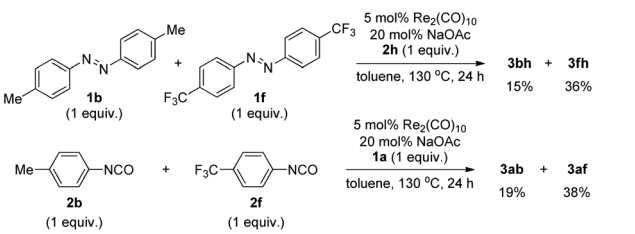
To get insight into the reaction mechanism, we performed the stoichiometric reaction of $Re_2(CO)_{10}$ with azobenzene **1a** (Scheme 4a). Gratifyingly, rhenacycle **A** was isolated in 6% yield by sublimation. The addition of NaOAc to the reaction doubled the yield of **A** indicating the acceleration effect of NaOAc for Re-promoted C–H activation.[7e] The stoichiometric reaction of **A** with isocyanate **2i** was then conducted and product **3ai** was formed in 57% isolated yield (Scheme 4b). Furthermore, it was shown that **A** did catalyze the reaction of azobenzene **1a** and isocyanate **2i** affording **3ai** in comparable yield (Scheme 4c). Collectively, these results suggested the involvement of rhenacycle **A** in the catalytic reaction.

To further probe the nature of the C–H activation step, the deuterium-labeling experiments were carried out. When fully deuterated azobenzene **1a-*d*$_{10}$** was employed in the reaction, partial deuterium-loss was detected in both the recovered starting material and the product (Scheme 5a), which implied that a reversible deprotonation/protonation equilibrium existed in the C–H activation step. To verify this assumption, azobenzene **1a** was treated with one equivalent of D_2O under the catalysis of $Re_2(CO)_{10}$ and NaOAc. As expected, 35% D-incorporation was observed at the *ortho* positions of **1a**. Interestingly, almost no D/H scrambling was detected for **1a** when the reaction was conducted in the absence of NaOAc. Meanwhile, only a very small amount of deuterium-loss was found when **1a-*d*$_{10}$** was subjected to the reaction conditions without NaOAc. These results suggested that NaOAc accelerated the deprotonation/protonation equilibrium in both directions. Furthermore, the kinetic isotope effect (KIE) experiments were performed by using two parallel reactions and the KIE value was determined to be 2.07 (Scheme 5b), which indicated that the C–H bond cleavage might be involved in the rate-limiting step.

In addition, the competition experiments between two different azobenzenes and isocyanates bearing electronically varied groups were tested (Scheme 6). It turned out that the



Scheme 5 Deuterium-labeling experiments.

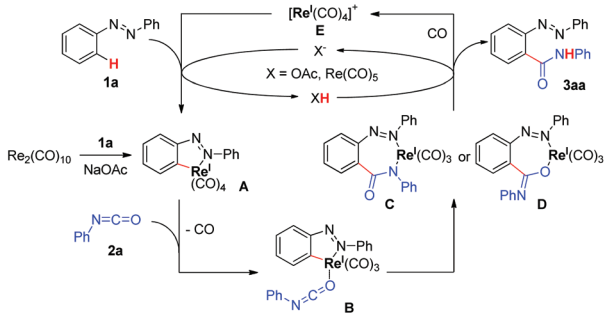


Scheme 6 Competition experiments.

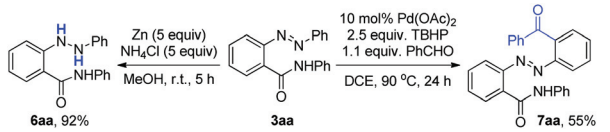
formation of products from azobenzene **1f** and isocyanate **2f**, both containing an electron-withdrawing group, were favored in the reaction, which might be ascribed to the easier deprotonative C–H activation and the higher affinity to nucleophilic attack for **1f** and **2f**, in comparison with **1b** and **2b**, respectively.

