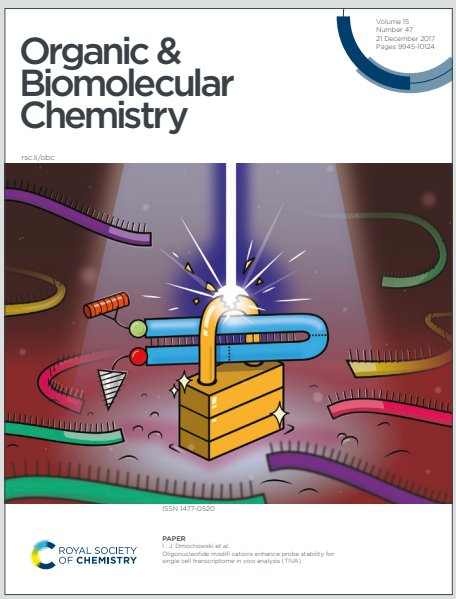
Check for updates

View Article Online
View Journal

Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Li, T. Yao, S. Sun, T. Yan, L. Wen and L. Zhang, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/D0OB00508H.




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 Information for Authors.

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 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.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/D0OB00508H

ARTICLE

# Ruthenium(II)-catalyzed C–H olefination of indoles with alkynes: facile construction of tetrasubstituted alkenes under aqueous conditions

Ming Li, Tian-Yu Yao, Sheng-Zheng Sun, Ting-Xun Yan, Li-Rong Wen, Lin-Bao Zhang*

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

DOI: 10.1039/x0xx00000x

An environmentally-friendly and facile protocol for the construction of tetrasubstituted alkenes has been established by Ru(II)-catalyzed C-H bond functionalizations under mild conditions. The method was featured by the usage of readily available substrates, without external oxidants and additives, 100% atom economy, and excellent regioselectivity, thus enhancing the practicability of this protocol. Moreover, this transformation underwent smoothly under aqueous conditions and could be extended to gram scale. *N*-Methoxy amide, as a directing group (DG) played a vital role in the transformation.

## Introduction

Transition-metal-catalyzed C–H activation has been recognized as a practical tool for the synthesis of biologically important molecular scaffolds and characterized by several appealing features, such as step- and atom-economy, unnecessity of preactivated substrates and synthetic practicality.[1] However, one of the challenges associated with the strategy is the low reactivity of C-H bonds, which suggests that harsh reaction conditions are often required in the process.[2] Moreover, the developments "in-water" reactions remain relatively scare, probably due to the decreasing the solubility of substrates or catalysts in water.[3] Moreover, 100% selective conversion of starting material is also one of the vital principles in green chemistry, which could minimize the generation of side products.[4] Therefore, the development of highly atom-economical organic reaction under aqueous conditions to construct valuable compounds is highly desirable.

Tetrasubstituted alkenes are widely existed in biologically active natural products and drugs such as Tamoxifen or Vioxx (Figure 1).[5] They are also key starting reagents for various transformations such as hydrogenations, epoxidations, and other processes.[6] However, the synthesis of tetrasubstituted alkenes remains a challenging topic due to the strong steric effect. Generally, the frequently applied synthetic routes to such molecules employ alkynyl carbometallation intermediate.[7] In addition, strategies such as the classical Wittig reactions, olefin metathesis, radical sequences, and ynolate chemistry could also be used as viable techniques to achieve the goal.[5a,8] In spite of the great development in this area, the relatively harsh reaction conditions including the use of the stoichiometric organometallic reagents or strong base limit their practical application in organic synthesis. In light of the importance of tetrasubstituted alkenes, there is an urgent demand to develop an efficient and practical synthetic protocol to construct such motifs.

Recently, the use of ruthenium(II)-catalysts has contributed to the discovery of milder reaction conditions and efficient catalytic systems, following the pioneering work of Oi, Inoue,[9] and Ackermann.[10] Especially, the development of Ru(II)-catalyzed C-H bond transformations "in-water" has attracted great attention due to the fact that water as the undoubtedly green solvent possesses the abundant, cheap, non-toxic, environmentally benign and safe property.[11] Such as, Dixneuf group performed the direct arylation of arenes with aryl chlorides in water under the assist of 2-phenylpyrimidine as the directing group without the requirement of surfactant (Scheme 1a).[12] The group of Ackermann reported an efficient direct arylations of unactivated C-H bonds using phenols as the coupling reagents under aqueous conditions (Scheme 1b).[13] Recently, they also disclosed a micellar catalysis system for Ru(II)-catalyzed C–H arylation in $H_2O$, which the weak coordinating thioketone group enable the transformation

