Domino Arylation **Hot Paper**

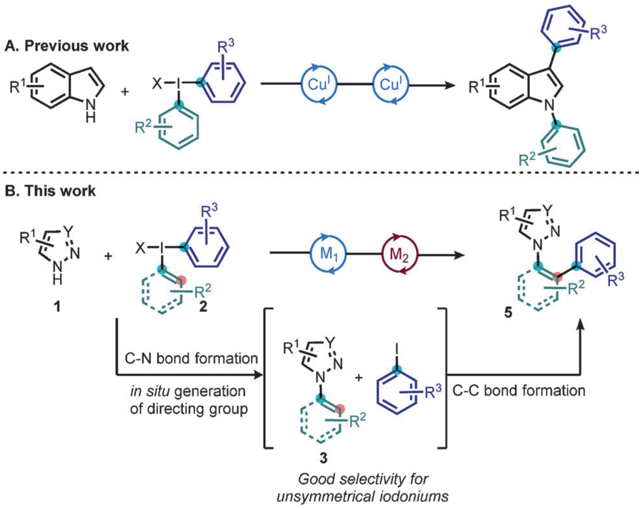
International Edition: DOI: 10.1002/anie.201701523
German Edition: DOI: 10.1002/ange.201701523

Domino *N*-/*C*-Arylation via In Situ Generation of a Directing Group: Atom-Efficient Arylation Using Diaryliodonium Salts

Christopher J. Teskey[+], *Shariar M. A. Sohel*[+], *Danielle L. Bunting, Sachin G. Modha, and Michael F. Greaney**

Abstract: *Both aryl components of diaryliodonium salts can be used in a domino one-pot reaction via in situ generation of a directing group. A number of heterocycles undergo N-arylation which is followed by ruthenium-catalyzed C-arylation. Notably the reaction extends well to unsymmetrical diaryliodonium salts with a number of highly selective examples shown.*

Diaryliodonium salts have seen extensive application as arylating agents in recent years, as they possess desirable qualities of high reactivity, ease of use as stable, crystalline solids, and compatibility with a wide variety of metal catalysts.[1] Their major drawback, however, is the generation of one equivalent of "waste" aryl iodide in the vast majority of transformations, an unsustainable feature that limits future exploitation. We recently addressed this issue by capturing the generated aryl iodide in an iodonium arylation through a one-pot, tandem *C*-/*N*-arylation of indole (Scheme 1 A).[2] Similar concepts of atom economy have been set out by Dauban and co-workers, who demonstrated a sequential oxidant/arylation role for $ArI(OAc)_2$,[3] Muñiz and co-workers, who performed tandem borylation/Suzuki–Miyaura cross-coupling of diaryliodoniums,[4] and Jiang and co-workers, who described diaryl sulfide synthesis from a single iodonium species.[5,6] In each case (and, perforce, all intramolecular applications of cyclic diaryliodoniums)[7] the iodonium compound undergoes functionalization at the two *ipso*-positions. We were interested in developing alternative pathways to create new arylation patterns from iodoniums while preserving the atom-economic approach. Our plan is set out in Scheme 1 B, which proposes a domino reaction whereby an intermediate generated in step 1 opens up new reactivity to harness the aryl iodide in step 2: The *N*-heterocycle **1** can undergo arylation with **2** to give an *N*-aryl product **3**, where the heterocycle can then act as a directing group for subsequent *ortho* C−H arylation taking place in situ with the released aryl iodide. Crucially, this second arylation breaks the symmetry of the starting iodonium, creating structures having greater diversity for application as building blocks in the chemical sciences.



Scheme 1. Atom-economical use of diaryliodoniums.

