Green Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: G. Hermann, C. Jung and C. Bolm, *Green Chem.*, 2017, DOI: 10.1039/C7GC00499K.



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 <u>Terms & Conditions</u> and the ethical guidelines, outlined in our <u>author and reviewer resource centre</u>, 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.



rsc.li/green-chem

Journal Name



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

DOI: 10.1039/x0xx00000x

www.rsc.org/

Published on 28 April 2017. Downloaded by University of California - San Diego on 28/04/2017 14:34:43.

Mechanochemical Indole Synthesis by Rhodium-Catalysed Oxidative Coupling of Acetanilides and Alkynes under Solventless Conditions in a Ball Mill

Gary N. Hermann^{*a*}, Celine L. Jung^{*a,b*} and C. Bolm^{*a*}

A mechanochemical indole synthesis by rhodium(III)-catalysed C– H bond functionalisation in a planetary mill has been developed. It occurs in the absence of any solvent, does not require additional heating and only needs catalytic quantities of $Cu(OAc)_2$ in combination with dioxygen as terminal oxidant. Accordingly, the process represents a powerful and environmentally benign alternative to the common solution-based standard protocols.

The indole framework represents one of the most abundant and relevant heterocyclic core structures in bioactive compounds and natural products, and consequently, its construction has attracted the attention of organic chemists since more than 100 years.¹ Supplementing traditional preparative methods such as the Fischer indole synthesis,² transition metal catalysis has greatly advanced the field. A milestone in this context is the palladium-catalysed approach towards indoles introduced by Larock.³ Newly developed strategies involving catalytic C-H bond activations appear attractive because they particularly allow utilising unfunctionalised substrates.⁴ Along these lines, several methods for accessing indoles have been described including intramolecular cross-couplings,⁵ annulations of anilides,⁶ and others.^{1f} An interesting ruthenium(II)-catalysed oxidative C-H bond functionalisation providing indoles from N-2-pyrimidylsubstituted anilines and internal alkynes was reported by Ackermann and Lygin in 2012.⁷ Although the yields were generally high it was noted that for the success of the reaction an over-stoichiometric amount of Cu(OAc)₂ and a reaction temperature of 100 °C was critically needed. Furthermore, water had to be used as reaction medium. Neat conditions led to poor yields of indoles.8

In the past decade, organic synthesis has greatly benefited from mechanochemistry.⁹ Applying this technique allowed performing reactions under solventless conditions and

This journal is © The Royal Society of Chemistry 20xx

compared to analogous transformations in solution, higher yields could often be achieved after shorter reaction times compared to analogous transformations using a solvent-based system. Positive effects of mechanochemical conditions have also been noted in metal catalysis,¹⁰ and altered reactivity has led to variations in the product portfolio.¹¹ In 2014, Stolle and co-workers reported a mechanochemically induced indole synthesis by intramolecular hydroamination reaction [Scheme 1, Eq. (1)].¹² In the absence of any solvent zinc bromide (100 mol%) activated 2-alkynylanilines providing the corresponding products in good to high yields. Considering literature reports⁶ and results from previous work on catalytic C-H bond functionalisations under mechanochemical conditions,¹³ we started wondering about an alternative approach towards indoles. It involved the use of a rhodium catalyst, its sitespecific activation of acetanilides and subsequent oxidative couplings with alkynes [Scheme 1, Eq. (2)]. The realisation of this concept is reported here.



Scheme 1 Mechanochemical indole synthesis in ball mills.

We initiated our study using reaction conditions similar to those reported by Fagnou, Stuart, and co-workers^{6a,6d} for the oxidative coupling of acetanilide (**1a**) and diphenylacetylene (**2a**) in *t*-amylOH at 60 °C with [Cp*Rh(MeCN)₃][SbF₆]₂ (5 mol%) as catalyst and Cu(OAc)₂ (2.1 equiv.) as oxidant. To our delight the switch to solventless mechanochemical conditions proved

^{a.} Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1,

D-52074 Aachen, Germany. E-mail: <u>carsten.bolm@oc.rwth-aachen.de</u>;

Fax: +49 241 80 92 391; Tel: +49 24 80 94 675.

