

Versatile ruthenium(II)-catalyzed C–H cyanations of benzamides†

Cite this: *Chem. Commun.*, 2014, 50, 1878

Received 15th December 2013,
Accepted 2nd January 2014

DOI: 10.1039/c3cc49502g

www.rsc.org/chemcomm

Direct cyanations of arenes and heteroarenes bearing only weakly coordinating amides were accomplished using a robust ruthenium(II) catalyst. The user-friendly C(sp²)–H activation occurred with the assistance of carboxylate with high site-selectivity, excellent functional group tolerance and ample scope.

Aromatic nitriles constitute key structural motifs of important pharmaceuticals, dyes, agrochemicals and natural products.^{1–3} The cyano group serves as a versatile functional group that can easily be transformed into amines, ketones or aldehydes, among others.⁴ The syntheses of aryl nitriles continue to rely on classical approaches, such as the Sandmeyer⁵ or the Rosenmund–von Braun reaction,^{6,7} which have severe limitations, including the use of stoichiometric or even super-stoichiometric amounts of metal cyanides as well as harsh reaction conditions. An alternative approach is represented by transition metal-catalyzed cyanations of aryl halides or boronic acids under milder reaction conditions.⁸ These catalyzed coupling reactions thereby also display a considerably improved functional group tolerance. However, this strategy exploits prefunctionalized substrates, the preparation of which requires numerous functional group interconversions and generates undesired waste.

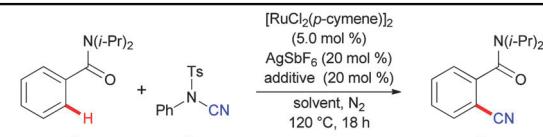
The catalytic activation of otherwise inert C(sp²)–H bonds as latent functional groups has in recent years emerged as an increasingly viable tool for improving the atom- and step-economy of organic synthesis.⁹ Thus, Yu developed direct cyanations of 2-arylpyridines.^{10,11} The research groups of Jiao¹² and Chang¹³ reported on oxidative cyanations of electron-rich substrates with nonmetallic cyano-group sources in the presence of stoichiometric sacrificial oxidants,^{14,15} while Hartwig disclosed a two-step iridium-catalyzed borylation/copper-mediated cyanation protocol.¹⁶ Very recently, rhodium-catalyzed C–H cyanations of arenes were accomplished, albeit exploiting rather strongly coordinating directing groups, such

as oxazolines, oximes, pyrazoles or pyridines.^{17–19} Herein, we wish to disclose an alternative strategy, which involves the use of relatively inexpensive²⁰ ruthenium(II) catalysts²¹ for the first time for C(sp²)–H cyanations. Importantly, the versatile ruthenium catalyst enabled expedient C–H cyanations with easily accessible *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS, 2) as the most user-friendly cyanation reagent for the functionalization of only weakly coordinating²² aromatic and heteroaromatic amides – key structural scaffolds in organic synthesis and medicinal chemistry.

We initiated our studies by probing the effect of different additives and solvents on the envisioned C–H bond cyanation using synthetically useful benzamide 1a (Table 1).

Thus, [RuCl₂(*p*-cymene)]₂ enabled the desired direct cyanation when using both AgSbF₆ and AgOAc as additives in DCE as the

Table 1 Optimization of C–H cyanation with benzamide 1a^a



Entry	Additive	Solvent	Yield (%)
1	AgOAc	DCE	77 (70)
2	Cu(OAc) ₂	DCE	30
3 ^b	AgOAc	DCE	80 (67)
4 ^c	AgOAc	DCE	<5
5 ^d	AgOAc	DCE	67 (54)
6	AgOAc	1,4-Dioxane	38
7	AgOAc	<i>o</i> -Xylene	21
8	AgOAc	Toluene	23
9	AgOAc	DMF	<2
10 ^e	AgOAc	DCE	<2
11	KOAc	DCE	<5
12	CsOAc	DCE	17
13	NaOAc	DCE	90 (80)
14 ^f	NaOAc	DCE	95 (84)

^a Reaction conditions: 1a (0.5 mmol), 2 (1.0 mmol), [RuCl₂(*p*-cymene)]₂ (5.0 mol%), AgSbF₆ (20 mol%), additive (20 mol%), solvent (2.0 mL), 120 °C, 18 h; GC-conversion, isolated yields are given in parentheses.