To develop the proposed sequence we required a heteroarene substrate offering versatile scope with respect to reaction conditions for the two arylations. Pyrazoles were appealing as they are known to react with iodoniums under both metal-catalyzed and metal-free conditions,[8] and functionalized pyrazoles have been extensively employed as privileged motifs in medicinal chemistry.[9] We elected to investigate ruthenium catalysis for the key C−H arylation step, given the robust literature precedent,[10] the affordability of many Ru catalysts,[11] and our own recent experiences in developing Ru-catalyzed C−H functionalization chemistry.[12]

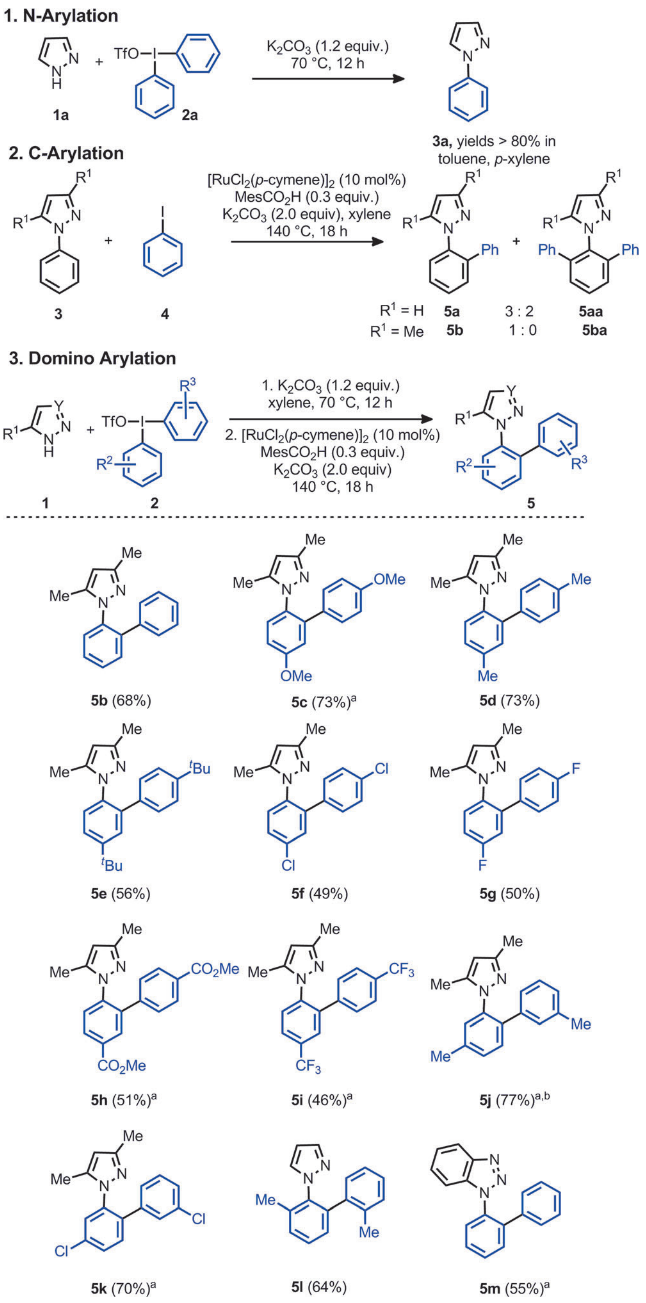
Preliminary reaction screening of the two steps in isolation established that the first *N*-arylation step could be performed in a variety of solvents with 1.2 equivalents of diphenyliodonium triflate (**2a**), pyrazole (**1a**), and potassium carbonate as base at 70 °C (Scheme 2). Catalytic copper iodide was observed to accelerate the reaction, but it was not a requirement for good conversions in this simple case. The second step was interrogated using *N*-phenyl pyrazole (**3a**), iodobenzene (**4**), and a $[RuCl_2(p\text{-cymene})]_2$ catalyst system. While conversions were good using xylene and, critically, the same K_2CO_3 base as in step 1, the system suffered from competitive diarylation with poor selectivity between mono-arylated **5a** and doubly arylated **5aa**. This presents a problem for the overall stoichiometry of the projected domino process. To prevent the unwanted second arylation we switched to the sterically hindered 1-phenyl,3,5-dimethyl pyrazole (**3b**),

---

[*] Dr. C. J. Teskey,[+] Dr. S. M. A. Sohel,[+] D. L. Bunting, Dr. S. G. Modha, Prof. Dr. M. F. Greaney
School of Chemistry, The University of Manchester
Oxford Road, Manchester, M13 9PL (UK)
E-mail: michael.greaney@manchester.ac.uk

[+] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201701523.

