ChemComm

RSCPublishing

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2013, **49**, 8830

Received 26th June 2013,
Accepted 30th July 2013

DOI: 10.1039/c3cc44787a

www.rsc.org/chemcomm

Aerobic Ru-catalyzed direct C2-olefination of N-heteroarenes with alkenes directed by a removable *N*-dimethylcarbamoyl group†

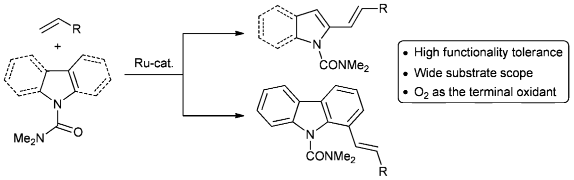
Luo-Qiang Zhang, Shiping Yang, Xiaolei Huang, Jingsong You and Feijie Song*

A highly efficient and selective Ru-catalyzed direct C2-olefination of indoles, pyrroles, and carbazoles assisted by a removable *N*-dimethylcarbamoyl group has been developed by using O_2 as the terminal oxidant. Both electron-deficient and unactivated alkenes are applicable to the protocol.

The indole unit is a ubiquitous skeleton found in a great number of pharmaceuticals and bioactive compounds.[1] Consequently, the modification of the indole ring has attracted significant attention from chemists for a long time.[2] The oxidative Heck coupling of indoles with alkenes through twofold C–H bond cleavage, as pioneered by Fujiwara and Moritani,[3] is one of the most sustainable and straightforward protocols for the functionalization of indoles. However, the reaction preferentially occurs at the more electron-rich C3 position of the indole ring due to the electrophilic nature of the coupling reaction. Therefore, the highly efficient and selective C2-olefination of 2,3-unsubstituted indoles, which can override the inherent selectivity of indoles, has been a challenging project. Palladium complexes have been demonstrated to be efficient catalysts for the oxidative coupling of indole C2–H bonds with alkenes. Palladium-catalyzed C2-olefination of indoles by using *N*-(2-pyridyl)methyl[4] and *N*-(2-pyridyl)sulfonyl[5] as the directing group has been reported by Ricci and Carretero, respectively. The reaction of indole-3-carboxylic acids with alkenes under Pd catalysis offers another method to obtain 2-alkenylated indoles through a tandem carboxylic acid-directed coupling–decarboxylation process.[6] Gaunt *et al.* have reported a practical, non-directed C2-olefination of indoles by the judicious choice of solvent using palladium as the catalyst.[7] One isolated example of Rh-catalyzed coupling of *N*-acetylindole with styrene has been reported in 2010, affording the 2-alkenylated product in 37% yield.[8] Following our recent work on the regioselective functionalization of indoles,[9] we are interested in the C2-olefination of indoles using an inexpensive, robust and highly selective ruthenium complex as the catalyst.

The Ru(II)-catalyzed Csp^2–H activation/C–C coupling reactions have made remarkable progress within the last few years.[10] In sharp contrast to the oxidative Heck coupling reaction of arenes,[11] the reactions of heteroarenes with alkenes catalyzed by ruthenium are very rare. In 2011, Miura and coworkers reported the carboxylic acid-assisted direct olefination of heteroarenes with alkenes to obtain the *ortho*-vinyl substituted heteroarene carboxylic acids in the presence of a ruthenium catalyst.[12] During the preparation of this manuscript, Lanke and Prabhu reported a Ru-catalyzed highly efficient C2-olefination of indoles with the aid of the *N*-benzoyl group.[13] However, stoichiometric amounts of $Cu(OAc)_2 \cdot H_2O$ are used as the oxidant and alkenes are limited to electron-deficient acrylates. Arguably, the development of new protocols that could employ environmentally benign oxidants and exhibit wide substrate scope for both coupling partners is still highly desirable and useful in this area. Herein, we would like to report a Ru-catalyzed direct C2-olefination of indoles/pyrroles with alkenes assisted by a removable *N*-dimethylcarbamoyl group using O_2 as the terminal oxidant (Scheme 1). Various alkenes including acrylates, acrylonitriles, sulfones, phosphonates and especially, styrene derivatives successfully participate in the olefination reaction. In addition, a highly selective metal-catalyzed mono-*ortho*-olefination of carbazoles is also disclosed in the paper.