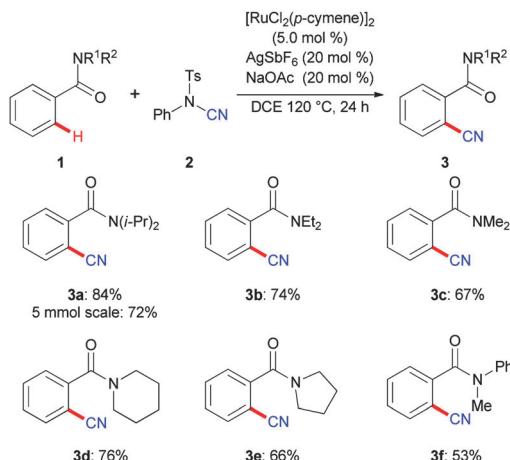
^b AgOAc (30 mol%). ^c Without AgSbF₆. ^d AgSbF₆ (30 mol%). ^e Without [RuCl₂(*p*-cymene)]₂. ^f 24 h.

Institut fuer Organische und Biomolekulare Chemie, Georg-August-Universitaet,
Tammannstrasse 2, 37077 Goettingen, Germany.

E-mail: Lutz.Ackermann@chemie.uni-goettingen.de

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra of products. See DOI: 10.1039/c3cc49502g

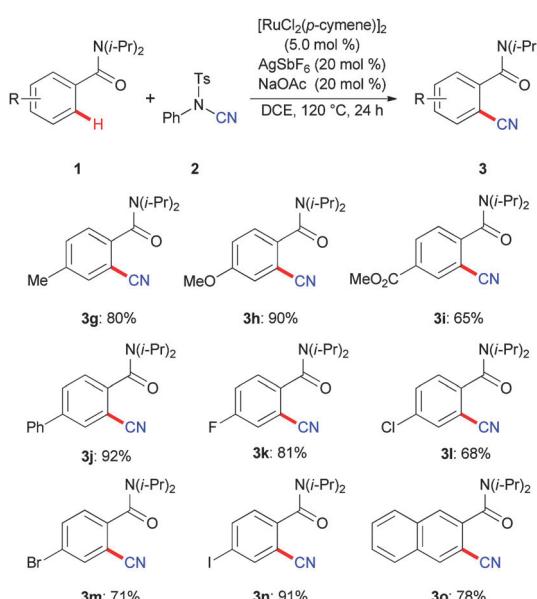
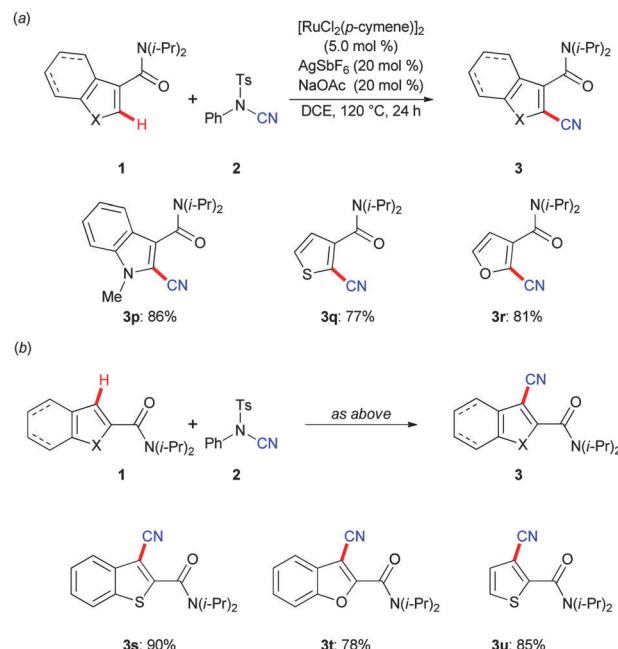


Scheme 1 Effect of *N*-substituents on C–H cyanations.

solvent (entries 1–5). DCE proved to be the solvent of choice (entries 1 and 6–9), while a test reaction illustrated that the C–H bond activation did not occur in the absence of the ruthenium catalyst (entry 10). Among a set of representative metal acetate additives,^{23,24} NaOAc furnished the highest yields of the product 3a (entries 11–14).

