

ChemComm

Accepted Manuscript



This article can be cited before page numbers have been issued, to do this please use: J. Leitch, C. Heron, J. McKnight, G. Kociok-Kohn, Y. Bhonoah and C. G. Frost, *Chem. Commun.*, 2017, DOI: 10.1039/C7CC07606A.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [author guidelines](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the ethical guidelines, outlined in our [author and reviewer resource centre](#), still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

COMMUNICATION

Ruthenium Catalyzed Remote C4-Selective C-H Functionalisation of Carbazoles *via* σ -Activation

Jamie A. Leitch,^a Callum J. Heron,^b Janette McKnight,^a Gabriele Kociok-Köhn,^c Yunas Bhonoah,^d and Christopher G. Frost^a

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

We report the C4-selective C-H alkylation of carbazole derivatives furnished with a pyrimidine directing group at N9. This was realized using ruthenium catalyzed σ -activation methodology, whereby C-H activation at C1 enables the interaction of this ruthenacycle, at the *para* position to the metal center, with tertiary alkyl radicals.

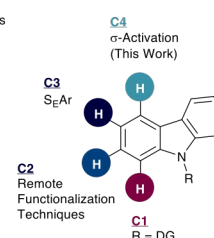
Transition metal catalyzed C-H functionalisation has emerged as a powerful asset to the synthetic toolkit in the synthesis and derivation of organic structures, especially biologically relevant motifs.¹ The inherent challenge in C-H functionalisation of arenes is the differentiation of electronically similar C-H bonds. To overcome this, a directing group (DG) strategy is often employed to enable site selective cyclometalation *via* chelation assistance.² Subsequent coordination of a coupling partner and reductive elimination pathways lead to *ortho*-C-H-functionalised products. To move away from *ortho*-selectivity, elegant remote C-H functionalisation techniques have come to the forefront of modern catalytic progress.³ This has enabled sophisticated routes to *meta*⁴ and *para*⁵-substituted arenes.

Carbazoles are a fused tricyclic heteroaromatic with important applications in drug discovery,⁶ sensing,⁷ and organic functional materials such as OLEDs.⁸ For these reasons, studies into the modification of this heterocycle have allowed selective C-H functionalisation of carbazoles and their derivatives. A majority of these techniques have been applied through furnishing the NH with a directing group. This enables directed C-H functionalisation at the C1 position (Scheme 1a). This research

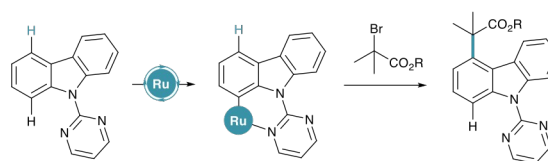
has permitted the formation of a number of C-C and C-X bonds utilizing a multitude of catalytic systems.⁹ Limited remote functionalisation techniques studied on the related indole heteroaromatic have also granted access to C2 substituted carbazoles, with notable contributions from Baran.¹⁰ C3-substitution has been widely studied due to the nucleophilic nature of this carbon enabling S_EAr chemistry.¹¹ To our knowledge, selective C-H functionalisation of the C4 position has yet to be reported.

Ruthenium-catalysed σ -activation has become a vital technique in the *meta*-functionalisation of arenes,¹² enabling the sulfonation,^{12,13} alkylation,¹⁴ bromination,¹⁵ nitration,¹⁶ and benzylation¹⁷ of aromatic systems. In this methodology, formation of a strong and stable ruthenacycle, allows *para*-functionalisation to the metal center, *via* the electronic influence of the Ru-C σ -bond, instead of traditional oxidative addition/reductive elimination pathways. This gives net *meta*-C-H functionalisation to the directing group.

