Cite this: Chem. Commun., 2012, 48, 6702-6704

www.rsc.org/chemcomm

COMMUNICATION

Metal-free arylation of benzene and pyridine promoted by amino-linked nitrogen heterocyclic carbenes[†]

Wen-Ching Chen,^{*a*} Yu-Chen Hsu,^{*ab*} Wei-Chun Shih,^{*a*} Ching-Yu Lee,^{*ac*} Wen-Han Chuang,^{*ad*} Yi-Fang Tsai,^{*a*} Peter Ping-Yu Chen^{**e*} and Tiow-Gan Ong^{**a*}

Received 8th April 2012, Accepted 8th May 2012 DOI: 10.1039/c2cc32519e

An amino-linked nitrogen heterocyclic carbene (amino-NHC), 1-*t*Bu, has been shown to mediate carbon-carbon coupling through the direct C-H functionalization of benzene and pyridine in the absence of a metal catalyst. Using EPR, the first spectroscopic evidence corroborating the single electron transfer mechanism for the metal-free carbon-carbon coupling manifold, as reported by others, is introduced.

Organocatalysts offer an economical and greener platform for mediating organic transformations as they exclude the use of highly toxic and expensive metallic catalysts.¹ Recent breakthroughs led by Kwong-Lei,² Shirakawa-Hayashi,³ Shi,⁴ Itami,⁵ Jiang,⁶ and Li-Jiang⁷ have propelled organic catalysis into the realm of aryl-aryl cross-coupling via C-H bond functionalization of arenes,⁸ an area that has been predominantly monopolized by transition-metal chemistry for decades. As a result, numerous reports related to metal-free cross-coupling manifolds have gradually appeared, demonstrating rich opportunities and hidden potentials for synthetic utility. Yet, the exact formalism with regards to the claim of "organocatalytic C-H bond activation reaction" remains debatable due to the lack of direct experimental evidence. Nonetheless, it is broadly accepted that the coupling process is initiated by base-promoted homolytic radical aromatic substitution (HAS).9

N-Heterocyclic carbenes (NHCs) have proven to be efficient metal-free catalysts for a wide variety of key organic reactions through Lewis acid–base-interactions.¹⁰ In this context, the use of NHCs as organic catalysts for aryl–aryl cross-coupling reactions *via* HAS constitutes an almost unexplored field. Thus, expanding such a proof of concept using NHCs would

be beneficial towards initiating exploration of other catalytic manifolds, as the steric, electronic and structural features of NHCs may be modified with ease for reaction diversification. Herein, we wish to report an amino-linked nitrogen heterocyclic carbene (amino-NHC), **1-tBu**,¹¹ that mediates a carbon–carbon coupling manifold through the direct C–H functionalization of benzene and pyridine.

The direct arylation of benzene with 4-iodotoluene, **2a**, was selected as a starting point for our investigations (Scheme 1), using 20 mol% amino-NHC in the presence of 3 equiv. KO'Bu at 80 °C. The desired cross-coupling product, **3a**, was obtained in good yield (78%) with **1-tBu**, but lower yield (11%) with the pyridine NHC derivative, **Py-IMes**. Monitoring the reaction mixture closely by NMR spectroscopy revealed that **1-tBu** remained intact after the catalytic reaction. Moreover, a similarly good catalytic yield could also be achieved using the much more robust imidazolium salt **1-tBu-Im** without preparing the moisture-sensitive free carbene.

Prior to investigating the cross-coupling arylation reactions, several control experiments were completed to remove the possibility that metal impurities may be responsible for the coupling reaction. First, the quality of KO'Bu, obtained from several commercially available sources, does not affect the rate of reaction to a great extent. We also took the extreme step of running the experiments in new glassware with ultra-pure KO'Bu, produced *via* sublimation, to reproducibly confirm this methodology. Spiking the reaction with 10 mol% of transition-metal salts, such as Fe(OAc)₂, PdCl₂ and CuBr, only diminished the efficiency of the process, further demonstrating the metal-free conditions. The importance of the NHC structure was



Scheme 1 Optimization of direct arylation of benzene. The reaction was performed under a nitrogen atmosphere using 2a (0.5 mmol), base (1.5 mmol) and benzene (4 mL) in a sealed tube. Yield determined by GC.