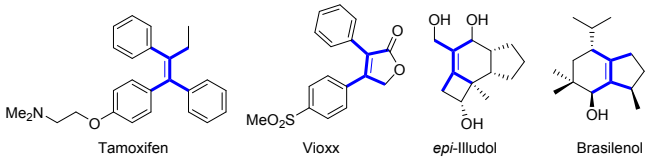



**Figure 1**. Selected examples of biologically active compounds bearing a tetrasubstituted alkene core.

*State Key Laboratory Base of Eco-Chemical Engineering, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, P. R. China. E-mail: zhang_linbao@126.com.*

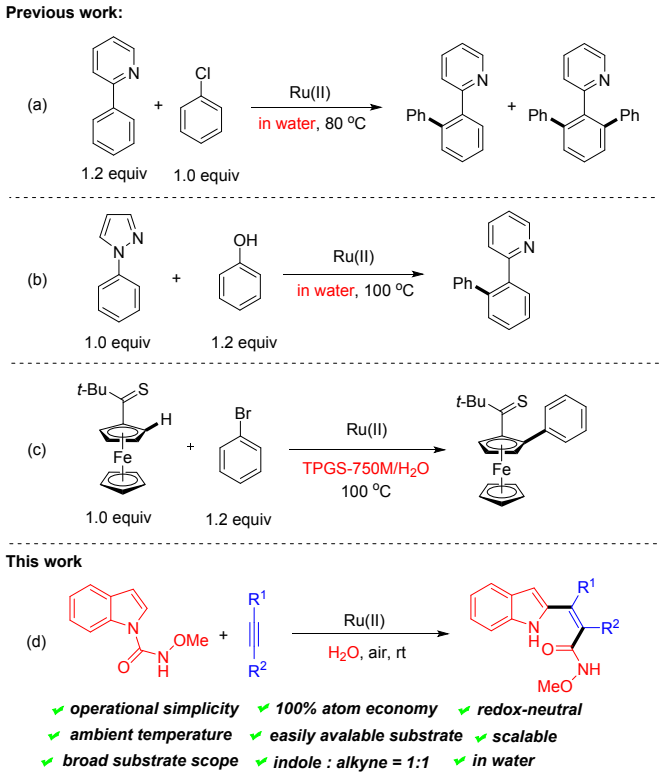
† Footnotes relating to the title and/or authors should appear here.

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

Published on 26 March 2020. Downloaded by University of Reading on 3/28/2020 9:47:27 PM.

Organic & Biomolecular Chemistry Accepted Manuscript

View Article Online
DOI: 10.1039/D0OB00508H



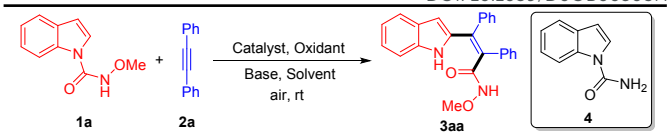

**Scheme 1**. The development of Ru(II)-catalyzed C-H bond transformations in water.

(Scheme 1c).[14] In these cases, high temperature was inevitable during the transformation. Beyond the arylation, the diverse reaction types need to be further developed in water. Within our constant interest in transition-metal-catalyzed C–H functionalizations and green chemistry,[15] we presented a C–H olefination of indoles assisted by CONHOMe directing group under aqueous conditions, providing an effective and practical route for the synthesis of tetrasubstituted alkenes (Scheme 1d).

## Results and discussion

We commenced the study by using *N*-methoxy-1*H*-indole-1-carboxamide **1a** and alkyne **2a** as the substrates. Initially, various metal catalysts were screened for this reaction. To our delight, when the reaction was performed in the presence of 5.0 mol % $[RuCl_2(p\text{-cymene})]_2$, 1.0 equivalent of $Cu(OAc)_2$, 2.0 equivalent of NaOPiv in DCM at room temperature for 1 hour, the desired product **3aa** was obtained in 43% yield along with 13% of by-product **4** (Table 1, entry 1). Other metal catalysts such as Rh, Ir, Co catalysts showed poor catalytic activity (Table 1, entries 2-4). No product was obtained in the absence of Ru catalyst (Table 1, entry 5). Subsequently, further exploration indicated that oxidants were dispensable as the yield was increased to 54% without oxidants (Table 1, entry 6). Next, various bases were screened and NaOAc could play as an effective base, the others such as $Na_2CO_3$, CsOAc or $Et_3N$, showed the inferior results (Table 1, entries 7-10). Only trace of **3aa** was afforded upon removal of NaOAc, indicating that base was critical to the reaction (Table 1, entry 11).[16] Moreover, decreasing the amount of **2a** to 1.0 equivalent, the product **3aa** could also be obtained without the loss of the yield (Table 1, entry 12). The solvents showed a profound effect on the transformation (Table 1, entries 13-16), $H_2O$ as a green solvent presented a better performance without the detection of by-product **4**, albeit a longer reaction time was required (Table 1, entry 16).