(a) C-H Functionalization of Carbazoles



(b) Remote C4-Selective C-H Alkylation of Carbazoles



Scheme 1: Selective C-H Functionalisation of Carbazoles and the Context of this Work

^a Department of Chemistry, University of Bath, Claverton Down, Bath, Somerset, BA2 7AY, United Kingdom

^b Centre for Sustainable Chemical Technologies, University of Bath, Bath, Somerset, BA2 7AY, United Kingdom

^c Chemical Characterisation and Analysis Facility, University of Bath, Somerset, BA2 7AY, United Kingdom

^d Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, United Kingdom

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



COMMUNICATION

Journal Name

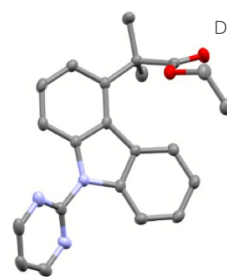
The ruthenium center has also been shown to act as a dual role catalyst, facilitating the redox formation of a radical which interacts with the *para* position of the arene. After our success in applying this technique to indole structures to enable selective C6 functionalisation,¹⁸ we sought to use this methodology on carbazole structures to give complementary C4 C-H functionalisation (Scheme 1b).

From ours and others previous contributions to *meta*-alkylation methodology,^{14,18} we began our investigations by applying previously reported conditions for catalytic σ -activation to *N*-pyrimidinylcarbazole (**1a**), using ethyl α -bromoisobutyrate as a coupling partner (**2a**) (Table 1, entries 1-4). To our delight we found that when using potassium acetate as base (entries 1-2), efficient C-H functionalisation was shown to take place. As with our previous report, the addition of acetic acid into the reaction mixture was also shown to be beneficial (entry 2).¹⁸ On screening different bases, we found that the sterically demanding potassium 2,4,6-trimethylbenzoate (MesCO₂K) was the most amenable to these reaction conditions (entries 6-9). MesCO₂H and AdCO₂H were shown to be reactive acids in this methodology however neither superior to AcOH (entries 10-11). We then found that reducing the quantity of acid to 1 equivalent led to the highest formation of product (entries 13-15). Reaction efficiency was also shown to reduce in an air atmosphere (entry 16) and was completely nullified in the absence of ruthenium catalyst (entry 17). The use of the pre-synthesized [Ru(O₂CMes)(*p*-cymene)] monomer was shown to lead to the highest formation of product thus far (entry 18).

Table 1: Ruthenium-Catalyzed C4 Selective C- Alkylation of Carbazole Derivatives^a

Entry	Base	Acid	Acid (eq)	3a % ^b
1	KOAc	-	-	53
2	KOAc	AcOH	2	68 (48) ^c
3	K ₂ CO ₃	-	-	7
4	(+ MesCO ₂ H 30 mol%)	-	-	7
5	(+ Piv-Val-OH 30 mol%)	-	-	-
6	K ₂ CO ₃	-	-	-
7	K ₂ Citrate	AcOH	2	45
8	K ₂ Tartrate	AcOH	2	56
9	AdCO ₂ Na	AcOH	2	58
10	MesCO ₂ K	AcOH	2	80 (61) ^c
11	MesCO ₂ K	MesCO ₂ H	2	64
12	MesCO ₂ K	AdCO ₂ H	2	66
13	MesCO ₂ K	TFA	2	15
14	MesCO ₂ K	AcOH	0.5	80
15	MesCO ₂ K	AcOH	1	84 (68)
16 ^d	MesCO ₂ K	AcOH	4	68
17 ^e	MesCO ₂ K	AcOH	1	61
18 ^f	MesCO ₂ K	AcOH	1	-
18 ^g	MesCO ₂ K	AcOH	1	90 (76)

^a General Conditions: 9-(pyrimidin-2-yl)-9H-carbazole (**1a**, 0.25 mmol), ethyl α -bromoisobutyrate (**2a**, 0.75 mmol), [RuCl₂(*p*-cymene)]₂ (5 mol%), 0.0125 mmol, Base (2 eq), Acid (x eq), 1,4-dioxane, 120 °C, 16 h, under argon atmosphere. ^b Direct conversion between starting material and product, as dictated by crude ¹H NMR. ^c Isolated yields given in brackets. ^d Reaction carried out at 100 °C. ^e Reaction carried out without [RuCl₂(*p*-cymene)]₂. ^f [Ru(O₂CMes)(*p*-cymene)] (10 mol%) used as catalyst.