^a Institute of Chemistry, Academia Sinica, Nangang, Taipei, Taiwan, Republic of China. E-mail: tgong@chem.sinica.edu.tw

^b Institute of Organic and Polymeric Materials, National Taipei University of Technology, Taipei, Taiwan, Republic of China

^c Taipei Municipal University of Education, Taiwan, Republic of China

^d Department of Chemistry, Tamkang University, Taiwan, Republic of China

^e Department of Chemistry, National Chung Hsing University, Taiwan, Republic of China

[†] Electronic supplementary information (ESI) available: Syntheses of **3** and **4** with characterization data. EPR spectrum of the mixture **5** and 18-crown-6 in toluene. See DOI: 10.1039/c2cc32519e

Table 1 Amino-NHC-catalyzed direct arylation of benzene with various $Ar-I^a$

	H	-I <u>20 mol</u> KO ^t Bu 80 %	% 1-tBu Ar -√ I (3 eq.) C, 4 h	3
Entry	Ar-group		Product 3	$\mathrm{Yield}^{b}\left(\%\right)$
1	4-MeC ₆ H ₄	2a	3a	73
2	3-MeC ₆ H ₄	2b	3b	54
3	$2 - MeC_6H_4$	2c	3c	39^c
4	4-MeOC ₆ H ₄	2d	3d	75^d
5	$3-MeOC_6H_4$	2e	3e	62^d
6	$2-MeOC_6H_4$	2f	3f	50^c
7	$4-CNC_6H_4$	2g	3g	59
8	3-Pvridvl	2h	3h	47^d
9	2-Pvridvl	2i	3i	44
10	1-Naphthyl	2j	3j	41 (45 ^e)

^{*a*} The reaction was carried out under a nitrogen atmosphere using **2** (0.5 mmol), KO'Bu (1.5 mmol) and benzene (4 mL) in a sealed tube. ^{*b*} Isolated yield based on **2**. ^{*c*} Reaction time was 24 h. ^{*d*} Reaction time was 3 h. ^{*e*} KHMDS was used instead of KO'Bu.

also probed early-on. Replacement of **1-tBu** with monodentate NHCs, namely **IMes** and **IPr**, furnished only disappointing outcomes, illustrating the importance of the two binding sites within the architectural framework in this process.¹²

With the optimized conditions in hand, additional aryl iodide-derived substrates were also examined in order to expand the generality of this arylation (Table 1). Good yields of the coupling products were observed for electron-rich arvl iodides 4-iodotoluene, 2a, (entry 1) and 4-iodoanisole, 2d, (entry 4) (\sim 75% yield). As expected, the more sterically demanding ortho substrates 2-iodotoluene, 2c, (entry 3) and 2-iodoanisole, 2f, (entry 6) gave slightly lower yields of coupling products, in the range of 50%. Aryl iodides containing electronwithdrawing groups, such as 4-iodobenzonitrile, 2g, also participated smoothly in the catalytic reaction, producing an average yield of 59% (entry 7). However, diminishing yields were witnessed for 3-pyridyl (47%), 2-pyridyl (44%) and 1-naphthyl (41%) derivatives (entries 8-10), suggesting sensitivity toward strong deactivators. In general, the overall catalytic efficiency of benzene cross-coupling mediated by amino-NHCs is somewhat lower than previous reports using phenanthroline derivatives,²⁻⁷ but we have established the viability of the NHC concept for the first time in this process.

In view of the importance of heterocyclic rings as a common motif in organic molecules, we turned our attention toward pyridine in order to broaden the applicability of our method. In the optimization process for the cross-coupling of pyridine (see Table 1, ESI⁺), 1-tBu-Im (84-85%) was found to be more effective than 1-tBu (80%) and NaO^tBu was found to possess same effect as its potassium counterpart. However, the statistically expected 2:2:1 isomeric ratio o:m:p suggests little to no regioselectivity. The scope of the reaction was then expanded using various aryl iodide derivatives (Table 2). Coupling products were observed for electron-rich para and meta-substituted aryl iodides bearing methoxy and methyl groups with an average $\sim 80\%$ yield (see entries 1-2 and 4-5). On the other hand, slightly diminished conversion was witnessed for ortho substrates (entries 3 and 6). Electron-withdrawing groups, such as 4-iodobenzonitrile, 2g, (53%, entry 7) and 1-fluoro-4-iodobenzene, 2l, (77%, entry 12),

Table 2 Imidazolium salt-catalyzed direct arylation of pyridine with various $Ar-I^a$

	N +	Ar—I 2	20 mol% 1-t l NaO ^t Bu (3 110 °C, 4	Bu-Im eq.) ⋅h 4	Ar
Entry	Ar-group		Product 4	$\operatorname{Yield}^{b}(\%)$	$(o/m/p)^c$
[4-MeC ₆ H₄	2a	4a	84	(2.5/2.1/1)
2	$3-MeC_6H_4$	2b	4b	78	(2.8/2.3/1)
3	$2 - MeC_6H_4$	2c	4c	40^d	(2.5/1.4/1)
1	$4 - MeOC_6H_4$	2d	4d	87	(3.4/2.8/1)
5	3-MeOC ₆ H ₄	2e	4 e	70	(3.4/2.7/1)
5	$2-MeOC_6H_4$	2f	4f	60^d	(2.4/2.7/1)
7	$4 - CNC_6 H_4$	2g	4g	53	
3	3-Pyridyl	2h	4ĥ	50	(3.2/1.9/1)
)	2-Pyridyl	2i	4i	46	(2.3/1.5/1)
0	1-Naphthyl	2j	4j	67	(3.1/2.2/1)
1	$4 - CF_3C_6H_4$	2k	4k	33^e	(3/3/1)
2	$4-FC_6H_4$	21	41	77	(3.2/3.1/1)