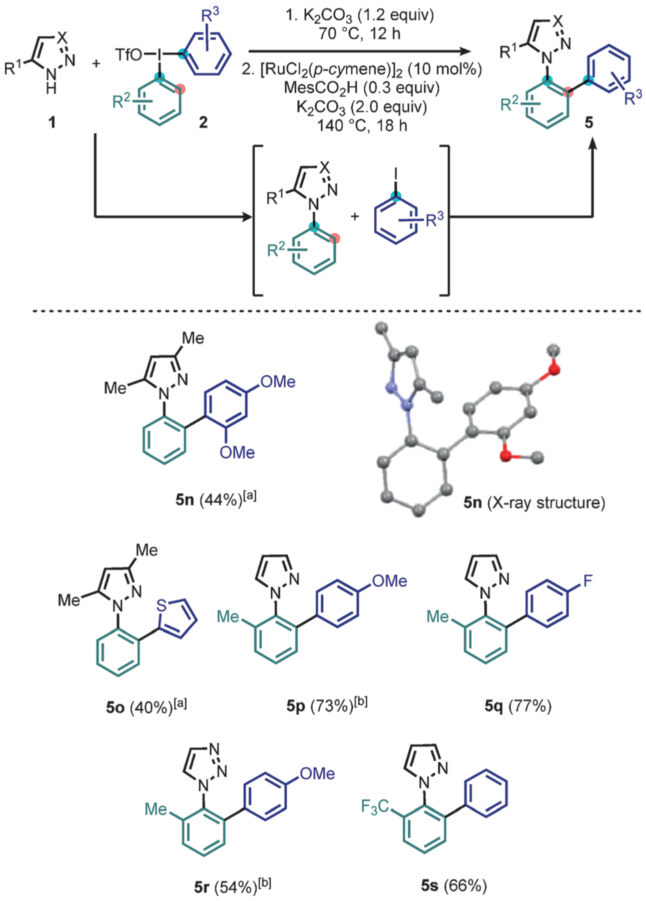


Scheme 2. Substrate scope with symmetrical diaryliodonium salts. [a] CuI (5 mol%) was added in the first step and the reaction run for 8 h. [b] Iodonium trifluoroacetate salt was used.

which gave the expected monoarylated product **5b** in good conversions. To merge the two processes we used *p*-xylene as solvent and an initial reaction temperature of 70 °C, increasing to 140 °C for the C–H arylation, and were delighted to isolate **5b** in good overall yield for the domino arylation process. Best results were obtained from adding the ruthenium catalyst to the reaction following completion of the initial *N*-arylation.

A comprehensive range of symmetrical diaryliodonium salts[13] proved to be successful under the optimized reaction conditions (Scheme 2). Salts with *para*-substitution (**5c**–**5i**) gave the diarylated products in very good yields considering that two new bonds are being formed. Both electron-rich (**5c**–**5e**) and electron-deficient (**5f**–**5i**) aromatics were tolerated well though 5 mol% of copper iodide was added for the first step in the most polarized of examples. *meta*-Substituted diaryliodoniums were also tolerated (**5j** and **5k**). We demonstrated that pyrazole itself can be used as a substrate with di-*ortho*-tolyl iodonium triflate to give product **5l** in good yield. Finally, we were gratified to find that benzotriazole was a competent heterocycle for our reaction conditions giving the diarylated compound **5m** in 55% yield.