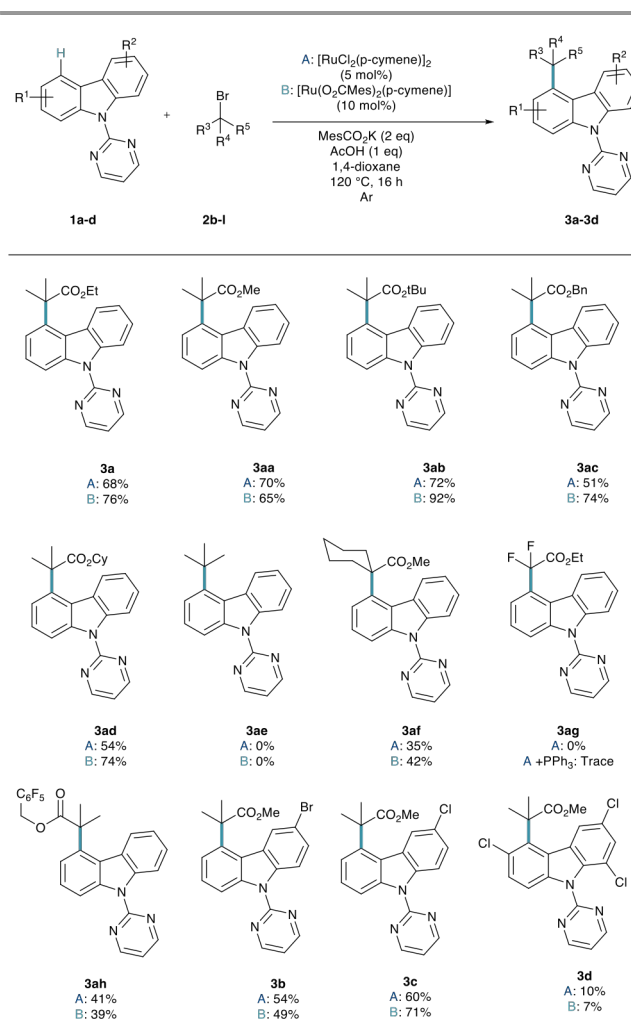


View Article Online
DOI: 10.1039/C7CC07606A

Figure 1: SCXRD Structure of **3a** Confirming Regioselectivity of Functionalisation. ^h CCDC 1574475.

In order to confirm regioselectivity, **3a** was characterized *via* single crystal X-ray diffraction (Figure 1).¹⁹

With optimal conditions in hand to enable efficient and selective C4 alkylation, we were intrigued to employ a number of coupling partners to the reaction conditions to explore their respective reactivity in this chemistry (Scheme 2).



Scheme 2: Ruthenium Catalysed C4-Selective C-H Alkylation of Carbazole Derivatives



The reaction methodology was explored using both the commercially available dimer (Conditions **A**) and the pre-synthesized monomer (Conditions **B**). A variety of ester substituents were shown to be very well tolerated in the remote functionalisation methodology (**3aa-3ad**) with impressive yields up to 92% for the *tert*-butyl ester variant. It is noteworthy to find that *tert*-butyl bromide was not amenable to this methodology (**3ae**) despite its use in several previous reports in σ -activation methodology.¹³ When the difluoro ester was reacted under the optimized conditions (**3ag**), unfortunately no product was observed, even with the addition of triarylphosphine co-catalysts, which has been shown to be vital in *meta*-difluoroalkylation strategies.^{14e-f} Perfluorobenzyl ester derivative (**3ah**) was also tolerated in the chemistry. It has been demonstrated that generally the preformed monomer outperforms the dimer however in not all cases. Following this, the variation of the aryl functionality was then studied. Mono-substituted bromo (**3b**) and chloro (**3c**) carbazole derivatives were shown to be effective substrates for this chemistry with exclusive selectivity for the non-substituted ring.²⁰ Trichloro-substituted structure (**3d**) was shown to proceed in reduced yields but exclusively at C4, truly highlighting the remote nature of the functionalisation, as this enables the C-H derivation between two substitution patterns. For further experiments and further unsuccessful coupling partners, see supporting information.