Considering that the carbamoyl group has been well recognized as a good removable directing group,[14] our study commenced with the coupling of *N*,*N*-dimethyl-1*H*-indole-1-carboxamide **1a** and butyl acrylate **2a** to optimize the reaction conditions (eqn (1), see ESI† for details). Initial attempt showed that **3a** could be obtained in 87%

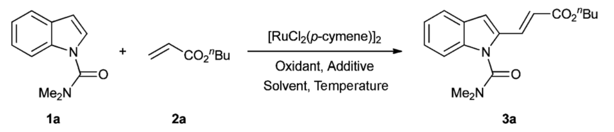


Scheme 1 Ru-catalyzed C2-olefination of N-heteroarenes with alkenes.

Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University, 29 Wangjiang Road, Chengdu 610064, PR China. E-mail: fsong@scu.edu.cn; Fax: +86-28-85412285

† Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data. See DOI: 10.1039/c3cc44787a

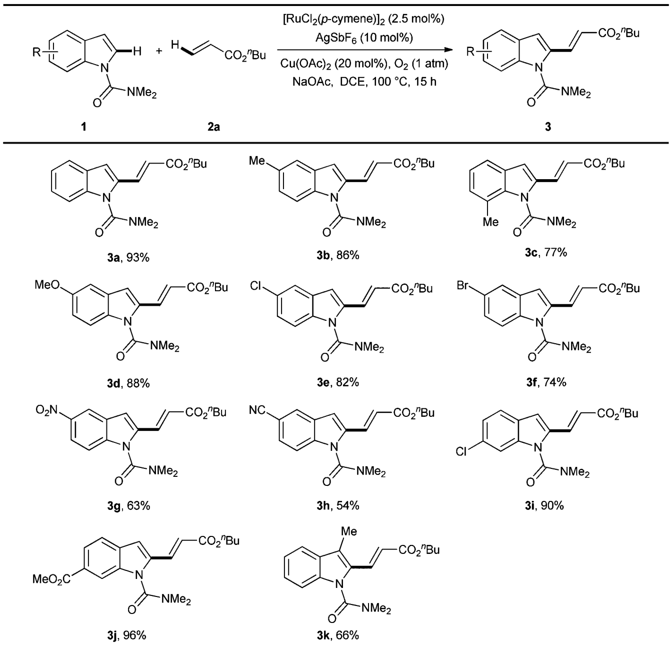
yield in the presence of 2.5 mol% $[RuCl_2(p\text{-cymene})]_2$ and 10 mol% $AgSbF_6$ by using 1.5 equiv. of $Cu(OAc)_2$ as the oxidant and toluene as the solvent at 130 °C for 24 h (ESI,† Table S1, entry 1). Further optimization showed that O_2 (1 atm) could be successfully employed as the oxidant in combination with 20 mol% of $Cu(OAc)_2$ (ESI,† Table S1, entry 6), which made the protocol greener and more attractive. Finally, the yield of **3a** reached 93% by using 30 mol% of NaOAc as the additive and changing the solvent to dichloroethane (DCE) at 100 °C (ESI,† Table S1, entry 14). Indoles with other potential directing groups such as *N*-acetyl, benzoyl, 2-pyrimidyl, and 4-toluenesulfonyl only afforded trace amounts of the alkenylated products, indicating that the *N*-dimethylcarbamoyl group served as both the directing and activating group with the use of oxygen as the oxidant.



(1)