^b New address: Institute of Technical and Macromolecular Chemistry, RWTH Aachen University

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

Published on 28 April 2017. Downloaded by University of California - San Diego on 28/04/2017 14:34:43.

possible providing indole 3a in 37% yield (Table 1, entry 1). Shorter milling times and reduced catalyst loadings resulted in lower yields (see ESI for details). Increasing the number of milling balls from 16 to 30 (with a diameter of 5 mm) and employing an excess of acetanilide 1a had positive effects on the coupling, and the yield of **3a** was raised to 42% and 48%, respectively (Table 1, entries 2 and 3). Changing Cu(OAc)₂ to Fe(OAc)₂ or NaOAc proved detrimental, and the product was formed in only 5% and 9% yield, respectively (Table 1, entries 4 and 5). Stuart and co-workers observed a positive effect when the reaction was performed under an atmosphere of dioxygen instead of air.^{6d} This behaviour was also found here, rendering the transformation even catalytic in Cu(OAc)₂. Thus, under mechanochemical conditions in an atmosphere of dioxygen with only 2.5 mol% of Cu(OAc)₂, 3a was obtained in 59% yield (Table 1, entry 6). In addition, the amount of 1a could be reduced from 3.0 equiv. to 2.0 equiv. without affecting the product yield (Table 1, entry 7). Finally, changing the limiting agent from 2a to 1a and increasing the milling speed from 800 rpm to 900 rpm increased the yield of 3a further allowing to isolate the product in 76% (NMR) yield (Table 1, entries 8 and 9).

Table 1 Optimisation of the mechanochemical indole synthesis^a

H H	O ∭ H Me Ph	Ph	Rh(MeCN) ₃][SbF ₆] ₂ (5 mol%) redox modulator ball milling, 800 rpm x (60 min. + 15 min. break)	Ph N N Me
1a		2a		3a
Entry	1a (equiv.)	2a (equiv.)	Redox modulator (equiv.)	Yield (%) ^b
1	1.0	3.0	Cu(OAc) ₂ (2.1)	37
2 ^{<i>c</i>}	1.0	3.0	Cu(OAc) ₂ (2.1)	42
3 ^c	3.0	1.0	Cu(OAc) ₂ (2.1)	48
4 ^{<i>c</i>}	3.0	1.0	Fe(OAc) ₂ (2.1)	5
5 [°]	3.0	1.0	NaOAc (2.1)	9
6 ^{c,d}	3.0	1.0	Cu(OAc) ₂ (0.025)	59
7 ^{c,d}	2.0	1.0	Cu(OAc) ₂ (0.025)	60
8 ^{<i>c,d</i>}	1.0	2.0	Cu(OAc) ₂ (0.025)	68
9 ^{<i>c,d,e</i>}	1.0	2.0	Cu(OAc) ₂ (0.025)	76

^{*a*} Reaction conditions: Pulverisette 7 premium line; vessels (20 mL) and balls (16 balls, 5 mm diameter) made of ZrO₂; 800 rpm. ^{*b*} Determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. ^{*c*} Use of 30 milling balls (with 5 mm diameter). ^{*d*} Performed under an atmosphere of O₂. ^{*e*} 900 rpm. Cp* = pentamethyl-cyclopentadienyl.

Several points are noteworthy at this stage: first, applying ball milling to this process led to a high product yield without the need of any solvent or additional heating. Then, dioxygen could be used as terminal oxidant allowing an 8-fold reduction of the amount of Cu(OAc)₂ compared to the standard solvent based protocol.^{6d}

Next, the scope of the mechanochemically induced indule synthesis was investigated, and each product 3Wa3Gs044ted (Scheme 2). First, the acetanilide was varied in reactions with **2a** as coupling partner. Using acetanilide (**1a**) led to the formation of **3a** in 70% yield.¹⁵ The presence of a fluoro or a methoxy substituent in *para*-position of the anilinic amide group reduced the yield of the corresponding products, and **3b** and **3c** were formed in only 45% and 58% yield, respectively. *Meta*-methyl-substituted acetanilide **1d** reacted with **2a** affording 70% of **3d** as single regioisomer. Presumably, the intrinsic high site-selectivity of the C–H-bond functionalisation had steric reasons. *Ortho*-substituted anilides reacted smoothly as well, and **3e** and **3f** were obtained in 48% and 62% yield, respectively.¹⁶