At this point, we were intrigued to see how the influence of the *N*-substitution pattern affected the efficiency of C4-functionalisation (Scheme 3a). To this end, we investigated non-coordinating (**1e**) and weakly metal-coordinating (**1f**) substituents. Unfortunately, neither of these structures were shown to give conversion to any regioselectivity of product. Interestingly, when we submitted unsubstituted carbazole (**1g**)

to the reaction conditions we observed selective C3-alkylation in low yields (Scheme 3b).

DOI: 10.1039/C7CC07606A

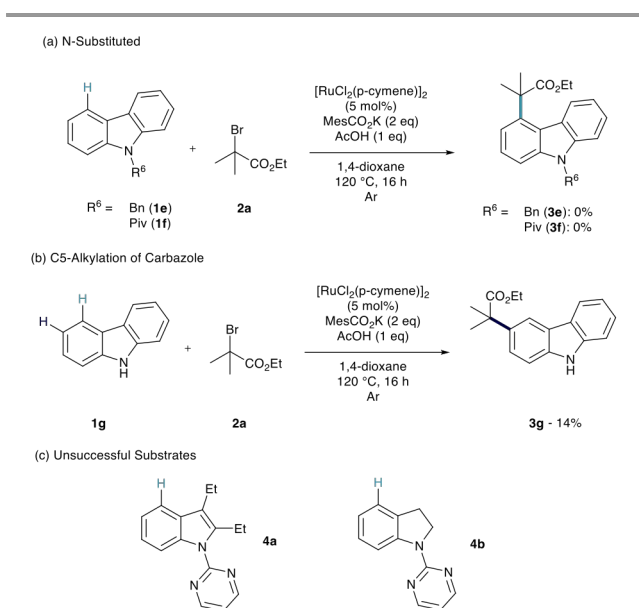
This manifests that without the directing group the C3 position is the most activated to interact with a radical. This shows that this σ -activation methodology not only produces a highly selective and efficient C-H functionalisation of carbazole, we also observe a complete switch in regioselectivity to the innate reactivity. It is also noteworthy that cf. **1f-g** (Scheme 3a), the presence of the NH is critical to any reactivity. 2,3-diethylindole and indoline derivatives were synthesised and submitted to the reaction conditions (Scheme 3c). To our surprise neither substrate showed any reactivity towards the remote functionalisation methodology (**5a-b**). This could be due to the indole substituent at C2 interfering with stable and planar cyclometalation or the ethyl at C3 blocking *tert*-alkylation on steric grounds (**4a**). In the case of the indoline, the cyclometalate formed on the benzenoid section of the structure may not be stable enough to permit remote σ -activation (**4b**).

We were intrigued to run radical trapping experiments to inform whether this reaction followed previous trends in σ -activation. We employed TEMPO trapping studies, where catalytic quantities (30 mol%) of the radical trapping agent gave a reduced conversion of 66% to product, and the use of stoichiometric quantities of TEMPO (1 eq) led to a sharp drop to 15% conversion. These findings suggest that a radical single electron transfer mechanism may be at play. It was then of interest to run H/D scrambling experiments using isotopically labelled acetic acid. This showed that there is deuterium incorporation in the C1 and C8 positions in both the starting material (10% each, see supporting information) and product (19% each). These observations suggest a reversible C-H activation at the *ortho*-positions. It must be noted that lack of scrambling at C5 in the product and at C4/C5 in the starting material rules out a readily reversible direct C-H metalation at these positions and lends itself to a C1 σ -activation protocol.