With the optimized catalytic system in hand, we explored the effect exerted by the *N*-substituent at the amide moiety (Scheme 1). A variety of tertiary amides **1a**–**1f** proved to be suitable substrates with optimal results being accomplished with the sterically hindered substrate **1a**.²⁵ A comparable catalytic efficacy was obtained when performing the C–H bond cyanation on a larger 5 mmol scale.

Subsequently, we tested the scope of the catalytic system for the cyanation of aromatic amides **1** (Scheme 2). The robust ruthenium(II) complex proved to be highly chemo-selective. Thus, the catalyst tolerated a set of valuable electrophilic functional groups, such as ester, fluoro, chloro, bromo and even iodo groups, which should be invaluable for the further diversification of the thus obtained products **3**.

Scheme 2 Scope of ruthenium-catalyzed C–H cyanation with amides **1**.Scheme 3 C–H cyanation with heteroaromatic amides **1**.

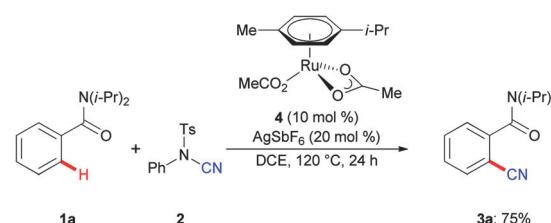
The user-friendly ruthenium(II) catalyst was not limited to the functionalization of arenes. Indeed, challenging heteroaromatic substrates **1p**–**1u** were efficiently directly functionalized both at positions C–2 (Scheme 3a) as well as C–3 (Scheme 3b). Thereby, cyanated thiophenes, furanes, benzothiophenes, benzofuranes and indoles were obtained in a chemo- and site-selective fashion.

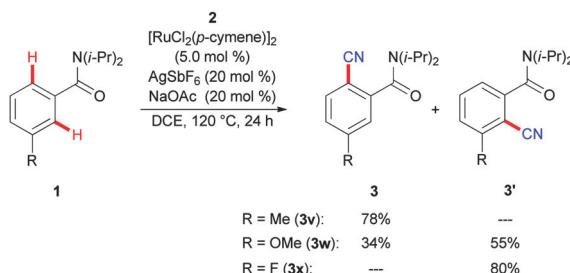
The well-defined ruthenium(II) biscarboxylate complex **4**²⁶ displayed a catalytic activity comparable to the one observed when using the *in situ* generated system, notably even in the absence of NaOAc (Scheme 4).

In consideration of the unique chemo-selectivity and outstanding efficacy of our ruthenium catalyst, we became interested in delineating its mode of action. To this end, intramolecular competition experiments with *meta*-substituted substrates **1v**–**1x** revealed a considerable secondary directing group effect²⁷ exerted by a methoxy substituent and, even more pronounced, by a fluoro group present in benzamides **1w** and **1x**, respectively (Scheme 5).

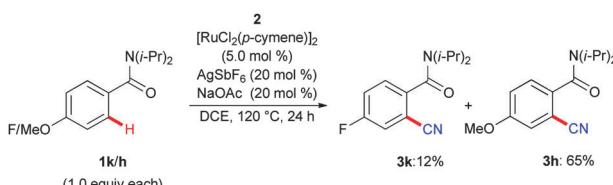
Intermolecular competition experiments between differently decorated amides indicated electron-rich arenes to be preferentially converted (Scheme 6), which can be rationalized in terms of an electrophilic-type activation mode of the cationic ruthenium species.

In support of this hypothesis, we observed a rather low kinetic isotope effect (KIE) of $k_H/k_D \approx 1.2$ (see the ESI†). Moreover, C–H bond activation conducted in the presence of D₂O as the cosolvent

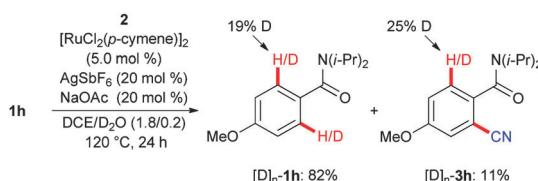
Scheme 4 Well-defined complex **4** as the catalyst.