**Table 1**. Optimization of the reaction conditions.[a,b]




| Entry | Catalyst | Base | Solvent | **3aa** | **4** |
|---|---|---|---|---|---|
| 1 | $[RuCl_2(p\text{-cymene})]_2$ | NaOPiv | DCM | 43% | 13% |
| 2 | $[Cp^*RhCl_2]_2$ | NaOPiv | DCM | 35% | 9% |
| 3 | $[Cp^*IrCl_2]_2$ | NaOPiv | DCM | trace | trace |
| 4 | $Cp^*Co(CO)I_2$ | NaOPiv | DCM | N.R. | - |
| 5 | None | NaOPiv | DCM | N.R. | - |
| 6[c] | $[RuCl_2(p\text{-cymene})]_2$ | NaOPiv | DCM | 54% | 12% |
| 7[c] | $[RuCl_2(p\text{-cymene})]_2$ | $Na_2CO_3$ | DCM | 49% | 11% |
| 8[c] | $[RuCl_2(p\text{-cymene})]_2$ | NaOAc | DCM | 76% | 14% |
| 9[c] | $[RuCl_2(p\text{-cymene})]_2$ | CsOAc | DCM | 65% | 13% |
| 10[c] | $[RuCl_2(p\text{-cymene})]_2$ | $Et_3N$ | DCM | 41% | 10% |
| 11[c] | $[RuCl_2(p\text{-cymene})]_2$ | None | DCM | trace | trace |
| 12[c,d] | $[RuCl_2(p\text{-cymene})]_2$ | NaOAc | DCM | 77% | 13% |
| 13[c,d] | $[RuCl_2(p\text{-cymene})]_2$ | NaOAc | DCE | 52% | 12% |
| 14[c,d] | $[RuCl_2(p\text{-cymene})]_2$ | NaOAc | DMF | 35% | 15% |
| 15[c,d] | $[RuCl_2(p\text{-cymene})]_2$ | NaOAc | MeOH | 73% | 14% |
| **16[c,d,e]** | **$[RuCl_2(p\text{-cymene})]_2$** | **NaOAc** | **$H_2O$** | **87%** | **-** |

[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.15 mmol, 1.5 equiv), catalyst (5.0 mol %), $Cu(OAc)_2$ (0.1 mmol, 1.0 equiv), NaOPiv (0.2 mmol, 2.0 equiv), DCM (1.0 mL), air, room temperature, 1 h. [b]Isolated yields. [c]No oxidant. [d]**2a** (0.1 mmol, 1.0 equiv). [e]Rection time: 10 h. N.R. = no reaction.

Under the optimized reaction conditions, we explored the substrate scope of indoles **1** for this reaction (Table 2). Various electron-donating and electron-withdrawing groups including methyl (**3ga**), methoxyl (**3ba** and **3fa**), fluoro (**3ha**), chloro (**3ca**, **3ia** and **3na**), bromo (**3da**, **3ja** and **3oa**), iodo (**3ka**) and ester (**3ea** and **3la**) at 4-, 5- and 6- positions of indole could be tolerated in the reaction, furnishing the desired products in good yields (75%-87%). However, when strong electron-withdrawing group nitro was at the C5 position of indole (**1m**), the transformation did not occur. Moreover, the desired products (**3pa** and **3qa**) could be obtained in good yields when the C3 position of indole was methyl substituent. However, the methyl was replaced by phenyl substituent at the C3 position of indole, the yields were greatly decreased due to steric hindrance factor (**3ra**-**3ua**). Noteworthy, natural product derivatives such as **1v** and **1w** were also applicable in the reaction, affording the target products **3va** and **3wa** in 73% and

Published on 26 March 2020. Downloaded by University of Reading on 3/28/2020 9:47:27 PM.