From these mechanistic investigations and from previous insights into this methodology, a plausible mechanism for the remote C4-alkylation of carbazole derivatives is proposed (see supporting information). It is suggested that the ruthenium monomer can facilitate C-H activation at the C1 position *ortho* to the pyrimidine directing group. A single electron transfer process with an inner sphere or outer sphere ruthenium complex can then form the *tertiary* α -halocarbonyl radical. This radical then interacts with the sterically encumbered ruthenacycle at the *para* position to the metal center *via* a σ -activation process (likely due to a shift in electron density to the C4 position). Redox electron shuttling and proton abstraction enables rearomatization of the arene and protodemetalation gives the C4-alkylate carbazole.

Conclusions

We have presented the remote C4-selective C-H alkylation of carbazole derivatives. As far as we are aware, there are no known selective methods to directly functionalize the carbazole at this position. We have demonstrated that furnishing the



Scheme 3: Remote Ruthenium-Catalysed Functionalisation of Carbazoles



carbazole heteroaromatic with a pyrimidine directing group enabled a σ -activation process whereby a stable and planar ruthenacycle at C1 enabled interaction of the *para* position (C4) with a *tertiary* alkyl radical. We also demonstrate the unique reactivity of α -halocarbonyl coupling partners cf. aliphatic alkyl halides.