Based on the above results, a plausible reaction mechanism is proposed in Scheme 7. Initially, rhenacycle **A** is generated from **1a** and $Re_2(CO)_{10}$ with or without the assistance of NaOAc. The ligand exchange of CO with isocyanate **2a** gives intermediate **B** followed by a migratory insertion leading to the formation of a seven-membered rhenacycle **C** or **D**. Protonation of **C**/**D** gives the target product **3aa** and forms the rhenium species **E**, which facilitates the C–H bond cleavage of **1a** regenerating rhenacycle **A**. The existence of NaOAc may accelerate the deprotonative C–H activation step of **1a** and the protonation step of species **C**/**D**, thus acting as a proton shuttle in the reaction.

Published on 09 June 2015. Downloaded by Dalhousie University on 25/06/2015 03:00:11.



Scheme 7 A plausible mechanism.



Scheme 8 Synthetic transformations of *o*-azobenzamides.

Finally, the exemplified synthetic transformations of product **3** are shown in Scheme 8. *o*-Azobenzamide **3aa** could be easily reduced by Zn/NH_4Cl to afford hydrazine **6aa** in 92% yield.[9] Also, the second C–H bond acylation reaction of **3aa** with benzaldehyde was achieved by using palladium catalysis[5f] to give unsymmetrical azoarene **7aa**, which is difficult to access *via* traditional methods.[4]

In conclusion, we have developed the first C–H aminocarbonylation of azoarenes with isocyanates by using rhenium-catalysis. This protocol provides an expedient, operationally practical, and chemo- and regioselective approach to mono-C–H functionalized *o*-azobenzamides with high atom-economy. Mechanistic studies revealed a deprotonative C–H activation pathway and identified a five-membered rhenacycle as the key reaction intermediate.

Financial support from the National Basic Research Program of China (973 Program) (no. 2011CB808600) and the National Natural Science Foundation of China (21322203, 21272238, 21472194) are gratefully acknowledged.

Notes and references

1 (*a*) K. Hunger, *Industrial Dyes: Chemistry, Properties, Applications*, Wiley-VCH, Weinheim, Germany, 2003; (*b*) A. Bafana, S. S. Devi and T. Chakrabarti, *Environ. Rev.*, 2011, **19**, 350; (*c*) S. Patai, *The Chemistry of the Hydrazo, Azo and Azoxy Groups*, Wiley, Chichester, U.K., 1997, vol. 2, pp. 729–730.

2 (*a*) G. S. Kumar and D. C. Neckers, *Chem. Rev.*, 1989, **89**, 1915; (*b*) E. Ishow, C. Bellaïche, L. Bouteiller, K. Nakatani and J. A. Delaire, *J. Am. Chem. Soc.*, 2003, **125**, 15744; (*c*) H. Dürr and H. Bouas-Laurent, *Photochromism: Molecules and Systems*, Elsevier, Amsterdam, 2003; (*d*) F. Puntoriero, P. Ceroni, V. G. Balzani and F. Voegtle, *J. Am. Chem. Soc.*, 2007, **129**, 10714; (*e*) T. Muraoka, K. Kinbara and T. Aida, *Nature*, 2006, **440**, 512; (*f*) V. Ferri, M. Elbing, G. Pace, M. D. Dickey, M. Zharnikov, P. Samori, M. Mayor and M. A. Rampi, *Angew. Chem., Int. Ed.*, 2008, **47**, 3407; (*g*) T. Ikeda and O. Tsutsumi, *Science*, 1995, **168**, 1873; (*h*) R. M. Parker, J. C. Gates, H. L. Rogers, P. G. R. Smith and M. C. Grossel, *J. Mater. Chem.*, 2010, **20**, 9118; (*i*) R. H. Berg, S. Hvilsted and P. S. Ramanujam, *Nature*, 1996, **383**, 505; (*j*) R. G. Anderson and G. Nickless, *Analyst*, 1967, **92**, 207.

