RESEARCH ARTICLE

Regio- and Stereoselective Synthesis of Tetrasubstituted Alkenes via Ruthenium(II)-Catalyzed C–H Alkenylation/Directing Group Migration

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Dedication ((optional))

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Abstract: Herein we report the regio- and stereoselective synthesis of tetrasubstituted alkenes from *N*-carbamoyl indoles and alkynes via ruthenium(II)-catalyzed C–H alkenylation/directing group migration, in which the carbamoyl directing group is endowed with a dual role of auxiliary group and migrating acylation reagent via C–N bond cleavage. This method features broad substrate scope, good to excellent yields, high atom- and step-economy, good functional group tolerance and mild redox-neutral conditions at room temperature.

Introduction

The tetrasubstituted alkene scaffold is widely found in active pharmaceutical ingredients (APIs). Representative examples include the estrogen receptor agonist Diethylstilbestrol,[1] the selective estrogen receptor modulator (SERM) Tamoxifen,[2] the selective cyclooxygenase-2 (COX-2) inhibitor Imrecoxib[3] and the calcium channel blocker Amlodipine (Figure 1).[4] Therefore, the construction of the tetrasubstituted alkene scaffold has captured the attention of scientific community and many efforts have been made to develop efficient methods to access this privileged

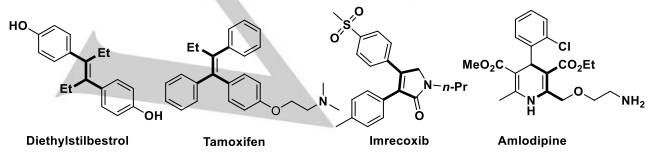
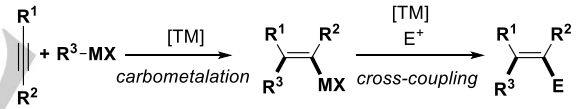


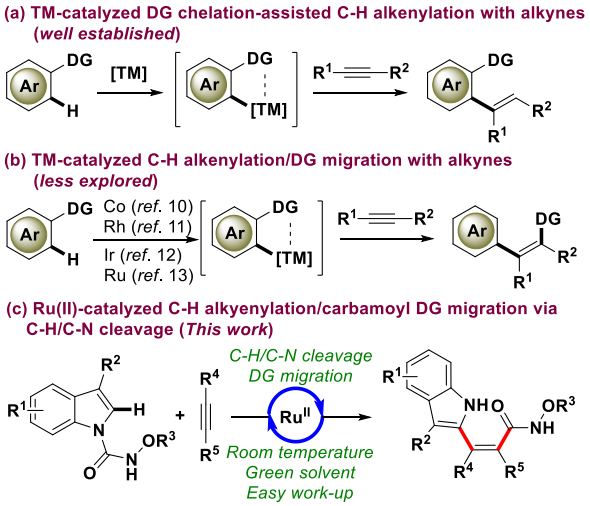
Figure 1. Representative APIs carrying the tetrasubstituted alkene scaffold.



Scheme 1. TM-catalyzed three-component carbometalation/cross-coupling reaction.

structure,[5] despite the challenge in achieving high levels of regio- and stereoselectivity in such a congested structure. A traditional and typical approach to tetrasubstituted alkenes is the transition-metal (TM)-catalyzed sequential three-component carbometalation/cross-coupling reaction of internal alkynes, organometallic reagents and electrophiles (Scheme 1).[6] However, this method suffers from harsh reaction conditions, multi-step synthesis, and the requirement of stoichiometric organometallic reagents. Obviously, it is still highly desirable to develop more convenient and straightforward methods to prepare tetrasubstituted alkenes.