Conflicts of interest

The authors declare no competing financial interest

Notes and references

- For reading on transition metal catalyzed C-H activation see: (a) L. Ackermann, *Chem. Rev.*, 2011, **113**, 1315. (b) P. B. Arockiam, C. Bruneau, P. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879. (c) X. Chen, K. M. Engle, D-H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.*, 2009, **48**, 5094. (d) K. M. Engle, T. S. Mei, M. Wasa, J. Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788. (e) H. M. L. Davies, D. Morton, *J. Org. Chem.*, 2016, **81**, 343. (f) T. Yoshino, S. Matsunaga, *Adv. Synth. Catal.*, 2017, **359**, 1245. For reading on the modification of biologically active molecules see: (g) J. A. Leitch, P. B. Wilson, C. L. McMullin, M. F. Mahon, Y. Bhonoah, I. H. Williams, C. G. Frost, *ACS Catal.*, 2016, **6**, 5520. (h) J. A. Leitch, H. P. Cook, Y. Bhonoah, C. G. Frost, *J. Org. Chem.*, 2016, **81**, 10081. (i) W. Ma, H. Dong, D. Wang, L. Ackermann, *Adv. Synth. Catal.*, 2017, **359**, 966.
- (a) K. M. Engle, T. S. Mei, M. Wasa, J. Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788. (b) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107.
- J. Li, S. De Sarkar, L. Ackermann, *Top Organomet. Chem.*, 2015, **55**, 217.
- For reviews see: (a) J. Yang, *Org. Biomol. Chem.*, 2015, **13**, 1930. (b) A. Dey, S. Agasti, D. Maiti, *Org. Biomol. Chem.*, 2016, **14**, 5440. For seminal publications see: (c) R. J. Phipps, M. J. Gaunt, *Science*, 2009, **323**, 1593. (d) D. Leow, G. Li, T. S. Mei, J. Q. Yu, *Nature*, 2012, **486**, 518. (e) X. C. Wang, W. Gong, L. Z. Fang, R. Y. Zhu, S. Li, K. M. Engle, J. Q. Yu, *Nature*, 2015, **519**, 334. (f) Y. Kuninobu, H. Ida, M. Nishi, M. Kanai, *Nat. Chem.*, 2015, **7**, 712. (g) J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, M. R. Smith, *Science*, 2002, **295**, 305.
- For review see: A. Dey, S. Maity, D. Maiti, *Chem. Commun.*, 2016, **52**, 12398.
- (a) F. F. Zhang, L. L. Gan, C. H. Zhou, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1881. (b) C. C. Chang, L. C. Kuo, J. J. Lin, Y. C. Lu, C. T. Chen, H. T. Back, P. J. Lou, T. C. Chang, *Chem. Biodiversity*, 2004, **1**, 1377. (c) M. H. Block, S. Boyer, W. Brailsford, D. R. Brittain, D. Carroll, S. Chapman, D. S. Clarke, C. S. Donald, K. M. Foote, L. Godfrey, A. Ladner, P. R. Marsham, D. J. Masters, C. D. Mee, M. R. O'Donovan, J. E. Pease, A. G. Pickup, J. W. Rayner, A. Robers, P. Schofield, A. Suleman, A. V. Turnbull, *J. Med. Chem.*, 2002, **45**, 3509.
- (a) C. C. Chang, I. C. Kuo, I. F. Ling, C. T. Chen, H. C. Chen, P. J. Lou, J. J. Lin, T. C. Chang, *Anal. Chem.*, 2004, **76**, 4490. (b) C. C. Chang, J. Y. Wu, C. W. Chien, W. S. Wu, H. Liu, C. C. Kang, L. J. Yu, T. C. Chang, *Anal. Chem.*, 2003, **75**, 6177.
- (a) K. Brunner, A. van Dijken, H. Börner, J. J. Am M. Bastiaansen, N. M. M. Kiggen, B. M. W. Langeweld, *J. Am. Chem. Soc.*, 2004, **126**, 6035. (b) J. Ding, J. Gao, Y. Cheng, Z. Xie, L. Wang, D. Ma, X. Jing, F. Wang, *Adv. Funct. Mater.*, 2006, **16**, 575.