^{*a*} The reaction was carried out under a nitrogen atmosphere using **2** (0.5 mmol), NaO'Bu (1.5 mmol) and pyridine (4 mL) in a sealed tube. ^{*b*} Isolated yield based on **2**. ^{*c*} Determined by ¹H NMR. ^{*d*} Reaction time was 24 h. ^{*e*} Reaction time was 48 h.

furnished a satisfactory yield, yet low yields were observed for the CF₃ derivative, **2k**, (entry 11). Finally, naphthyl and 3-pyridyl iodides also underwent a smooth transformation to give coupling products **4j** and **4h**. Amongst these organic-mediated cross-coupling reactions *via* aryl C–H bond activation, there exists to date only one report involving the coupling of pyridine with aryl iodide using KO'Bu in DMF solvent, albeit producing lower yields.⁵

In order to understand the role played by amino-NHC in these reactions, several experiments were performed. First, competition experiments revealed small kinetic isotope effects (KIE) for benzene (1.05) as well as pyridine (1.22–1.67) (Scheme 2), indicating that the C–H bond-breaking step is not the rate-limiting step of the reaction. More importantly, heating the model reaction of benzene or pyridine in the presence of 1 equiv. of TEMPO, a radical scavenger, completely halts the reactivity. These results demonstrate that radical intermediates are involved in such a reaction.

To further verify our assumption regarding radical generation by amino-NHCs, a solution of freshly prepared potassium *tert*butoxide was mixed stoichiometrically with amino-NHC **1-tBu** in toluene at room temperature, and a dark red solution was observed after one day. Electron paramagnetic resonance (EPR) analysis of the reaction mixture showed a very broad signal (Fig. 1, green dotted line), implying the production of a radical,



Scheme 2 KIE experiments.



Fig. 1 Room-temperature EPR spectrum of a solution containing equivalent amounts of **1-tBu**, KO'Bu and crown ether (black) dissolved in toluene and the best-fit simulated spectrum (red) of a radical anion with $g_{iso} = 2.0031$, $A_{\rm H} = 2.1$, 7.1, 8.6 G, and $A_{\rm N} = 2.9$, 3.2 G.



Scheme 3 Plausible mechanism.

portrayed as 7 in Scheme 3. Unfortunately, the signal is too broad to make any meaningful interpretation on the nature of the radical species. Subsequently, crown-ether was added to lessen the quadrupole effect derived from the potassium ion, with the aim of resolving the line broadening of the signal and the complication of the EPR spectrum (dark, straight line). Fig. 1 displays the EPR signal with a distinct splitting at $g \sim 2.0031$. The corresponding simulation, highlighted by the red spectrum, was obtained with the involvement of three proton nuclei and two nitrogen nuclei in hyperfine coupling interactions. The simulated hyperfine coupling constants are 7.1, 8.6 and 2.1 G for the protons, and 2.9 and 3.2 G for the nitrogen atoms. This result rationally infers that an unpaired spin is located within the NHC-imidazole ring coupled with its two ethylene H atoms, the distant methylene H atom and two nitrogen atoms. Performing the reaction with phenyl iodide and using the solution of 7 in catalytic amounts generated the aryl-aryl coupling product in good yield, implying that 7 is an intermediate radical species in the catalytic cycle. To our knowledge, this data represents the first spectroscopic evidence corroborating a metal-free carbon-carbon coupling manifold via a single-electron transfer mechanism and confirming the formation of NHC-derived radical intermediates, 7.13 Interestingly, the Arnold group has isolated and observed a similar NHC radical via potassium reduction.¹⁴

On the basis of experimental evidence and literature precedents,^{3,9} we propose that the preliminary NHC-mediated cross-coupling mechanism proceeds through the following steps, as shown in Scheme 3: (1) a single-electron transfer from the KO'Bu-amino-NHC adduct **5** to the aryl iodide gives a new NHC radical cation **7** and the radical anion **6**, which

subsequently transforms to the transient aryl radical **8**; (2) benzene reacts with the aryl radical **8** to generate the cyclo hexadienyl radical **9**; and (3) subsequent coupling of **7** and **9** occurs to afford the biaryl. Metal *tert*-butoxides are known to behave as single electron donors in many cases, such as towards alkyl halides, ketones and polyaromatic substrates.¹⁵ It is quite clear that the presence of amino-NHC **1-tBu** is essential to promote or assist KO'Bu in generating the radical species **7**, which is more likely to be a cation radical species. Nonetheless, the identity of **7** remains to be ascertained by detailed mechanistic studies.