Scheme 5 Intramolecular competition experiments with *meta*-substituted arenes **1**.



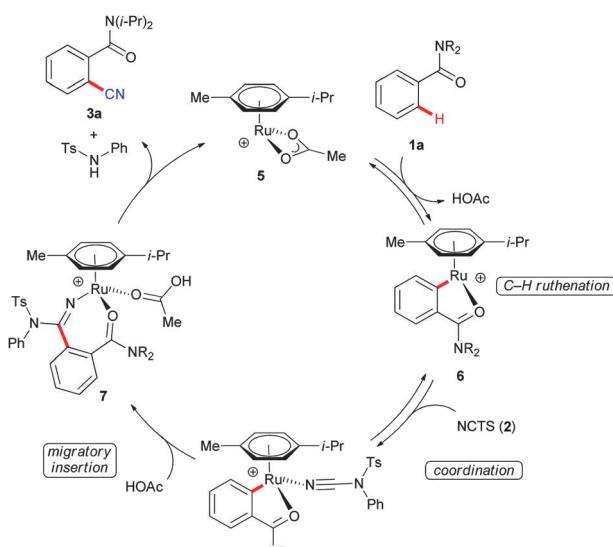
Scheme 6 Intermolecular competition experiments with arenes **1**.



Scheme 7 H/D exchange reaction.

revealed a reversible H/D-exchange reaction, as was observed for the reisolated starting material $[D]_n\text{-1h}$ as well as the product $[D]_n\text{-3h}$ (Scheme 7).

Based on these mechanistic studies we propose a plausible catalytic cycle to initiate a reversible C–H bond metatlation on amides **1**²⁸ to furnish cationic complex **6** (Scheme 8). Thereafter, coordination and



Scheme 8 Plausible catalytic cycle.

insertion of NCTS (2) give rise to key intermediate **7**. Subsequently, β -elimination provides the desired product **3**, while proto-demetalation regenerates the cationic ruthenium(II) carboxylate catalyst **5**.

In summary, we have reported on the use of relatively inexpensive ruthenium-catalyzed C(sp²)-H bond cyanation on arenes for the first time. The robust direct cyanation^{29,30} occurred site-selectively on synthetically useful aromatic and heteroaromatic amides with ample scope. Experimental mechanistic studies provided strong support for a reversible C–H metatlation mechanism by a cationic ruthenium(II) complex.

Support from the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement no. 307535 and the Chinese Scholarship Council (fellowship to W.L.) is gratefully acknowledged.