Subsequently, the influence of the alkyne was investigated using anilide **1a** as representative coupling partner. Various aryl/alkyl-disubstituted alkynes performed well affording the corresponding products (**3g-3i**) in yields up to 77% and with exclusive regioselectivity. In each case the aromatic substituent was located at C2 of the indole core (Scheme 2).¹⁷ A significant drop in yield was observed when dialkylsubstituted alkyne **2j** was applied. For this substrate, the yield of the resulting indole **3j** was only 9%.¹⁴



Scheme 2 Scope of the mechanochemical rhodium-catalysed indole synthesis. The yields refer to isolated product quantities. For **3***j*: when 1.1 equiv. of the alkyne was used the yield was 10%.

As demonstrated from **3a**, mechanochemical conditions also allowed removing the *N*-acetyl groups from the products (Scheme 3). Noteworthy, a significantly lower amount of KOH was needed than in MeOH/H₂O solution (2.0 equiv. versus 5.0 equiv.)^{6a} for achieving a comparable yield of **4a** (90%).

Journal Name

Published on 28 April 2017. Downloaded by University of California - San Diego on 28/04/2017 14:34:43.



Scheme 3 Mechanochemical cleavage of the directing group.

In summary, we have developed a mechanochemically induced indole synthesis by rhodium-catalysed C–H bond functionalisation in a ball mill. The reaction takes place in the absence of any solvent and forms the corresponding products in moderate to good yields. No additional heating is required and only catalytic amounts of Cu(OAc)₂ are needed by employing dioxygen as the terminal oxidant.

Acknowledgements

This research was supported by the Distinguished Professorship Program at RWTH Aachen University funded by the Excellence Initiative of the German federal and state governments. We are grateful to Dr. José Gregorio Hernández (RWTH Aachen University) for proofreading the manuscript.

Notes and References

- For selected reviews, see: (a) D. F. Taber and P. K. Tirunahari, *Tetrahedron*, 2011, **67**, 7195; (b) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, PR215; (c) M. Platon, R. Amardeil, L. Djakovitch and J.-C. Hierso, *Chem. Soc. Rev.*, 2012, **41**, 3929; (d) Z. Shi and F. Glorius, *Angew. Chem. Int. Ed.*, 2012, **51**, 9220; (e) M. Inman and C. J. Moody, *Chem. Sci.*, 2013, **4**, 29; (f) T. Guo, F. Huang, L. Yu and Z. Yu, *Tetrahedron Lett.*, 2015, **56**, 296.
- 2 E. Fischer and F. Jourdan, Ber. Dtsch. Chem. Ges., 1883, 16, 2241.
- 3 R. C. Larock and E. K. Yum, J. Am. Chem. Soc., 1991, **113**, 6689.
- For selected reviews on C-H functionalisations, see: (a) T. 4 Satoh and M. Miura, Chem. Eur. J., 2010, 16, 11212; (b) D. A. Colby, R. G. Bergman and J. A. Ellman, Chem. Rev., 2010, 110, 624; (c) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy and J. F. Hartwig, Chem. Rev., 2010, 110, 890; (d) T. W. Lyons and M. S. Sanford, Chem. Rev., 2010, 110, 1147; (e) L. Ackermann, Chem. Rev., 2011, 111, 1315; (f) P. Herrmann and T. Bach, Chem. Soc. Rev., 2011, 40, 2022; (g) C. Liu, H. Zhang, W. Shi and A. Lei, Chem. Rev., 2011, 111, 1780; (h) C. S. Yeung and V. M. Dong, Chem. Rev., 2011, 111, 1215; (i) O. Baudoin, Chem. Soc. Rev., 2011, 40, 4902; (j) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, Chem. Soc. Rev., 2011, 40, 5068; (k) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, Chem. Soc. Rev., 2011, 40, 4740; (I) B.-J. Li and Z.-J. Shi, Chem. Soc. Rev., 2012, 41, 5588; (m) G. Song, F. Wang and X. Li, Chem. Soc. Rev., 2012, 41, 3651; (n) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, Acc. Chem. Res., 2012, 45, 814; (o) K. M. Engle, T.-S. Mei, M. Wa and J.-Q. Yu, Acc. Chem. Res., 2012, 45, 788; (p) S. R. Neufeldt and M. S. Sanford, Acc. Chem. Res., 2012, 45, 936; (q) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, Chem. Rev., 2012, 112, 5879; (r) K. Hirano and