Organic & Biomolecular Chemistry Accepted Manuscript



This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

View Article Online

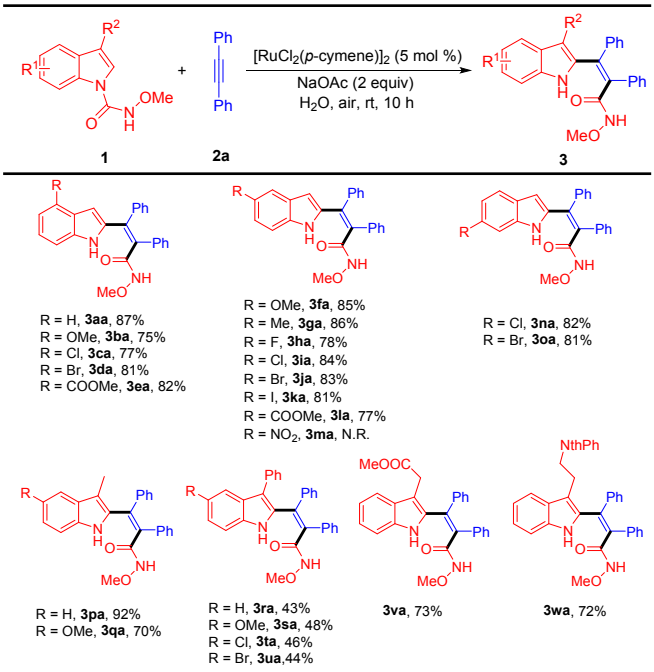
ARTICLE

DOI: 10.1039/D0OB00508H

Published on 26 March 2020. Downloaded by University of Reading on 3/28/2020 9:47:27 PM.

72% yields, respectively.

**Table 2**. Scope of *N*-alkoxyamides.[a,b]

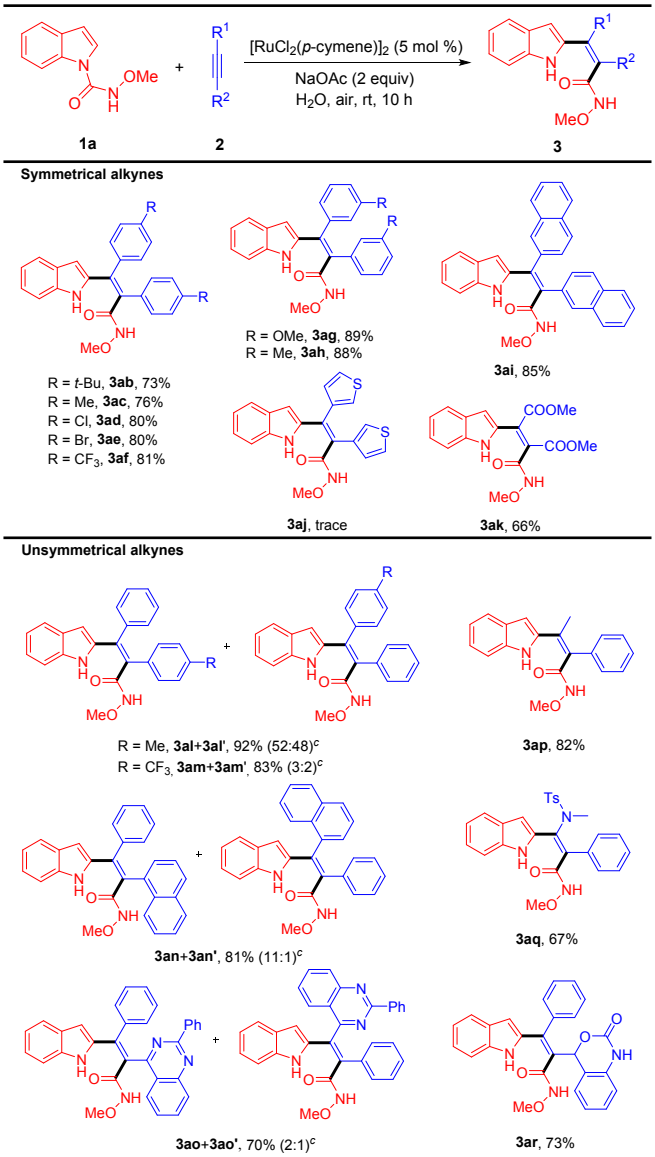



[a]Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), NaOAc (0.2 mmol, 2.0 equiv), $H_2O$ (1.0 mL), air, room temperature, 10 h. [b]Isolated yields.