Notes and references

- P. Anbarasan, T. Schareina and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 5049.
- C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 3027.
- M. Sundermeier, A. Zapf and M. Beller, *Eur. J. Inorg. Chem.*, 2003, 3513.
- R. C. Larock, *Comprehensive Organic Transformations*, Wiley-VCH, Weinheim, 1999.
- T. Sandmeyer, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1633.
- K. W. Rosenmund and E. Struck, *Ber. Dtsch. Chem. Ges.*, 1919, **2**, 1749.
- J. von Braun and G. Manz, *Justus Liebigs Ann. Chem.*, 1931, **488**, 111.
- For selected examples, see: (a) T. D. Senecal, W. Shu and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 10035; (b) P. Anbarasan, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2011, **50**, 519; (c) P. Anbarasan, H. Neumann and M. Beller, *Chem.-Eur. J.*, 2011, **17**, 4217; (d) O. Grossman and D. Gelman, *Org. Lett.*, 2006, **8**, 1189; (e) J. Zanon, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 2890 and references cited therein.
- Recent reviews on C–H bond functionalization: (a) K. M. Engle and J.-Q. Yu, *J. Org. Chem.*, 2013, **78**, 8927; (b) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369; (c) X. Shang and Z.-Q. Liu, *Chem. Soc. Rev.*, 2013, **42**, 3253; (d) A. J. Hickman and M. S. Sanford, *Nature*, 2012, **484**, 177; (e) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (f) L. Ackermann, *Chem. Commun.*, 2010, **46**, 4866; (g) M. Livendahl and A. M. Echavarren, *Isr. J. Chem.*, 2010, **50**, 630; (h) R. G. Bergman, *Nature*, 2007, **446**, 391 and cited references.
- X. Chen, X. S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790.
- For pioneering functionalizations of tertiary amines, see: (a) S.-I. Murahashi, T. Nakae, H. Terai and N. Komiya, *J. Am. Chem. Soc.*, 2008, **130**, 11005; (b) S.-I. Murahashi, N. Komiya and H. Terai, *Angew. Chem., Int. Ed.*, 2005, **44**, 6931; (c) S.-I. Murahashi, N. Komiya, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312 and cited references.
- S. Ding and N. Jiao, *J. Am. Chem. Soc.*, 2011, **133**, 12374.
- J. Kim, J. Choi, K. Shin and S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 2528.
- S. Ding and N. Jiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 9226.
- J. Kim, H. J. Kim and S. Chang, *Angew. Chem., Int. Ed.*, 2012, **51**, 11948.
- C. W. Liskey, X. Liao and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 11389.
- T.-J. Gong, B. Xiao, W.-M. Cheng, W. Su, J. Xu, Z.-J. Liu, L. Liu and Y. Fu, *J. Am. Chem. Soc.*, 2013, **135**, 10630.
- M. Chaitanya, D. Yadagiri and P. Anbarasan, *Org. Lett.*, 2013, **15**, 4960.
- See also: (a) Y. Yang, Y. Zhang and J. Wang, *Org. Lett.*, 2011, **13**, 5608; (b) H.-Q. Do and O. Daugulis, *Org. Lett.*, 2010, **12**, 2517.
- The prices of platinum, rhodium, gold, iridium, palladium and ruthenium were 1482, 1015, 1363, 800, 701 and 80 US\$ per troy oz, respectively, as of September 2013. See: <http://taxfreegold.co.uk/preciousmetalpricesusdolars.html>.
- For recent reviews on ruthenium-catalyzed C–H functionalization, see: (a) V. S. Thirunavukkarasu, S. I. Kozhushkov and L. Ackermann, *Chem. Commun.*, 2014, **50**, 29; (b) L. Ackermann, *Acc. Chem. Res.*, 2013, **46**, DOI: 10.1021/ar3002798; (c) B. Li and P. H. Dixneuf, *Chem. Soc. Rev.*, 2013, **42**, 5744; (d) S. I. Kozhushkov and L. Ackermann,

- Chem. Sci.*, 2013, **4**, 886; (e) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (f) L. Ackermann, *Pure Appl. Chem.*, 2010, **82**, 1403; (g) F. Kakiuchi and S. Murai, *Acc. Chem. Res.*, 2002, **35**, 826 and cited references.
- 22 K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788.
- 23 L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315.
- 24 D. Lapointe and K. Fagnou, *Chem. Lett.*, 2010, **39**, 1118.
- 25 The mass balance of the cyanation reactions with substrates **1b–1f** is accounted for by the unreacted starting materials.
- 26 L. Ackermann, P. Novák, R. Vicente and N. Hofmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 6045.
- 27 D. Balcells, E. Clot and O. Eisenstein, *Chem. Rev.*, 2010, **110**, 749.
- 28 Preliminary experiments with anilides or aryl carbamates as the substrates provided thus far less satisfactory results.
- 29 For recent examples of ruthenium(II)-catalyzed C–H oxygenations, see: (a) W. Liu and L. Ackermann, *Org. Lett.*, 2013, **15**, 3484; (b) F. Yang and L. Ackermann, *Org. Lett.*, 2013, **15**, 718; (c) V. S. Thirunavukkarasu and L. Ackermann, *Org. Lett.*, 2012, **14**, 6206; (d) V. S. Thirunavukkarasu, J. Hubrich and L. Ackermann, *Org. Lett.*, 2012, **14**, 4210; (e) Y. Yang, Y. Lin and Y. Rao, *Org. Lett.*, 2012, **14**, 2874.
- 30 A recent ruthenium(II)-catalyzed C–H halogenation: L. Wang and L. Ackermann, *Chem. Commun.*, 2014, **50**, 1083.