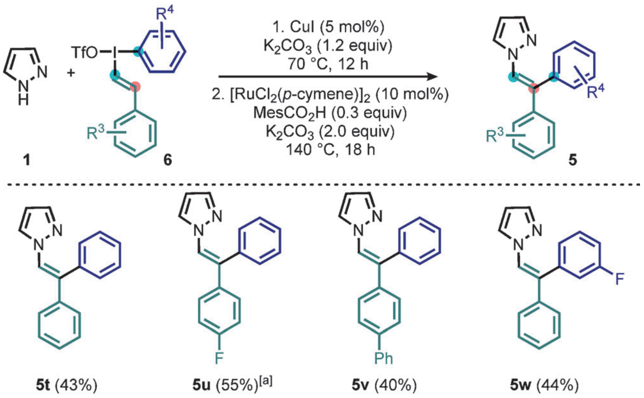
With these results in hand, we turned our attention to unsymmetrical iodonium salts (Scheme 3). Recent work from Novak and co-workers has described selective arylation of 3,5-diphenylpyrazole with diaryliodoniums,[8a] suggesting that a selective domino arylation reaction could be developed. Beginning with electronic differentiation, we found that treatment of 3,5-dimethylpyrazole (**1b**) with (2,4-dimethoxyphenyl)(phenyl)iodonium tosylate afforded product **5n** exclusively, in 44% yield, where the *N*-arylation has been selective for the less electron-rich phenyl group. Similar selectivity was observed with phenyl(2-thiophenyl)iodonium triflate, which transferred the phenyl group initially in the *N*-arylation, followed by *C*-arylation with the 2-iodothiophene



Scheme 3. [15] Substrate scope with unsymmetrical diaryliodonium salts. [a] Iodonium tosylate salt was used. [b] CuI (5 mol%) was added in the first step.

generated in situ. Turning to steric differentiation, which is known to significantly influence aryl transfer in diaryliodonium chemistry,[14] we treated pyrazole with (*o*-tolyl)aryliodonium salts and found that regardless of the electronics of the second aryl group, the *ortho*-tolyl aromatic transferred first with complete selectivity (**5p** and **5q**). In these two examples, despite the second aromatic group being more electron rich in one case, and more electron deficient in the other, we still obtain products where the more sterically hindered group transfers first. Pleasingly, both compounds were obtained in excellent yield. To further explore this steric control, we showed that 1,2,3-triazole reacted smoothly under the reaction conditions with an unsymmetrical iodonium to give compound **5r**. Finally, given the importance of trifluoromethyl groups in medicinal chemistry and agrochemistry we synthesized compound **5s** where the aromatic group bearing an *ortho* CF_3 group selectively transfers in the first step.

Given the excellent selectivity obtained with sterically and electronically differentiated iodonium salts, we were interested to see if the domino process could extend to alternative motifs such as alkenes, which could in principle be introduced using (*E*)-styryl(phenyl)iodoniums (**6**, Scheme 4).[16,17] Gratifyingly, upon treating pyrazole with the triflate salt of **6** under our previously optimized conditions we observed complete selectivity for transfer of the styryl component in the first step, enabling a rare C–H arylation of an enamine derivative in situ to give product **5t** in 43% yield. Preferential transfer of the styryl substituent in step 1 was observed for both electron-poor styryl (**5u**) and aryl (**5w**) residues, providing a one-pot route to geometrically defined, trisubstituted alkenes.[18]



Scheme 4. Use of aryl-styryl iodonium salts for preparation of trisubstituted alkenes. [a] Yield calculated by ^1H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard.

In conclusion, we have demonstrated the feasibility of one-pot domino reactions which form new C–C bonds between aryl and alkenyl groups from iodonium reagents and *N*-heteroarenes. The transformation captures the aryl iodide residue from the iodonium, frequently thrown away as waste in other applications, to effect *ortho* C–H arylation for the synthesis of nitrogenated biaryls in a single step. The reaction is responsive to steric control, enabling predictable and selective transfer of aryl residues through tuning the steric demand of *N*-heteroarene and/or iodonium components.

Acknowledgements

We thank the EPSRC (Doctoral Prize Fellowship to C.J.T.), and Marie Curie actions (intra-European fellowship to S.M.A.S.) for funding.