- For review see: (a) J. A. Leitch, Y. Bhonoah, C. G. Frost, *ACS Catal.*, 2017, **7**, 5618. For selected examples see: (b) V. P. Reddy, R. Qiu, T. Iwasaki, N. Kambe, *Org. Lett.*, 2013, **15**, 1290. (c) R. Qiu, V. P. Reddy, T. Iwasaki, N. J. Kambe, *Org. Chem.*, 2015, **80**, 367. (d) L. Zhu, X. Cao, T. Iwasaki, V. P. Reddy, X. Xu, S. F. Yin, N. Kambe, *RSC Adv.*, 2015, **5**, 39358. (e) W. Ai, X. Yang, Y. Wu, X. Wang, Y. Li, Y. Yang, B. Zhou, *Chem. Eur. J.*, 2014, **20**, 17653. (f) X. Hong, H. Wang, G. Qian, Q. Tan, B. Xu, *J. Org. Chem.*, 2014, **79**, 3228. (g) S. Sharma, Y. Shin, N. K. Mishra, J. Park, S. Han, T. Jeong, Y. Oh, Y. Lee, M. Choi, I. S. Kim, *Tetrahedron*, 2015, **71**, 245.
- Y. Feng, D. Holte, J. Zoller, S. Umehiya, L. R. Simke, P. S. Baran, *J. Am. Chem. Soc.*, 2015, **137**, 10160.
- M. Majchrzak, M. Grzelak, B. Marciniec, *Org. Biomol. Chem.*, 2016, **14**, 9406.
- J. A. Leitch and C. G. Frost, *Chem. Soc. Rev.*, 2017, DOI: 10.1039/C7CS00496F
- (a) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Kohn, M. K. Whittlesey, C. G. Frost, *J. Am. Chem. Soc.*, 2011, **133**, 19298. (b) P. Marcé, A. J. Paterson, M. F. Mahon, C. G. Frost, *Catal. Sci. Technol.*, 2016, **6**, 7068. (b) G. Li, X. Lv, K. Guo, Y. Wang, S. Yang, L. Yu, Y. Yu, Wang, *J. Org. Chem. Front.*, 2017, **4**, 1145.
- (a) N. Hofmann, L. Ackermann, *J. Am. Chem. Soc.*, 2013, **135**, 5877. (b) A. J. Paterson, S. St John Campbell, M. F. Mahon, N. J. Press, C. G. Frost, *Chem. Commun.*, 2015, **51**, 12807. (c) J. Li, S. Warratz, D. Zell, S. De Sarkar, E. E. Ishikawa, L. Ackermann, *J. Am. Chem. Soc.*, 2015, **137**, 13894. (d) G. Li, X. Ma, C. Jia, Q. Han, Y. Wang, J. Wang, L. Yu, S. Yang, *Chem. Commun.*, 2017, **53**, 1261. (e) Z. Ruan, S. K. Zhang, C. Zhu, P. N. Ruth, D. Stalke, L. Ackermann, *Angew. Chem. Int. Ed.*, 2017, **129**, 2077. (f) Z. Y. Li, L. Li, Q. L. Li, K. Jing, H. Xu, G. W. Wang, *Chem. Eur. J.*, 2017, **23**, 3285. (g) J. Li, K. Korvorapun, S. De Sarkar, T. Rogge, D. J. Burns, S. Warratz, L. Ackermann, *Nat. Commun.*, 2017, **8**, 15430. (h) A. J. Paterson, C. J. Heron, C. L. McMullin, M. F. Mahon, N. J. Press, C. G. Frost, *Org. Biomol. Chem.*, 2017, **15**, 5993.
- (a) C. J. Teskey, Y. W. Lui, M. F. Greaney, *Angew. Chem. Int. Ed.*, 2015, **54**, 11677. (b) Q. Yu, L. Hu, Y. Wang, S. Zheng, J. Huang, *Angew. Chem. Int. Ed.*, 2015, **54**, 15284. (c) S. Warratz, D. J. Burns, C. Zhu, K. Korvorapun, T. Rogge, J. Scholz, C. Jooss, D. Gelman, L. Ackermann, *Angew. Chem. Int. Ed.*, 2017, **56**, 1557.
- (a) Z. Fan, J. Ni, A. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 8470. (b) Z. Fan, J. Li, H. Lu, D. Y. Wang, C. Wang, M. Uchiyama, A. Zhang, *Org. Lett.*, 2017, **19**, 3199.
- (a) G. Li, D. Li, J. Zhang, D. Q. Shi, Y. Zhao, *ACS Catal.*, 2017, **7**, 4138. (b) B. Li, S. L. Fang, D. Y. Huang, B. F. Shi, *Org. Lett.*, 2017, **19**, 3950.
- J. A. Leitch, C. L. McMullin, M. F. Mahon, Y. Bhonoah, C. G. Frost, *ACS Catal.*, 2017, **7**, 2616.
- Crystallographic data.** Intensity data were collected at 150 K on a RIGAKU Xcalibur EosS2 diffractometer, using graphite monochromated MoK α radiation ($\lambda = 0.71073$ Å). (**3a**) C₂₂H₂₁N₃O₂, M = 359.42, P-1, $a = 8.3732(5)$ Å, $b = 9.5046(5)$ Å, $c = 11.9276(4)$ Å, $\alpha = 69.880(4)^\circ$, $\beta = 88.812(4)^\circ$, $\gamma = 84.255(4)^\circ$, $V = 886.74(8)$ Å³, $Z = 2$, $\mu = 0.088$ mm⁻¹, unique reflections = 4064 [R(int) = 0.0571], $R_1 = 0.061$, $wR_2 = 0.1490$ [$I > 2\sigma(I)$], $R_1 = 0.0735$, $wR_2 = 0.1576$ (all data). **CCDC 1574475**.
- Unfortunately, 3,6-dihalocarbazole derivatives were not amenable to this methodology due to perceived lack of solubility in the reaction medium (see supporting information).