COMMUNICATION

M. Miura, *Chem. Commun.*, 2012, **48**, 10704; (s) N. Kuhl, M. Hopkinson, J. Wencel-Delord ans DIF10 Glogius, *Cheme Online Chem. Int. Ed.*, 2012, **51**, 10236; (t) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369; (u) N. Kuhl, N. Schröder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443; (v) G. Shi and Y. Zhang, *Adv. Synth. Catal.*, 2014, **356**, 1443; (v) G. Shi and Y. Zhang, *J. Zhang*, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.*, 2015, **2**, 1107; (x) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900; (y) Y. Yang, K. Li, Y. Cheng, D. Wan, M. Li and J. You, *Chem. Commun.*, 2016, **52**, 2872.

- 5 (a) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge and F. Glorius, Angew. Chem. Int. Ed., 2008, 47, 7230; (b) K. Tsuchikama, Y. Hashimoto, K. Endo and T. Shibata, Adv. Synth. Catal., 2009, 351, 2850; (c) J. J. Neumann, S. Rakshit, T. Dröge, S. Würtz and F. Glorius, Chem. Eur. J., 2011, 17, 7298; (d) Y. Wei, I. Deb and N. Yoshikai, J. Am. Chem. Soc., 2012, 134, 9098; (e) J. Zoller, D. C. Fabry, M. A. Ronge and M. Rueping, Angew. Chem. Int. Ed., 2014, 53, 13264.
- (a) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess and K. 6 Fagnou, J. Am. Chem. Soc., 2008, 130, 16474; (b) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui and N. Jiao, Angew. Chem. Int. Ed., 2009, 48, 4572; (c) J. Chen, G. Song, C.-L. Pan and X. Li, Org. Lett., 2010, 12, 5426; (d) D. R. Stuart, P. Alsabeh, M. Kuhn and K. Fagnou, J. Am. Chem. Soc., 2010, 132, 18326; (e) Y. Su, M. Zhao, K. Han, G. Song and X. Li, Org. Lett., 2010, 12, 5462; (f) M. P. Huestis, L. Chan, D. R. Stuart and K. Fagnou, Angew. Chem. Int. Ed., 2011, 50, 1338; (g) J. Chen, Q. Pang, Y. Sun and X. Li, J. Org. Chem., 2011, 76, 3523; (h) H. Wang, C. Grohmann, C. Nimphius and F. Glorius, J. Am. Chem. Soc., 2012, **134**, 9098; (*i*) A. Cajaraville, S. López, J. A. Varela and C. Saá, Org. Lett., 2013, 15, 4576; (j) D. Zhao, Z. Shi and F. Glorius, Angew. Chem. Int. Ed., 2013, 52, 12426; (k) B. Liu, C. Song, C. Sun, S. Zhou and J. Zhu, J. Am. Chem. Soc., 2013, 135, 16625; (/) C. Wang and Y. Huang, Org. Lett., 2013, 15, 5294; (m) C. Wang, H. Sun, Y. Fang and Y. Huang, Angew. Chem. Int. Ed., 2013, 52, 5795; (n) G. Zhang, H. Yu, G. Qin and H. Huang, Chem. Commun., 2014, 50, 4331; (o) S. Cai, K. Yang and D. Z. Wang, Org. Lett., 2014, 16, 2606; (p) L. Zheng and R. Hua, Chem. Eur. J., 2014, 20, 2352; (q) G.-D. Tang, C.-L. Pan and X. Li, Org. Chem. Front., 2016, 3, 87; (r) Z.-Z. Zhang, B. Liu, J.-W. Xu, S.-Y. Yan, and B.-F. Shi, Org. Lett., 2016, 18, 1776; (s) Y. Li, Z. Qi, H. Wang, X. Yang and X. Li, Angew. Chem. Int. Ed., 2016, 55, 11877; (t) S. Zhou, J. Wang, P. Chen, K. Chen and J. Zhu, Chem. Eur. J., 2016, 22, 14508; (u) Y. Liang and N. Jiao, Angew. Chem. Int. Ed., 2016, 55, 4035; (v) A. Lerchen, S. Vásquez-Céspedes and F. Glorius, Angew. Chem. Int. Ed., 2016, 55, 3208.
- 7 L. Ackermann and A. V. Lygin, *Org. Lett.*, 2012, **14**, 764.
- 8 For a solventless oxidative alkyne annulation under nickel catalysis at 160 °C, see: W. Song and L. Ackermann, *Chem. Commun.*, 2013, **49**, 6638.
- 9 For selected reviews on mechanochemistry, see: (a) B. Rodríguez, A. Bruckmann, T. Rantanen and C. Bolm, Adv. Synth. Catal., 2007, 349, 2213; (b) A. Bruckmann, A. Krebs and C. Bolm, Green Chem., 2008, 10, 1131; (c) A. Stolle, T. Szuppa, S. E. S. Leonhardt and B. Ondruschka, Chem. Soc. Rev., 2011, 40, 2317; (d) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Frisčić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, Chem. Soc. Rev., 2012, 41, 413; (e) G.-W. Wang, Chem. Soc. Rev., 2013, 42, 7668; (f) J. G. Hernández and T. Frisčić, Tetrahedron Lett., 2015, 56, 4253; (g) D. Tan, L. Loots and T. Frisčić, Chem. Commun., 2016, 52, 7760.