Conflict of interest

The authors declare no conflict of interest.

Keywords: arylation · C–H activation · iodonium compounds · N-heterocycles

---

[1] E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052–9070; *Angew. Chem.* **2009**, *121*, 9214–9234.
[2] S. G. Modha, M. F. Greaney, *J. Am. Chem. Soc.* **2015**, *137*, 1416–1419.
[3] a) J. Buendia, B. Darses, P. Dauban, *Angew. Chem. Int. Ed.* **2015**, *54*, 5697–5701; *Angew. Chem.* **2015**, *127*, 5789–5793; b) J. Buendia, G. Grelier, B. Darses, A. G. Jarvis, F. Taran, P. Dauban, *Angew. Chem. Int. Ed.* **2016**, *55*, 7530–7533; *Angew. Chem.* **2016**, *128*, 7656–7659.
[4] N. Miralles, R. M. Romero, E. Fernández, K. Muñiz, *Chem. Commun.* **2015**, *51*, 14068–14071.
[5] M. Wang, J. Wei, Q. Fana, X. Jiang, *Chem. Commun.* **2017**, *53*, 2918–2921.
[6] For the atom-economical capture of 2-iodobenzoic acid residues from ethynylbenziodoxole reagents, see: a) B. Lu, J. Wu, N. Yoshikai, *J. Am. Chem. Soc.* **2014**, *136*, 11598–11601; b) D. P. Hari, J. Waser, *J. Am. Chem. Soc.* **2016**, *138*, 2190–2193.
[7] For examples of cyclic iodonium reagents employed in sequential bond formations, see: a) S. Riedmüller, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2013**, *9*, 1202–1209; b) D. Zhu, Q. Liu, B. Luo, M. Chen, R. Pi, P. Huang, S. Wen, *Adv. Synth. Catal.* **2013**, *355*, 2172–2178; c) B. Wu, N. Yoshikai, *Angew. Chem. Int. Ed.* **2015**, *54*, 8736–8739; *Angew. Chem.* **2015**, *127*, 8860–8863; d) B. Luo, Q. Cui, H. Luo, Y. Hu, P. Huang, S. Wen, *Adv. Synth. Catal.* **2016**, *358*, 2733–2738; e) M. Shimizu, M. Ogawa, T. Tamagawa, R. Shigitani, M. Nakatani, Y. Nakano, *Eur. J. Org. Chem.* **2016**, 2785–2788; f) M. Wang, Q. Fan, X. Jiang, *Org. Lett.* **2016**, *18*, 5756–5759.
[8] a) Z. Gonda, Z. Novak, *Chem. Eur. J.* **2015**, *21*, 16801–16806; b) T. Bihari, B. Babinszki, Z. Gonda, S. Kovacs, Z. Novak, A. Stirling, *J. Org. Chem.* **2016**, *81*, 5417–5422; c) S.-K. Kang, S.-H. Lee, D. Lee, *Synlett* **2000**, 1022–1024.
[9] A. Ansari, A. Ali, M. Asif, Shamsuzzaman, *New J. Chem.* **2017**, *41*, 16–41.
[10] a) L. Ackermann, *Org. Lett.* **2005**, *7*, 3123–3125; b) L. Ackermann, A. Althammer, R. Born, *Angew. Chem. Int. Ed.* **2006**, *45*, 2619–2622; *Angew. Chem.* **2006**, *118*, 2681–2685; c) Y. Matsuura, M. Tamura, T. Kochi, M. Sato, N. Chatani, F. Kakiuchi, *J. Am. Chem. Soc.* **2007**, *129*, 9858–9859; d) S. Oi, R. Funayama, T. Hattori, Y. Inoue, *Tetrahedron* **2008**, *64*, 6051–6059; e) P. B. Arockiam, C. Fischmeister, C. Bruneau, P. H. Dixneuf, *Angew. Chem. Int. Ed.* **2010**, *49*, 6629–6632; *Angew. Chem.* **2010**, *122*, 6779–6782; f) E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf, A. Jutand, *J. Am. Chem. Soc.* **2011**, *133*, 10161–10170.