With the significant advances made in TM-catalyzed C−H functionalization assisted by directing groups (DGs) in recent decades,[7] the DG chelation-assisted C−H alkenylation with alkynes has become a powerful tool for the synthesis of structurally diverse alkenes (Scheme 2a).[8] However, in most cases, di- or trisubstituted alkenes are obtained in this type of reaction. This is because the alkenyl-metal intermediate produced by the sequential C–H activation/alkyne insertion preferred to undergo proto-demetalation to construct a C(sp^2)–H bond, thus providing di- or trisubstituted alkenes. It should also be noted that DGs were only designed as auxiliary groups to enhance reactivity



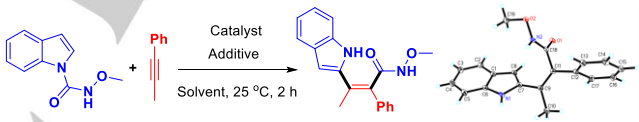
Scheme 2. TM-catalyzed DG chelation-assisted C−H alkenylation with alkynes.

as well as regioselectivity and stayed at their original locations in the abovementioned reactions. By contrast, the recently developed strategy of C–H alkenylation/DG migration cascades between aromatic substrates and alkynes constitutes an efficient method to assemble tetrasubstituted alkenes in a regio- and stereoselective manner (Scheme 2b).[9] Neverthless, the reported C–H alkenylation/DG migration cascades were mainly achieved through Cp*Co(III),[10] Cp*Rh(III)[11] and Cp*Ir(III)[12] catalysis, and reports via Ru catalysis are rare. To the best of our knowledge, only one elegant example on Ru(II)-catalyzed C–H alkenylation/DG migration for the synthesis of tetrasubstituted alkenes was reported very recently by Zhang's group.[13] However, this methodology was mostly focused on symmetrical alkynes, and unsatisfactory regioselectivities were observed when some representative unsymmetrical alkynes were employed, thus leading to a relatively limited scope of alkynes. Moreover, despite the remarkable advantages such as excellent stereoselectivity and high atom-economy, this method still shows some minor drawbacks such as the usage of excessive additives and the requirement of chromatography for the purification of products. Considering the low cost and outstanding catalytic performance of Ru catalysts in C–H activation,[14] and together with our interests in TM-catalyzed C−H functionalization[11d-g, 12, 15] and indole compound synthesis,[16] herein we report an efficient Ru(II)-catalyzed C–H alkenylation/DG migration cascade between *N*-carbamoyl indoles and alkynes for the regio- and stereoselective assembly of tetrasubstituted alkenes carrying the privileged indole substituent (Scheme 2c). Notably, the carbamoyl DG[17] is endowed with a dual role of auxiliary group and internal acylation reagent via C–N bond cleavage, which migrates onto the alkene moiety of the products to deliver tetrasubstituted α,β-unsaturated amides. Beneficial features of our protocol are not limited to improved substrate scope for unsymmetrical alkynes with excellent regioselectivities. Indeed, our method also avoids using excessive additives as well as chromatography in most cases, thus affording a convenient and practical approach for the synthesis of tetrasubstituted alkenes.

Results and Discussion

As shown in Table 1, initial screening experiments began with the reaction of *N*-methoxy-1*H*-indole-1-carboxamide **1aa** and 1-phenyl-1-propyne **2aa** in the green solvent EtOH[18] in the presence of 5 mol% of various catalysts and 1 equivalent of NaOAc as the additive at 25 °C for 2 h (entries 1-6). Among the catalysts tested, $MnBr(CO)_5$, $CoCp^*_2PF_6$, $NiCl_2(PPh_3)_3$, $RuCl_3$ and $Ru(acac)_3$ turned out to be ineffective but with the substrates recovered (entries 1-5). Gratifyingly, $[RuCl_2(p\text{-cymene})]_2$ could catalyze the C–H alkenylation/DG migration cascade highly stereo- and regioselectively, delivering the *cis*-adduct **3aa** with the indole moiety exclusively located at the less hindered position as the only isomer in a quantitative yield (entry 6). Of note, the tetrasubstituted alkene **3aa** precipitated out in EtOH as white solids and could be simply collected by filtration. The structure of **3aa** was unambiguously confirmed by X-ray crystallography. Then a variety of solvents were studied using $[RuCl_2(p\text{-cymene})]_2$ and NaOAc as the catalyst and additive, respectively (entries 7-13). Toluene, DCE, acetone and CH_3CN were also found to be suitable solvents, in which product **3aa** was still obtained with 81-96% yields (entries 7, 8, 10 and 12). While lower yields (30-49%) of **3aa** were observed in THF, 1,4-dioxane and DMF because of the incomplete consumption of the substrates (entries 9, 11 and 13). Therefore, the study of solvents disclosed that EtOH is the best choice. Next, a series of additives were investigated in EtOH (entries 14-19). KOAc and CsOAc were also proved to be effective additives, with which the desired product **3aa** was obtained in high yields (entries 14 and 15). While Na_2CO_3, K_2CO_3,