COMMUNICATION

Published on 28 April 2017. Downloaded by University of California - San Diego on 28/04/2017 14:34:43.

- 10 (a) A. Stolle and B. Ondruschka, Pure Appl. Chem., 2011, 83, 1343; (b) R. Schmidt, R. Thorwirth, T. Szuppa, A. Stolle, B. Ondruschka and H. Hopf, Chem. Eur. J., 2011, 17, 8129; (c) R. Thorwirth, A. Stolle, B. Ondruschka, A. Wild and U. S. Schubert, Chem. Commun., 2011, 47, 4370; (d) W. Su, J. Yu, Z. Li and Z. Jiang, J. Org. Chem., 2011, 76, 9144; (e) V. Declerck, E. Colacino, X. Bantreil, J. Martinez and F. Lamaty, Chem. Commun., 2012, 48, 11778; (f) X. Zhu, J. Liu, T. Chen and W. Su, Appl. Organomet. Chem., 2012, 26, 145; (g) G. Cravotto, D. Garella, S. Tagliapietra, A. Stolle, S. Schüßler, S. E. S. Leonhardt and B. Ondruschka, New J. Chem., 2012, 36, 1304; (h) G.-P. Fan, Z. Liua and G.-W. Wang, Green Chem., 2013, 15, 1659; (i) J. Yu, Z. Li, K. Jia, Z. Jiang, M. Liu and W. Su, Tetrahedron Lett., 2013, 54, 2006; (j) K. Tanaka, A. Asakura, T. Muraoka, P. Kalicki and Z. Urbanczyk-Lipkowska, New J. Chem., 2013, 37, 2851; (k) H. Sharma, N. Singh and D. O. Jang, Green Chem., 2014, 16, 4922; (/) L. Chen, B. E. Lemma, J. S. Rich and J. Mack, Green Chem., 2014, 16, 1101; (m) D. Tan, V. Štrukil, C. Mottillo and T. Frisčić, Chem. Commun., 2014, 50, 5248; (n) D. Tan, C. Mottillo, A. D. Katsenis, V.Štrukil and T. Frisčić, Angew. Chem. Int. Ed., 2014, 53, 9321; (o) V. Kumar, N. Taxak, R. Jangir, P. V. Bharatam and K. P. R. Kartha, J. Org. Chem., 2014, 79, 3427; (p) Y.-J. Tan, Z. Zhang, F.-J. Wang, H.-H. Wu and Q.-H. Li, RSC Adv., 2014, 4, 35635; (q) J.-L. Do, C. Mottillo, D. Tan, V. Štrukil and T. Frisčić, J. Am. Chem. Soc., 2015, 137, 2476; (r) Z. Li, Z. Jiang and W. Su, Green Chem., 2015, 17, 2330; (s) L. Chen, M. O. Bovee, B. E. Lemma, K. S. M. Keithley, S. L. Pilson, M. G. Coleman and J. Mack, Angew. Chem. Int. Ed., 2015, 54, 11084; (t) L. Chen, M. Regan and J. Mack, ACS Catal., 2016, 6, 868; (u) Z.-J. Jiang, Z.-H. Li, J.-B. Yu and W.-K. Su, J. Org. Chem., 2016, 81, 10049; (v) Y. Zhao, S. V. Rocha and T. M. Swager, J. Am. Chem. Soc., 2016, 138, 13834; (w) J.-B. Yu, Y. Zhang, Z.-J. Jiang and W.-K. Su, J. Org. Chem., 2016, 81, 11514.
- 11 (a) J. G. Hernández and C. Bolm, J. Org. Chem., DOI: 10.1021/acs.joc.6b02887; (b) J.-L. Do and T. Frisčić, ACS Cent. Sci., 2017, **3**, 13.
- M. Zille, A. Stolle, A. Wild and U. S. Schubert, *RSC Adv.*, 2014, 4, 13126.