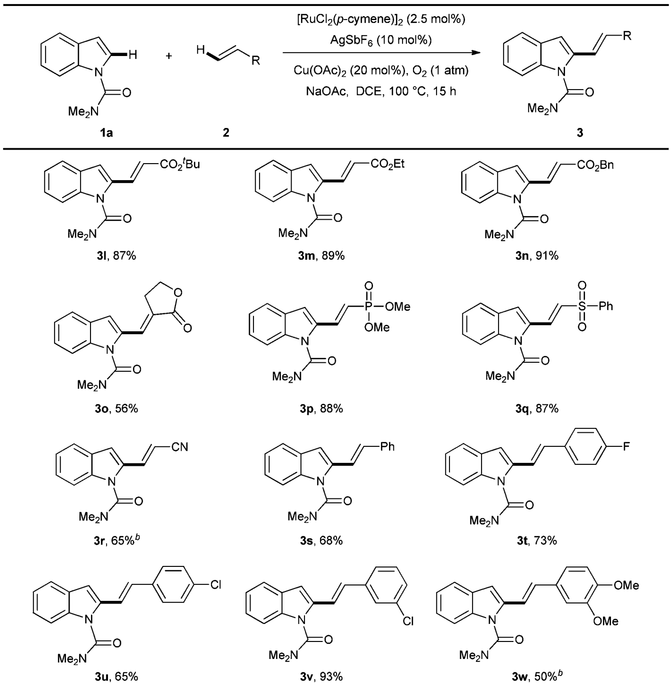
Next, we decided to explore the scope of indoles with butyl acrylate **2a** as the model olefin (Table 1). Various indoles with substituents at the C5, C6, or C7 position of the indole ring smoothly coupled with **2a** to afford the desired 2-alkenylated indoles. It seems that the weak electron-withdrawing and electron-donating groups in indoles had negligible effects on the olefination reaction. However, the strong electron-withdrawing groups such as nitro and cyano groups decreased the reactivity of indoles to some extent (Table 1, **3g** and **3h**). Chloro and bromo atoms were well tolerated under the standard conditions, demonstrating the high functional group tolerance of the Ru catalysis. The 3-methyl substituent on the indole ring did not hinder the olefination reaction, affording the desired **3k** in 66% yield. However, the 2-methyl-substituted **1a** failed to couple with **2a**, indicating that the C3 position of indoles was unreactive under the current catalytic conditions.

Table 1 Scope of substituted indoles[a]



[a] Conditions: **1** (1.0 equiv.), **2a** (1.5 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (20 mol%), O_2 (1 atm), and NaOAc (30 mol%) in DCE (1.0 mL) at 100 °C for 15 h. Isolated yields.

Table 2 Scope of substituted alkenes[a]

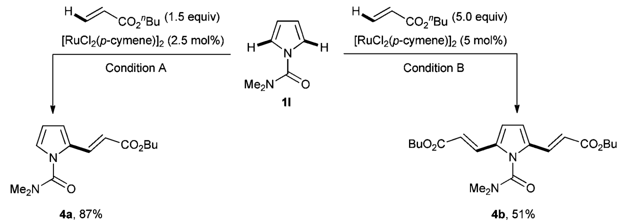


[a] Conditions: **1a** (1.0 equiv.), **2** (1.5 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (20 mol%), O_2 (1 atm), and NaOAc (30 mol%) in DCE (1.0 mL) at 100 °C for 15 h. Isolated yields. [b] 3 equiv. of alkenes were used.

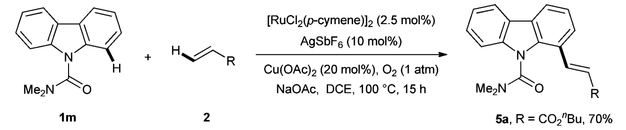
Subsequently, the scope of alkenes was examined and the results are summarized in Table 2. A wide range of electrophilic alkenes including ester, cyano, phosphonate, and sulfonyl substituted alkenes coupled efficiently with indole **1a** to give 2-alkenylated indoles in satisfactory yields (Table 2, **3l**–**3r**). Importantly, the challenging non-activated styrene derivatives successfully participated in the olefination reaction and their reactivities were comparable to the electron-deficient alkenes (Table 2, **3s**–**3w**). In a few cases, increased amounts of alkenes were required in order to obtain synthetically useful yields (Table 2, **3r** and **3w**).

Application of this protocol to other related N-heteroarenes has gained encouraging success. The coupling of pyrrole **1l** with butyl acrylate **2a** resulted in a highly selective formation of 2-alkenylated pyrrole **4a** in 87% yield (Scheme 2). Interestingly, the double alkenylated product **4b** could also be obtained in 51% yield by the use of Ag_2CO_3 as the oxidant.

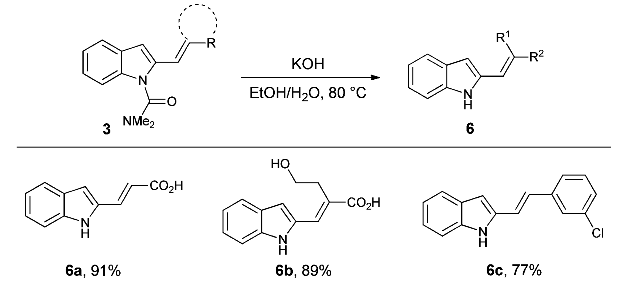
Despite the importance of carbazole derivatives in various biologically active compounds and materials science,[15] the C–H functionalization of carbazoles is much less developed than other heteroarenes. Very recently, Carretero *et al.* reported the first Pd-catalyzed olefination of carbazoles directed by the *N*-(2-pyridyl)-sulfonyl group, which mainly afforded di-*o*-alkenylated products.[16] However, the metal-catalyzed highly selective mono-*o*-olefination of carbazoles is scarce. Gratifyingly, this reaction was realized by the utilization of the method described herein (Scheme 3). Not only butyl acrylate, but also non-activated styrene coupled with carbazole