Table 1. Optimization of the reaction conditions[a]

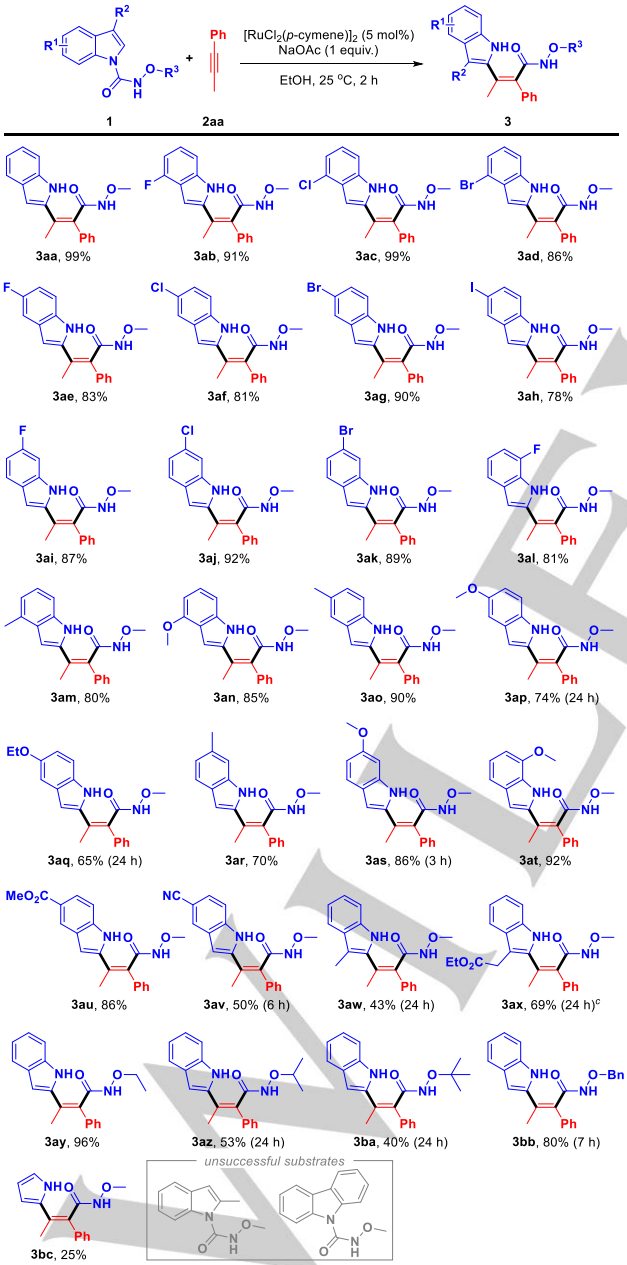


Entry	Catalyst	Additive	Solvent	Yield of **3aa** (%)[b]
1	$MnBr(CO)_5$	NaOAc	EtOH	0
2	$CoCp^*_2PF_6$	NaOAc	EtOH	0
3	$NiCl_2(PPh_3)_3$	NaOAc	EtOH	0
4	$RuCl_3$	NaOAc	EtOH	0
5	$Ru(acac)_3$	NaOAc	EtOH	<10
6	**$[RuCl_2(p\text{-cymene})]_2$**	**NaOAc**	**EtOH**	**99**
7	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	Toluene	81
8	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	DCE	93
9	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	THF	48
10	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	Acetone	95
11	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	dioxane	49
12	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	CH_3CN	96
13	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	DMF	30
14	$[RuCl_2(p\text{-cymene})]_2$	KOAc	EtOH	91
15	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	EtOH	92
16	$[RuCl_2(p\text{-cymene})]_2$	Na_2CO_3	EtOH	31
17	$[RuCl_2(p\text{-cymene})]_2$	K_2CO_3	EtOH	trace
18	$[RuCl_2(p\text{-cymene})]_2$	NaCl	EtOH	<5
19	$[RuCl_2(p\text{-cymene})]_2$	NH_4Cl	EtOH	0
20[c]	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	EtOH	73
21[d]	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	EtOH	79
22	$[RuCl_2(p\text{-cymene})]_2$	-	EtOH	trace
23	-	NaOAc	EtOH	0

[a]Reaction conditions: **1aa** (0.25 mmol), **2aa** (0.275 mmol), catalyst (5 mol%), additive (0.25 mmol), solvent (4.0 mL), 25 °C, 2 h. [b]Isolated yield. [c]$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) was used. [d]NaOAc (0.025 mmol) was used.