- (a) G. N. Hermann, P. Becker and C. Bolm, Angew. Chem. Int. Ed., 2015, 54, 7414; (b) J. G. Hernández and C. Bolm, Chem. Commun., 2015, 51, 12582; (c) G. N. Hermann, P. Becker and C. Bolm, Angew. Chem. Int. Ed., 2016, 55, 3781; (d) S.-J. Lou, Y.-J. Mao, D.-Q. Xu, J.-Q. He, Q. Chen and Z.-Y. Xu, ACS Catal., 2016, 6, 3890; (e) K.-Y. Jia, J.-B. Yu, Z.-J. Jiang and W.-K. Su, J. Org. Chem., 2016, 81, 6049.
- 14 This observation was in accordance with results reported by Stuart and co-workers (ref. 6d), who found a negative effect, when the reaction was carried out with a high amount of an alkyl/alkyl-disubstituted alkyne. Reducing the quantity of **2**j from the standard 2.0 equiv. to 1.1 equiv. had essentially no influence here (9% versus 10% yield of **3**j). Ref. 6a also contains a detailed comparison of the reactivity of alkyl/alkyl-disubstituted alkynes with the one of aryl/arylbearing substrates. In general, the former proved less suitable for the reported catalysis.
- 15 Attempts to recover the catalyst remained unsuccessful. Scaling up the reaction to 3 mmol (using the same-size ball milling equipment) led to a lower yield of **3a** (37%) presumably due to the altered reaction environment.

- 16 In addition to the electronic properties, the physical characteristics of the substrates have: 101009/(taken04090 account in reactions under mechanochemical conditions, as in many cases a homogenous dispersion of the reactants is essential for achieving high conversions and product yields. The reaction parameters utilized here [900 rpm, 15 x (60 min. + 15 min. break)] led to a temperature increase of the reaction mixture to ca. 70 °C (± 2 °C) as measured using an infrared thermometer after opening the milling beaker. Thus, substrate 2a (mp: 59 - 61 °C) must have melted and the reaction mixture been blended well. As alkynes 2g-j were liquids, the same should be true for the reaction with those substrates (see ESI for all mp). (a) For a discussion of masstransport limitations under ball-milling conditions, see: F. Schneider, T. Szuppa, A. Stolle, B. Ondruschka, H. Hopf, Green Chem., 2009, 11, 1894; (b) for a discussion of thermal effects under mechanochemical conditions, see: K. S. McKissic, J. T. Caruso, R. G. Blair, J. Mack, Green Chem., 2014, 16. 1628.
- 17 For a detailed discussion on the regioselectivity, see ref. 6d.

TOC:



Indoles are prepared by rhodium(III)-catalysed C–H bond functionalisation under mechanochemical conditions in a planetary mill.

This journal is © The Royal Society of Chemistry 20xx