In summary, an amino-linked nitrogen heterocyclic carbene (amino-NHC) **1-tBu** was shown to mediate the carbon–carbon coupling of benzene and pyridine through direct C–H functionalization in the absence of a metal catalyst. We have also disclosed the first spectroscopic evidence corroborating the metal-free carbon–carbon coupling mechanism *via* single electron transfer, as reported by others. Ongoing work seeks to further explore the mechanistic aspect and the utility of the amino-NHC manifold for the development of new metal-free organic catalysts for C–H functionalization.

Notes and references

- (a) A. Dondoni and A. Massi, Angew. Chem., Int. Ed., 2008, 47, 4638; (b) A. Grossmann and D. Enders, Angew. Chem., Int. Ed., 2012, 51, 314; (c) S. Schenker, A. Zamfir, M. Freund and S. B. Tsogoeva, Eur. J. Org. Chem., 2011, 2209; (d) C. Grondal, M. Jeanty and D. Enders, Nat. Chem., 2010, 2, 167; (e) S. Bertelsen and K. A. Jørgensen, Chem. Soc. Rev., 2009, 38, 2178.
- 2 W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, J. Am. Chem. Soc., 2010, 132, 16737.
- 3 E. Shirakawa, K. Itoh, T. Higashino and T. Hayashi, J. Am. Chem. Soc., 2010, 132, 15537.
- 4 C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem.*, 2010, 2, 1044.
- 5 S. Yanagisawa, K. Ueda, T. Taniguchi and K. Itami, *Org. Lett.*, 2008, **10**, 4673.
- 6 Y. Qiu, Y. Liu, K. Yang, W. Hong, Z. Li, Z. Wang, Z. Yao and S. Jiang, *Org. Lett.*, 2011, **13**, 3556.
- 7 H. Liu, B. Yin, Z. Gao, Y. Li and H. Jiang, *Chem. Commun.*, 2012, **48**, 2033.
- (a) O. Vakuliuk, B. Koszarna and D. T. Gryko, Adv. Synth. Catal., 2011, 353, 925; (b) C.-L. Sun, Y.-F. Gu, W.-P. Huang and Z.-J. Shi, Chem. Commun., 2011, 47, 9813; (c) M. Rueping, M. Leiendecker, A. Das, T. Poisson and L. Bui, Chem. Commun., 2011, 47, 10629; (d) G.-P. Yong, W.-L. She, Y.-M. Zhang and Y.-Z. Li, Chem. Commun., 2011, 47, 11766; (e) D. S. Roman, Y. Takahashi and A. B. Charette, Org. Lett., 2011, 13, 3242.
- 9 A. Studer and D. P. Curran, Angew. Chem., Int. Ed., 2011, 50, 5018.
- (a) A. T. Biju, N. Kuhl and F. Glorius, Acc. Chem. Res., 2011,
 44, 1182; (b) D. Enders, O. Niemeier and A. Henseler, Chem. Rev.,
 2007, 107, 5606; (c) V. Nair, S. Vellalath and B. P. Babu, Chem.
 Soc. Rev., 2008, 37, 2691.
- 11 (a) C.-Y. Li, Y.-Y. Kuo, J.-H. Tsai, G. P. A. Yap and T.-G. Ong, *Chem.-Asian J.*, 2011, **6**, 1520; (b) W.-C. Shih, C.-H. Wang, Y.-T. Chang, G. P. A. Yap and T.-G. Ong, *Organometallics*, 2009, **28**, 1060.
- 12 Based upon reviewer's suggestion, we replaced 1-tBu with its amine precursor, 2-(*tert*-butylamino)ethanol and found 35% yield of coupling product.
- Literatures for EPR studies with metal-free coupling using hypervalent iodine: (a) Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai and S. Oka, J. Am. Chem. Soc., 1994, **116**, 3684; (b) Y. Kita, T. Takada and H. Tohma, Pure Appl. Chem., 1996, **68**, 627; (c) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka and Y. Kita, Angew. Chem., Int. Ed., 2010, **49**, 3334.
- 14 P. L. Arnold and S. T. Liddle, Organometallics, 2006, 25, 1485.
- 15 (a) E. C. Ashby, A. B. Goel and R. N. DePriest, J. Org. Chem., 1981, 46, 2429; (b) E. C. Ashby and J. N. Argyropoulos, J. Org. Chem., 1986, 51, 3593.