NaCl and NH_4Cl were found to be less effective or ineffective additives, with which the desired product **3aa** was obtained in less than 31% yields (entries 16-19). In addition, the amount of the catalyst and additive were investigated. Reducing the amount of $[RuCl_2(p\text{-cymene})]_2$ from 5 mol% to 2.5 mol% or NaOAc from 1 to 0.1 equivalent led to the incomplete conversion of the starting materials, thus resulting in a remarkable decrease in the yield (entries 20 and 21). At last, blank experiments, in which $[RuCl_2(p\text{-cymene})]_2$ or NaOAc was selectively removed, were performed (entries 22 and 23). The results showed no formation of the product **3aa** was observed in the presence of single catalyst or additive, clearly indicating the crucial catalytic role of the $[RuCl_2(p\text{-cymene})]_2$/NaOAc system. It should be noted that no regio- or stereoisomer of **3aa** was obtained in any reaction, indicating the excellent regio- and stereoselectivity of this C–H alkenylation/DG migration cascade.

Table 2. Substrate scope of *N*-alkoxyl-1*H*-indole-1-carboxamides.[a,b]



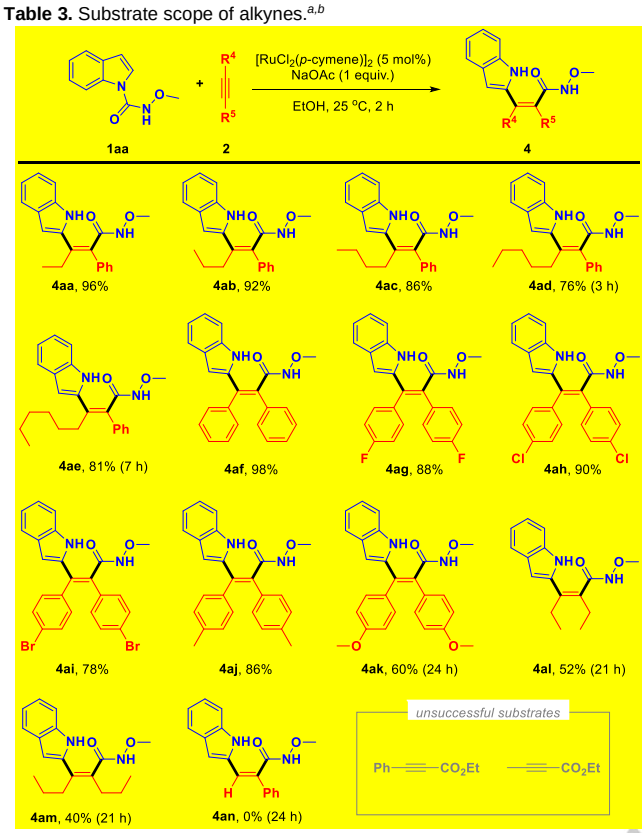
[a]Reaction conditions: **1** (0.25 mmol), **2aa** (0.275 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), NaOAc (0.25 mmol), EtOH (4.0 mL), 25 °C, 2 h. [b]Isolated yield. [c]$[RuCl_2(p\text{-cymene})]_2$ (10 mol%) and NaOAc (0.5 mmol) were used.