Scheme 2 Ru-catalyzed direct olefination of *N*-dimethylcarbamoyl pyrrole. Condition A: **1l** (1.0 equiv.), $AgSbF_6$ (10 mol%), $Cu(OAc)_2$ (20 mol%), O_2 (1 atm), and NaOAc (30 mol%) in DCE (1.0 mL) at 100 °C for 15 h. Condition B: **1l** (1.0 equiv.), $AgSbF_6$ (20 mol%), Ag_2CO_3 (2.5 equiv.), and NaOAc (60 mol%) in DCE (1.0 mL) under N_2 at 100 °C for 15 h.



Scheme 3 Ru-catalyzed direct olefination of *N*-dimethylcarbamoyl carbazole.



Scheme 4 The deprotection of the directing group.

1m to form the corresponding mono-*o*-alkenylated products selectively, although styrene exhibited lower reactivity than acrylate.

To further demonstrate the synthetic utility of this methodology, the deprotection of the *N*-dimethylcarbamoyl group was then attempted. As expected, it can be easily removed after the coupling reaction under basic conditions, affording the corresponding free (N–H) indoles in good yields (Scheme 4).[14]

In conclusion, we have developed a highly efficient and selective Ru-catalyzed C2-olefination of indoles and other related N-heteroarenes by using the *N*-dimethylcarbamoyl as the unique and removable directing group. Key features of this protocol include the employment of an atmosphere of O_2 as the terminal oxidant and the wide substrate scope with respect to both heteroarenes and alkenes. Further studies to explore the reaction mechanism are currently underway in the lab.

We thank the financial support from the National Basic Research Program of China (973 Program, 2011CB808600) and the National NSF of China (J1103315/J0104, 21202105, 21025205, and 21021001).

Notes and references

1 (*a*) G. W. Gribble, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, New York, 1996, vol. 2, p. 207; (*b*) R. J. Sundberg, *Indoles*, Academic, New York, 1996; (*c*) T. Kawasaki and K. Higuchi, *Nat. Prod. Rep.*, 2005, **22**, 761; (*d*) S. Massa, R. Di Santo and M. Artico, *J. Heterocycl. Chem.*, 1990, **27**, 1131.

2 (*a*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873; (*b*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (*c*) L. Joucla and L. Djakovitch, *Adv. Synth. Catal.*, 2009, **351**, 673; (*d*) E. M. Beck and M. J. Gaunt, *Top. Curr. Chem.*, 2010, **292**, 85; (*e*) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608; (*f*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, PR 215.

3 (*a*) I. Moritani and Y. Fujiwara, *Tetrahedron Lett.*, 1967, 1119; (*b*) Y. Fujiwara, I. Moritani, S. Danno, R. Asano and S. Teranishi, *J. Am. Chem. Soc.*, 1969, **91**, 7166.

4 E. Capito, J. M. Browna and A. Ricci, *Chem. Commun.*, 2005, 1854.

5 (*a*) A. García-Rubia, R. G. Arrayás and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2009, **48**, 6511; (*b*) A. García-Rubia, B. Urones, R. G. Arrayás and J. C. Carretero, *Chem.–Eur. J.*, 2010, **16**, 9676.

6 A. Maehara, H. Tsurugi, T. Satoh and M. Miura, *Org. Lett.*, 2008, **10**, 1159.

7 N. P. Grimster, C. Gauntlett, C. R. A. Godfrey and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2005, **44**, 3125.

8 F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9982.

9 (*a*) Z. Wang, F. Song, Y. Zhao, Y. Huang, L. Yang, D. Zhao, J. Lan and J. You, *Chem.–Eur. J.*, 2012, **18**, 16616; (*b*) X. Qin, H. Liu, D. Qin, Q. Wu, J. You, D. Zhao, Q. Guo, X. Huang and J. Lan, *Chem. Sci.*, 2013, **4**, 1964.