3 (*a*) S. Keiper and J. S. Vyle, *Angew. Chem., Int. Ed.*, 2006, **45**, 3306; (*b*) F. Ravalico, S. L. James and J. S. Vyle, *Green Chem.*, 2011, **13**, 1778; (*c*) A. J. Harvey and A. D. Abell, *Tetrahedron*, 2000, **56**, 9763; (*d*) H. Kumar, P. Kumar, B. Narasimhan, K. Ramasamy, V. Mani, R. K. Mishra and A. B. A. Majeed, *Med. Chem. Res.*, 2013, **22**, 1957; (*e*) N. Kaloyanov and R. Stoyanova, *Arzneim.-Forsch./Drug Res.*, 2000, **50**, 652; (*f*) H. Noda, G. Erős and J. W. Bode, *J. Am. Chem. Soc.*, 2014, **136**, 5611; (*g*) C. M. McKeen, L. J. Brown, J. T. G. Nicol, J. M. Mellor and T. Brown, *Org. Biomol. Chem.*, 2003, **1**, 2267; (*h*) E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel and D. F. Worth, *J. Med. Chem.*, 1963, **6**, 646; (*i*) R. C. Brown, Z. Li, A. J. Rutter, X. Mu, O. H. Weeks, K. Smith and I. Weeks, *Org. Biomol. Chem.*, 2009, **7**, 386.

4 For a review, see: (*a*) F. Hamon, F. Djedaini-Pilard, F. Barbot and C. Len, *Tetrahedron*, 2009, **65**, 10105. For recent examples, see: (*b*) E. Drug and M. Gozin, *J. Am. Chem. Soc.*, 2007, **129**, 13784; (*c*) C. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 6174; (*d*) Y. Takeda, S. Okumura and S. Minakata, *Angew. Chem., Int. Ed.*, 2012, **51**, 7804; (*e*) S. Cai, H. Rong, X. Yu, X. Liu, D. Wang, W. He and Y. Li, *ACS Catal.*, 2013, **3**, 478; (*f*) Y. Zhu and Y. Shi, *Org. Lett.*, 2013, **15**, 1942.

5 For selected examples, halogenation: (*a*) D. R. Fahey, *J. Organomet. Chem.*, 1971, **27**, 283; (*b*) D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Tetrahedron*, 2006, **62**, 11483; (*c*) X.-T. Ma and S.-K. Tian, *Adv. Synth. Catal.*, 2013, **355**, 337; Arylation: (*d*) S. Miyamura, H. Tsurugi, T. Satoh and M. Miura, *J. Organomet. Chem.*, 2008, **693**, 2438; (*e*) C. Qian, D. Lin, Y. Deng, X.-Q. Zhang, H. Jiang, G. Miao, X. Tang and W. Zeng, *Org. Biomol. Chem.*, 2014, **12**, 5866; Acylation: (*f*) H. Li, P. Li and L. Wang, *Org. Lett.*, 2013, **15**, 620; (*g*) Z. Y. Li, D. D. Li and G. W. Wang, *J. Org. Chem.*, 2013, **78**, 10414; (*h*) F. Xiong, C. Qian, D. Lin, W. Zeng and X. Lu, *Org. Lett.*, 2013, **15**, 5444; (*i*) H. Song, D. Pi, C. Chen, X. Cui and Y. Wu, *J. Org. Chem.*, 2014, **79**, 2955. Oxygenation: (*j*) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300; (*k*) Z. Yin, X. Jiang and P. Sun, *J. Org. Chem.*, 2013, **78**, 10002. Nitrogenation: (*l*) X. F. Jia and J. Han, *J. Org. Chem.*, 2014, **79**, 4180; (*m*) H. Wang, Y. Yu, X. Hong, Q. Tan and B. Xu, *J. Org. Chem.*, 2014, **79**, 3279; (*n*) T. Ryu, J. Min, W. Choi, W. H. Jeon and P. H. Lee, *Org. Lett.*, 2014, **16**, 2810; (*o*) B. Majhi, D. Kundu, S. Ahammed and B. C. Ranu, *Chem. – Eur. J.*, 2014, **20**, 9862. Cyanation: (*p*) J. Han, C. Pan, X. Jia and C. Zhu, *Org. Biomol. Chem.*,

 This journal is © The Royal Society of Chemistry 2015

Published on 09 June 2015. Downloaded by Dalhousie University on 25/06/2015 03:00:11.