After determining the optimal reaction conditions, the scope of *N*-alkoxyl-1*H*-indole-1-carboxamides was explored at first (Table 2). In general, the catalytic system consisting of $[RuCl_2(p\text{-cymene})]_2$/NaOAc exhibited an outstanding catalytic performance in catalyzing the C–H alkenylation/DG migration of a broad range of indoles **1** carrying diverse substituents at R^1, R^2 and R^3, providing the desired tetrasubstituted alkene products **3** with excellent regio- and stereoselectivity in good to quantitative yields. For example, indoles having halogens (F, Cl, Br, I) at C4-C7 position of the indole ring reacted well with **2aa** to give the corrspongding products **3ab**-**3al** in high yields (78-99%). Likewise, electron-rich indoles carrying Me, MeO or EtO at C4-C7 position of the indole ring could smoothly add to **2aa** to yield products **3am**-**3at** in good to high yields (65-92%). Electron-deficient indoles carrying CO_2Me or CN at C5 position of the indole ring also underwent this reaction with **2aa** to produce products **3au** and **3av** in 86% and 50% yields, respectively. In addition, indoles bearing substituents at C3 position of the indole ring could also participate in this transformation, although lower yields (43-69%) of the desired products **3aw** and **3ax** were observed. This may be attributed to the steric hindrance caused by the C3 substituents. Moreover, indoles possessing various alkyl groups at R^3 were also proved to be suitable substrates, which were converted into the corresponding products **3ay**-**3bb** in moderate to excellent yields (40-96%). A *N*-carbamoyl pyrrole substrate was also tolerated, albeit with a lower yield (25%) of the desired product **3bc**. Attempts to achieve the cascade reaction at the C7 position of 2-Me substituted indole substrate or C1 position of carbazole substrate turned out to be unsuccessful, but with the starting materials recovered. It is noteworthy that the indicated products in Table 2 were obtained as single isomers in all cases, suggesting the excellent regio- and stereoselectivity of this reaction.

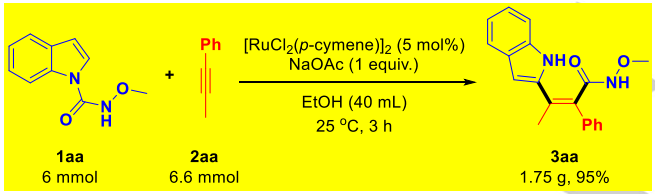
Next, the generality of this transformation with respect to the alkyne partner was investigated (Table 3). Overall, a broad range of unsymmetrical and symmetrical alkynes could participate in this cascade reaction without obvious deleterious effects on the reaction efficiency. For instance, a diversity of unsymmetrical alkyl/phenyl alkynes engaged in this reaction successfully to provide the desired products **4aa**-**4ae** with excellent regio- and stereoselectivities in high yields (76-96%). By contrast, unsymmetrical alkynes such as ethyl 3-phenylpropiolate and ethyl but-2-ynoate failed to react with **1aa** but with the starting materials untouched. It is delightful to find that steric hindered symmetrical diarylalkynes carrying halogens (F, Cl, Br) and electron-donating groups (Me, MeO) on the benzene ring could be converted into the corresponding products **4af**-**4ak** in good to high yields (60-98%) with perfect *cis*-stereoselectivity. Symmetrical dialkylalkynes also underwent this reaction uneventfully to give the desired *cis*-adducts **4al**-**4am** exclusively in moderate yields (40-52%). By contrast, phenylacetylene failed to interact with **1aa** to give the corresponding product **4an** under standard conditions even after a prolonged time, but with the recovery of the starting materials, suggesting that this reaction is not compatible with terminal alkynes. We speculated that terminal alkynes might interact with the ruthenium catalyst to form the Ru(II)-acetylide species,[19] which prevented the formation of the desired product.