To investigate the generality of this reaction, the scope of alkynes **2** was also evaluated (Table 3). For symmetrical alkynes, both electron-donating and electron-withdrawing groups at the *para*-position of the benzene ring were tolerated, providing the desired products (**3ab**-**3af**) in good yields (73%-81%). Substitution at the *meta*-position with methoxyl (**3ag**) and methyl (**3ah**) provided the 89% and 88% yields, respectively. Besides, 2-naphthyl alkyne also worked well to give the desired product (**3ai**) in good yield of 85%. However, it did not provide the desired product (**3aj**) using 3-thienyl alkyne as the substrate. Surprisingly, the ester-substituted alkyne was used as the candidate, the desired product (**3ak**) was obtained in a yield of 66%. For unsymmetrical alkynes with phenyl group on one side of the alkynes and 4-methylphenyl, 4-trifluoromethylphenyl or 1-naphthyl groups on another side, they gave two unseparated isomers (**3al**-**3an**) in 81%-92% yields. Natural product derivative **2o** also can work well, provided two isomers (**3ao**+**3ao'**) in total 70% yield. Interestingly, it was found that only single products (**3ap**-**3ar**) were obtained while unsymmetrical alkynes (**2p**-**2r**) were employed in the reaction.

Several control experiments had been performed to explore the mechanism (Scheme 2). The kinetic isotope effect (KIE) experiments were conducted, and an intermolecular KIE ($K_H/K_D$ = 0.88) was observed for the competition reactions of **1a** and deuteriumlabeled **1a-D** with **2a** (Scheme 2, eq 1). Two parallel reactions gave a similar KIE value of 0.8 (Scheme 2, eq 2). These results suggested that C-H bond cleavage was unlikely involved in the rate-limiting step.[17] Intermolecular competition

**Table 3**. Scope of alkynes.[a,b]




[a]Conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), NaOAc (0.2 mmol, 2.0 equiv), $H_2O$ (1.0 mL), air, room temperature, 10 h. [b]Isolated yields. [c]The ratio is determined by $^1H$ NMR analysis.

experiments between **1g** (R = Me) and **1h** (R = F) with **2a** were performed, and the results revealed electron-withdrawing *N*-alkoxyamides **1** to be functionalized preferentially (Scheme 2, eq 3). However, the effect of substituents on the transformation was negligible in terms of alkynes **2** (Scheme 2, eq 4). The presence of a radical quencher such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-diisopropyl-4-methylphenol (BHT) did not inhibit the reaction, suggesting that radical process was not involved in the transformation (Scheme 2, eq 5). Only two products (**3pa** and **3Aa**) were obtained when the two different amides (**1p** and **1A**) reacted with the alkyne **2a**, indicating that the process of intramolecular nucleophilic

Organic & Biomolecular Chemistry Accepted Manuscript



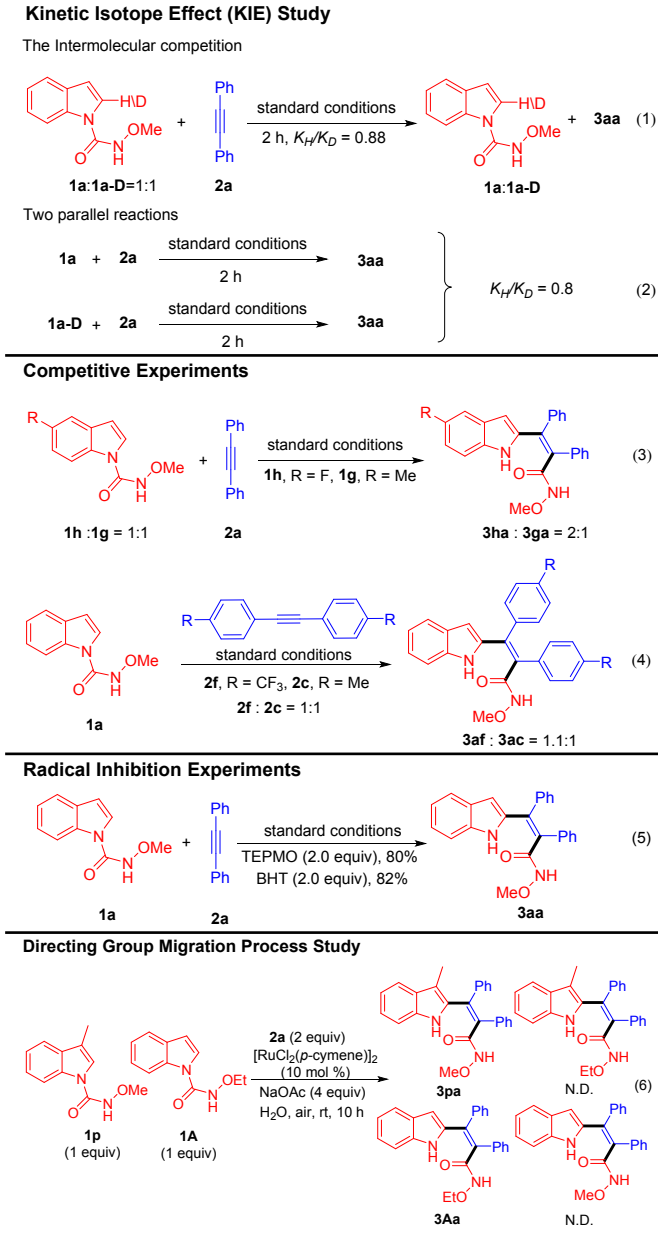
Please do not adjust margins

View Article Online
DOI: 10.1039/D0OB00508H

Published on 26 March 2020. Downloaded by University of Reading on 3/28/2020 9:47:27 PM.