2014, **12**, 8603; Aminoalkylation: (*q*) A. Wangweerawong, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2014, **136**, 8520; Cyclization: (*r*) U. R. Aulwurm, J. U. Melchinger and H. Kisch, *Organometallics*, 1995, **14**, 3385; (*s*) D. Zhao, Q. Wu, X. Huang, F. Song, T. Lv and J. You, *Chem. – Eur. J.*, 2013, **19**, 6239; (*t*) K. Muralirajan and C.-H. Cheng, *Chem. – Eur. J.*, 2013, **19**, 6198; (*u*) D. Zhao, S. Vásquez-Céspedes and F. Glorius, *Angew. Chem., Int. Ed.*, 2015, **54**, 1657; Alkylation: (*v*) H. Deng, H. Li and L. Wang, *Org. Lett.*, 2015, **17**, 2450.

6 For a review, see: (*a*) Y. Kuninobu and K. Takai, *Chem. Rev.*, 2011, **111**, 1938. For selected examples, see: (*b*) H. Chen and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1999, **38**, 3391; (*c*) R. Hua and X. Tian, *J. Org. Chem.*, 2004, **69**, 5782; (*d*) H. Takaya, M. Ito and H. Murahashi, *J. Am. Chem. Soc.*, 2009, **131**, 10824; (*e*) Q. Liu, Y.-N. Li, H.-H. Zhang, B. Chen, C.-H. Tung and L.-Z. Wu, *J. Org. Chem.*, 2011, **76**, 1444; (*f*) Y. Fukumoto, M. Daijo and N. Chatani, *J. Am. Chem. Soc.*, 2012, **134**, 8762; (*g*) H. Peng, A. Lin, Y. Zhang, H. Jiang, J. Zhou, Y. Cheng, C. Zhu and H. Hu, *ACS Catal.*, 2012, **2**, 163.

7 (*a*) D. Xia, Y. Wang, Z. Du, Q.-Y. Zheng and C. Wang, *Org. Lett.*, 2012, **14**, 588; (*b*) Q. Tang, D. Xia, X. Jin, Q. Zhang, X.-Q. Sun and C. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 4628; (*c*) Y. Wang, L. Zhang, Y. Yang, P. Zhang, Z. Du and C. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 18048; (*d*) G. Mao, B. Jia and C. Wang, *Chin. J. Org. Chem.*, 2015, **35**, 284; (*e*) X. Geng and C. Wang, *Org. Lett.*, 2015, **17**, 2434; (*f*) H. Gu and C. Wang, *Org. Biomol. Chem.*, 2015, **13**, 5880.

8 For C–H activation reactions of other types of arenes with isocyanates, see: (*a*) Y. Kuninobu, Y. Tokunaga, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2006, **128**, 202; (*b*) Y. Kuninobu, K. Kikuchi, Y. Tokunaga, Y. Nishina and K. Takai, *Tetrahedron*, 2008, **64**, 5974; (*c*) K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430; (*d*) K. Muralirajan, K. Parthasarathy and C.-H. Cheng, *Org. Lett.*, 2012, **14**, 4262; (*e*) S. Sueki, Y. Guo, M. Kanai and Y. Kuninobu, *Angew. Chem., Int. Ed.*, 2013, **52**, 11879; (*f*) B. Zhou, W. Hou, Y. Yang and Y. Li, *Chem. – Eur. J.*, 2013, **19**, 4701; (*g*) X.-Y. Shi, A. Renzetti, S. Kundu and C.-J. Li, *Adv. Synth. Catal.*, 2014, **356**, 723; (*h*) S. De Sarkar and L. Ackermann, *Chem. – Eur. J.*, 2014, **20**, 13932; (*i*) J. R. Hummel and J. A. Ellman, *Org. Lett.*, 2015, **17**, 2400; (*j*) J. Li and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, DOI: 10.1002/anie.201501926.

9 For more details, see ESI.†