To further prove the practicality and efficiency of this method, a gram-scale reaction between **1aa** and **2aa** was conducted

Table 3. Substrate scope of alkynes.[a,b]



[a]Reaction conditions: **1aa** (0.25 mmol), **2** (0.275 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), NaOAc (0.25 mmol), EtOH (4.0 mL), 25 °C, 2 h. [b]Isolated yield.



Scheme 3. Gram-scale experiments.

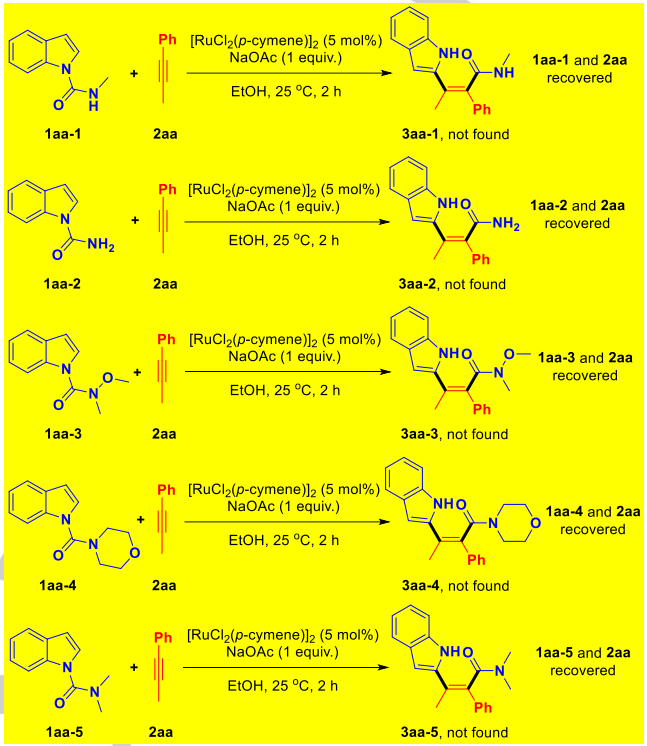
(Scheme 3). Impressively, the desired product **3aa**, which precipitated out when reaction finished, was still prepared in an excellent yield (95%), suggesting the potential industrial application of this transformation.

Additionally, a preliminary biological screening of the obtained tetrasubstituted alkenes **3** and **4** to evaluate their inhibitory activities against human cancer cell line HL60 led to the identification of hit compound **3av**, which showed a good inhibition activity with an IC_{50} value of 7.4 μM (Table 4). This further highlights the advantages and potential applications of this methodology.

Table 4. Antiproliferative activities of compounds **3aq**, **3au** and **3av** against human cancer cell line HL60.