Organic & Biomolecular Chemistry Accepted Manuscript

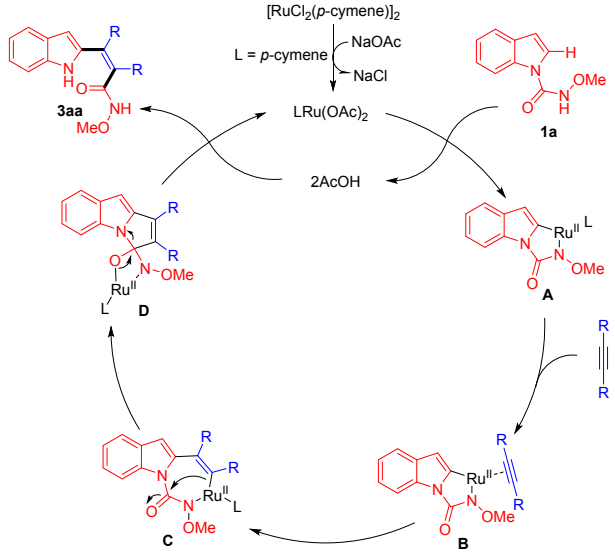
substitution was more likely compared with procedure of directing group removal (Scheme 2, eq 6).[18] Further exploration



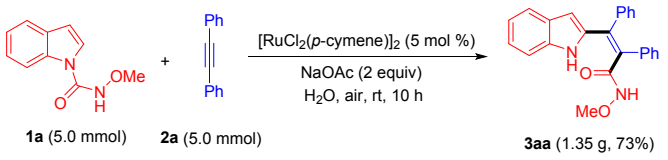

**Scheme 2**. Mechanistic studies.

indicated *N*-alkoxyamide moiety was critical for the transformation since other amides installing hydroxyl (**1B**) and alkyl group (**1C**) did not work. No reaction was detected in the case of the structurally similar but methylation of directing groups in **1D** (Figure 2).

Based on the preliminary mechanistic experiments and the previous literatures, a possible reaction pathway is proposed (Scheme 3). Initially, a catalytically active Ru catalyst is generated through the chloride ligand of $[RuCl_2(p\text{-cymene})]_2$ as well as ligand exchange to sodium acetate. After coordination of *N*-alkoxyamide **1a** to the active Ru catalyst, C–H bond metalation generates the ruthenacycle **A** through a concerted




**Scheme 3**. Proposed mechanism.




**Scheme 4**. Gram scale experiment.

metalation-deprotonation (CMD) mechanism. Subsequently, $Ru^{II}$-species coordinates to the internal alkynes **2** to form complex **B** and migratory insertion of internal alkynes **2** results in intermediate **C**. Then, **C** undergoes an intramolecular nucleophilic substitution to provide directing group migrated species **D**. Product **3aa** is obtained followed by proto-demetalation of **D** with AcOH, while AcOH regenerates the active catalyst to complete the catalytic cycle.

To further test the utility of the reaction, we conducted the reaction on gram scale of *N*-alkoxyamide **1a** with internal alkyne **2a**, and **3aa** was isolated in 73% yield (Scheme 4).

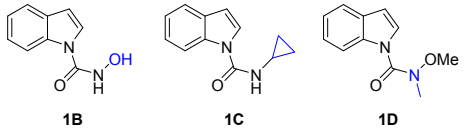



**Figure 2**. Unsuccessful directing groups.



This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

View Article Online



## Conclusions

In conclusion, we have developed a Ru(II)-catalyzed C–H olefination of at the C-2 position of *N*-methoxycarbamoyl indoles by reacting with internal alkynes, furnishing tetrasubstituted alkenes in high yields assisted by CONHOMe directing group. This redox-neutral reaction is featured by the mild reaction conditions, compatibility with various functional groups, operational simplicity, 100% atom economy, and excellent regioselectivity. In addition, the transformation could be completed at room temperature under aqueous conditions and easily performed on gram scale, which meet the vital principles of green chemistry.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (21801152 and 21572110), the Natural Science Foundation of Shandong Province (ZR2019BB005 and ZR2019MB010), the Youth Innovation Science and Technology Plan of Colleges and Universities in Shandong Province (2019KJC003).