[11] Johnson Matthey month average cost for all time zones in Jan 2017: Ru: $40/troy oz., Pd: $752/troy oz., Rh: $834/troy oz.

[12] a) C. J. Teskey, A. Y. W. Lui, M. F. Greaney, *Angew. Chem. Int. Ed.* **2015**, *54*, 11677–11680; *Angew. Chem.* **2015**, *127*, 11843–11846; b) V. P. Mehta, J.-A. Garcia-Lopez, M. F. Greaney, *Angew. Chem. Int. Ed.* **2014**, *53*, 1529–1533; *Angew. Chem.* **2014**, *126*, 1555–1559.

[13] For syntheses of iodonium salts used in this study, see: a) M. Bielawski, M. Zhu, B. Olofsson, *Adv. Synth. Catal.* **2007**, *349*, 2610–2618; b) N. Jalalian, E. E. Ishikawa, E. Eloisa, L. F. Silva, B. Olofsson, *Org. Lett.* **2011**, *13*, 1552–1555; c) M. Bielawski, D. Aili, B. Olofsson, *J. Org. Chem.* **2008**, *73*, 4602–4607; d) Y. Gu, D. Chang, X. Leng, Y. Gu, Q. Shen, *Organometallics* **2015**, *34*, 3065–3071; e) B. S. L. Collins, M. G. Suero, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2013**, *52*, 5799–5802; *Angew. Chem.* **2013**, *125*, 5911–5914; f) M. Zhu, N. Jalalian, B. Olofsson, *Synlett* **2008**, 592–596; g) M. Ochiai, M. Toyonari, T. Nagaoka, D.-W. Chen, M. Kida, *Tetrahedron Lett.* **1997**, *38*, 6709–6712.

[14] a) K. M. Lancer, G. H. Wiegand, *J. Org. Chem.* **1976**, *41*, 3360–3364; b) V. V. Grushin, I. I. Demkina, T. Tolstaya, *J. Chem. Soc. Perkin Trans. 2* **1992**, 505–511.

[15] CCDC 1528067 (**5n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[16] N. Sh. Pirkuliev, V. K. Brel, N. S. Zefirov, *Russ. Chem. Rev.* **2000**, *69*, 105–120.

[17] For an example of *N*-alkenylation with iodonium reagents, see: J.-M. Chen, X. Huang, *Synlett* **2004**, 552–554.

[18] For use of Ru^{IV} precatalysts for direct arylation of alkenes, see: L. Ackermann, R. Born, P. Álvarez-Bercedo, *Angew. Chem. Int. Ed.* **2007**, *46*, 6364–6367; *Angew. Chem.* **2007**, *119*, 6482–6485.

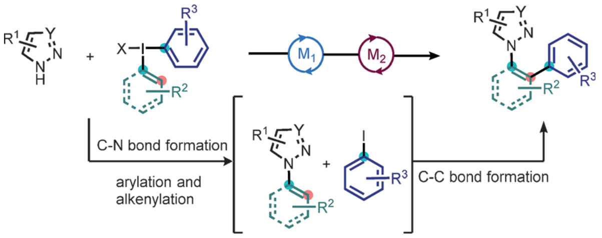
Manuscript received: February 11, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Domino Arylation

C. J. Teskey, S. M. A. Sohel, D. L. Bunting,
S. G. Modha,
M. F. Greaney* ________ ▮▮▮▮–▮▮▮▮

Domino *N*-/*C*-Arylation via In Situ Generation of a Directing Group: Atom-Efficient Arylation Using Diaryliodonium Salts



First the one, then the other: Diaryl- and alkenyl(aryl)iodonium salts react with N-heteroarenes in domino fashion. *N*-functionalization is followed by *ortho*-arylation under ruthenium catalysis, capturing the aryl iodide by-product of the first step.