10 For reviews on Ru-catalyzed C–H functionalization, see: (*a*) F. Kakiuchi and S. Murai, *Acc. Chem. Res.*, 2002, **35**, 826; (*b*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (*c*) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886; (*d*) L. Ackermann, *Acc. Chem. Res.*, 2013, **46**, DOI: 10.1021/ar3002798. For selected recent examples, see: (*e*) J. C. Leung, L. M. Geary, T.-Y. Chen, J. R. Zbieg and M. J. Krische, *J. Am. Chem. Soc.*, 2012, **134**, 15700; (*f*) V. S. Thirunavukkarasu, M. Donati and L. Ackermann, *Org. Lett.*, 2012, **14**, 3416; (*g*) Y. Goriya and C. V. Ramana, *Chem.–Eur. J.*, 2012, **18**, 13288; (*h*) J. Zhang and T.-P. Loh, *Chem. Commun.*, 2012, **48**, 11232; (*i*) N. Hofmann and L. Ackermann, *J. Am. Chem. Soc.*, 2013, **135**, 5877; (*j*) M. C. Reddy and M. Jeganmohan, *Chem. Commun.*, 2013, **49**, 481; (*k*) M. C. Reddy, R. Manikandan and M. Jeganmohan, *Chem. Commun.*, 2013, **49**, 6060; (*l*) Y. Aihara and N. Chatani, *Chem. Sci.*, 2013, **4**, 664; (*m*) M. Schinkel, I. Marek and L. Ackermann, *Angew. Chem., Int. Ed.*, 2013, **52**, 3977.

11 For selected examples, see: (*a*) M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art and M. Nomura, *J. Org. Chem.*, 1998, **63**, 5211; (*b*) H. Weissman, X. Song and D. Milstein, *J. Am. Chem. Soc.*, 2001, **123**, 337; (*c*) K. Padala and M. Jeganmohan, *Org. Lett.*, 2011, **13**, 6144; (*d*) Y.-Y. Liu, R.-J. Song, C.-Y. Wu, L.-B. Gong, M. Hu, Z.-Q. Wang, Y.-X. Xie and J.-H. Li, *Adv. Synth. Catal.*, 2012, **354**, 347; (*e*) L. Ackermann, L. Wang, R. Wolfram and A. V. Lygin, *Org. Lett.*, 2012, **14**, 728; (*f*) K. Padala and M. Jeganmohan, *Org. Lett.*, 2012, **14**, 1134; (*g*) K. Padala, S. Pimparkar, P. Madasamy and M. Jeganmohan, *Chem. Commun.*, 2012, **48**, 7140; (*h*) K. Graczyk, W. Ma and L. Ackermann, *Org. Lett.*, 2012, **14**, 4110; (*i*) B. Li, J. Ma, N. Wang, H. Feng, S. Xu and B. Wang, *Org. Lett.*, 2012, **14**, 736.

12 T. Ueyama, S. Mochida, T. Fukutani, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2011, **13**, 706. For some sporadic examples, see ref. 11*e*–*g* and *i*.

13 V. Lanke and K. R. Prabhu, *Org. Lett.*, 2013, **15**, 2818.

14 (*a*) B. Zhou, Y. Yang, S. Lin and Y. Li, *Adv. Synth. Catal.*, 2013, **355**, 360; (*b*) D. J. Schipper, M. Hutchinson and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6910; (*c*) C. G. Hartung, A. Fecher, B. Chapell and V. Snieckus, *Org. Lett.*, 2003, **5**, 1899.

15 (*a*) G. Bubniene, T. Malinauskas, M. Daskeviciene, V. Jankauskas and V. Getautis, *Tetrahedron*, 2010, **66**, 3199; (*b*) H.-Y. Wang, F. Liu, L.-H. Xie, C. Tang, B. Peng, W. Huang and W. Wei, *J. Phys. Chem. C*, 2011, **115**, 6961; (*c*) A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, 3193; (*d*) J. Roy, A. K. Jana and D. Mal, *Tetrahedron*, 2012, **68**, 6099; (*e*) W.-L. Gong, F. Zhong, M. P. Aldred, Q. Fu, T. Chen, D.-K. Huang, Y. Shen, X.-F. Qiao, D. Ma and M.-Q. Zhu, *RSC Adv.*, 2012, **2**, 10821; (*f*) H. Huang, Y. Wang, B. Pan, X. Yang, L. Wang, J. Chen, D. Ma and C. Yang, *Chem.–Eur. J.*, 2013, **19**, 1828.

16 B. Urones, R. G. Arrayás and J. C. Carretero, *Org. Lett.*, 2013, **15**, 1120.