## Notes and references

1 (a) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev.,* 2019, **119**, 2192; (b) C.-S. Wang, P. H. Dixneuf and J.-F. Soulé, *Chem. Rev.*, 2018, **118**, 7532; (c) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*,2017, **117**, 8754; (d) J. R. Hummel, J. A. Boerth and J. A. Ellman, *Chem. Rev.*, 2017, **117**, 9163; (e) Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247; (f) L. Ackermann, *Acc. Chem. Res.*, 2020, **53**, 84; (g) S. M. Khake and N. Chatani, *Trends Chem.*, 2019, **1**, 524; (h) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (i) X. Zhou, Y. Luo, L. Kong, Y. Xu, G. Zheng, Y. Lan and X. Li, *ACS Catal.*, 2017, **7**, 7296; (j) R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen and J.-Q. Yu, *Angew. Chem. Int. Ed.*, 2016, **55**, 10578; (k) M. Gulías and J. L. Mascareñas, *Angew. Chem. Int. Ed.*, 2016, **55**, 11000; (l) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga and M. Kanai, *J. Am. Chem. Soc.*, 2014, **136**, 5424; (m) H. Ikemoto, R. Tanaka, K. Sakata, M. Kanai, T. Yoshino and S. Matsunaga, *Angew. Chem. Int. Ed*., 2017, **56**, 7156; (n) G. Liao and B.-F. Shi, *Acta Chim. Sinica*. 2015, **73**, 1283; (o) W.-H. Rao and B.-F. Shi, *Org. Chem. Front*. 2016, **3**, 1028.

2 (a) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev*., 2016, **45**, 2900; (b) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev*., 2011, **40**, 4740.

3 (a) B. Li and P. H. Dixneuf, *Chem. Soc. Rev.*, 2013, **42**, 5744; (b) L.-Y. Xie, S. Peng, F. Liu, Y.-F. Liu, M. Sun, Z.-L. Tang, S. Jiang, Z. Cao and W.-M. He, *ACS Sustainable Chem. Eng*., 2019, **7**, 7193; (c) L. Liu, Q. Sun, Z. Yan, X. Liang, Z. Zha, Y. Yang and Z. Wang, *Green Chem*., 2018, **20**, 3927; (d) Y. Yang, Y. Bao, Q. Guan, Q. Sun, Z. Zha and Z. Wang, *Green Chem*., 2017, **19**, 112; (e) P. B. Arockiam, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Angew. Chem. Int. Ed.*, 2010, **49**, 6629.

4 P. Anastas and N. Eghbali, *Chem. Soc. Rev*., 2010, **39**, 301.

5 (a) A. B. Flynn and W. W. Ogilvie, *Chem. Rev*., 2007, **107**, 4698; (b) A. S. Levenson and V. C. Jordan, *Eur. J. Cancer*, 1999, **35**, 1628; (c) J. Wang, Z. Dong, C. Yang and G. Dong, *Nat. Chem.*, 2019, **11**, 1106; (d) M. Rychlet Elliot, A.-L. Dhimane and M. Malacria, *J. Am. Chem.Soc*., 1997, **119**, 3427.

6 (a) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu and K.-X. Su, *Chem. Rev*., 2005, **105**, 1603; (b) H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483; (c) D. H. Woodmansee and A. Pfaltz, *Chem. Commun*., 2011, **47**, 7912; (d) K. Morikawa, J. Park, P. G. Andersson, T. Hashiyama and K. B. Sharpless, *J. Am. Chem. Soc*., 1993, **115**, 8463.

7 F. Xue, J. Zhao, T. S. A. Hor and T. Hayashi, *J. Am. Chem. Soc.*, 2015, **137**, 3189.

8 (a) E. Negishi, Z. Hunag, G. Wang, S. Mohan, C. Wang and H. Hattori, *Acc. Chem. Res*., 2008, **41**, 1474; (b) W. You, Y. Li and M. K. Brown, *Org. Lett*., 2013, **15**, 1610.

9 (a) S. Oi, S. Fukita, N. Hirata, N. Watanuki, S. Miyano and Y, Inoue, *Org. Lett.*, 2001, **3**, 2579; (b) S. Oi, Y. Ogino, S. Fukita and Y. Inoue, *Org. Lett.*, 2002, **4**, 1783; (c) S. Oi, K. Sakai and Y. Inoue, *Org. Lett.*, 2005, **7**, 4009; (d) S. Oi, E. Aizawa, Y. Ogino and Y. Inoue, *J. Org. Chem.*, 2005, **70**, 3113; (e) S. Oi, Y. Tanaka and Y. Inoue, *Organometallics*, 2006, **25**, 4773.

10 (a) L. Ackermann, Org. Lett., 2005, **7**, 3123; (b) L. Ackermann, A. Althammer and R. Born, *Angew. Chem. Int. Ed.*, 2006, **45**, 2619; (c) J. Li, S. Warratz, D. Zell, S. D. Sarkar, E. E. Ishikawa and L. Ackermann, *J. Am. Chem. Soc.*, 2015, **137**, 13894; (d) S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke and L. Ackermann, *Angew. Chem. Int. Ed.*, 2015, **54**, 5513; (e) N. Y. P. Kumar, A. Bechtoldt, K. Raghuvanshi and L. Ackermann, *Angew. Chem. Int. Ed.*, 2016, **55**, 6929; (f) A. Schischko, H. Ren, N. Kaplaneris and L. Ackermann, *Angew. Chem. Int. Ed.*, 2017, **56**, 1576; (g) Q. Bu, T. Rogge, V. Kotek and L. Ackermann, *Angew. Chem. Int. Ed.*, 2018, **57**, 765; (h) K. Korvorapun, N. Kaplaneris, T. Rogge, S. Warratz, A. C. Stückl and L. Ackermann, *ACS Catal.*, 2018, **8**, 886; (i) A. Bechtoldt, M. E. Baumert, L. Vaccaro and L. Ackermann, *Green Chem.*, 2018, **20**, 398; (j) T. Rogge and L. Ackermann, *Angew. Chem. Int. Ed.*, 2019, **58**, 15640.

11 (a) R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302; (b) P. Gandeepan, N. Kaplaneris, S, Santoro, L. Vaccaro and L. Ackermann, *ACS Sustainable Chem. Eng.*, 2019, **7**, 8023; (c) D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, A. Abou-Shehada and P. J. Dunn, *Green Chem.*, 2016, **18**, 288.

12 P. B. Arockiam, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Green Chem.*, 2013, **15**, 67.

13 L. Ackermann, J. Pospech and H. K. Potukuchi, *Org. Lett.*, 2012, **14**, 2146.

14 S. R. Yetra, T. Rogge, S. Warratz, J. Struwe, W. Peng, P. Vana and L. Ackermann, *Angew. Chem. Int. Ed.*, 2019, **58**, 7490.

15 (a) L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, Z.-J. Liu, X.-X. Zheng, J.-F. Gong, J.-L. Niu and M.-P. Song, *Angew. Chem. Int. Ed*., 2015, **54**, 272; (b) L.-B. Zhang, X.-Q. Hao, S.-K. Zhang, Z.-J. Liu, X.-X. Zheng, S.-K. Zhang, J.- L. Niu and M.-P. Song, *Angew. Chem. Int. Ed*., 2015, **54**, 10012; (c) L.-B. Zhang, M.-H. Zhu, S.-F. Ni, L.-R. Wen and M. Li, *ACS Catal.,* 2019, **9**, 1680; (d) L.-B. Zhang, M.-H. Zhu, W.-B. Du, S.-F. Ni, L.-R. Wen and M. Li, *Chem. Commun.,* 2019, **55**, 14383; (e) W.-K. Yuan, M.-H. Zhu, R.-S. Geng, G.-Y. Ren, L.-B. Zhang, L.-R. Wen and M. Li, *Org. Lett.*, 2019, **21**, 1654; (f) L.-B. Zhang, R.-S. Geng, Z.-C. Wang, G.-Y. Ren, L.-R. Wen and M. Li, *Green Chem.,* 2020, **22**, 16.

16 L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315.

17 (a) X. Wu and H. Ji, *Org. Lett.*, 2018, **20**, 2224; (b) Y. Xie, X. Wu, C. Li, J. Wang, J. Li and H. Liu, *J. Org. Chem.*, 2017, **82**, 5263.

18 (a) J. Zhang, H. Xie, H. Zhu, S. Zhang, M. R. Lonka and H. Zou, *ACS Catal*., 2019, **9**, 10233; (b) X. Zhou, Z. Li, Z. Zhang, P. Lu and Y. Wang, *Org. Lett*., 2018, **20**, 1426.

Published on 26 March 2020. Downloaded by University of Reading on 3/28/2020 9:47:27 PM.

Organic & Biomolecular Chemistry Accepted Manuscript



Please do not adjust margins