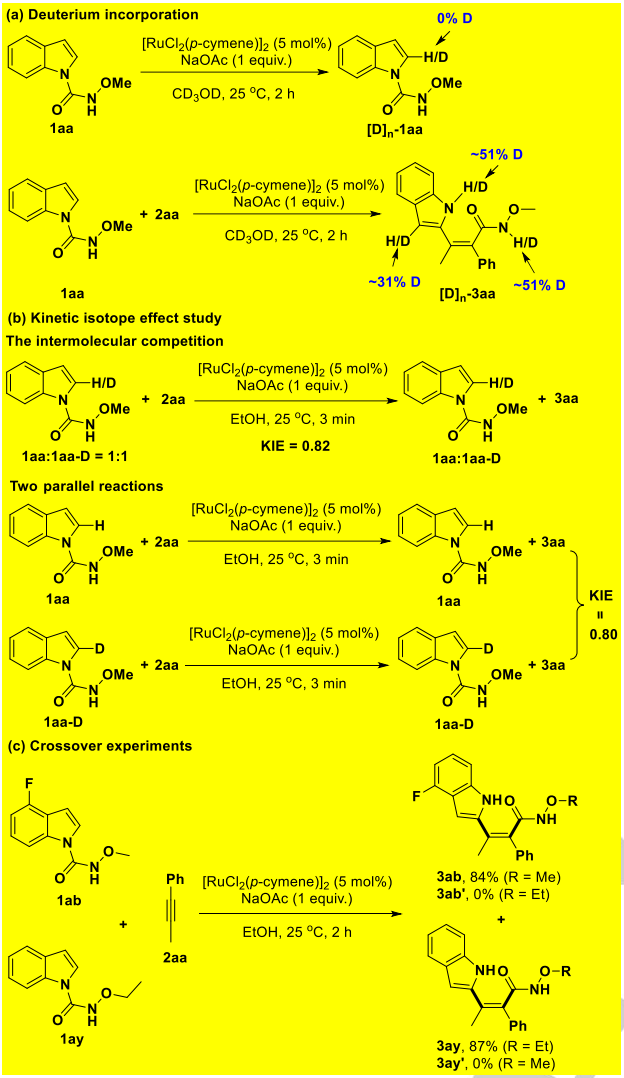
Compound	IC_{50} ± SD (μM)
3aq	>100
3au	>100
3av	7.4 ± 1.7

To investigate the role of DG, five 1*H*-indole-1-carboxamides carrying different substituents at the amide nitrogen were tested as the substrates (Scheme 4). The results show that the alkoxyl groups like OMe and the free hydrogen tethered to the amide nitrogen are both crucial for the title transformation.



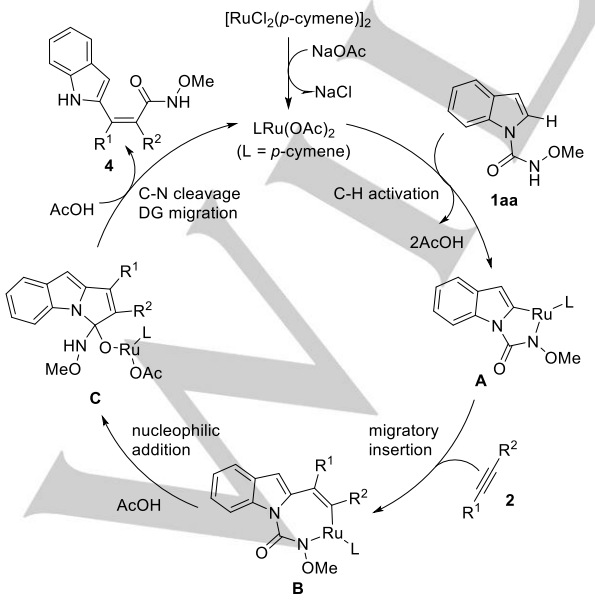
Scheme 4. Investigation of the directing groups.

Mechanistic studies were performed to probe the reaction mechanism. At first, isotope labeling experiments were carried out (Scheme 5a). When indole **1aa** was treated with CD_3OD under standard conditions in the absence of alkyne **2aa**, no deuterium incorporation at C2 position of indole **1aa** was observed. This suggests the irreversible nature of the C–H bond cleavage. In addition, treatment of **1aa** in CD_3OD under standard conditions in the presence of alkyne **2aa** resulted in deuterated **3aa** with 51%, 31% and 51% deuteration at the indole N1, indole C3 and amide N positions, respectively. This deuteration results may be attributed to the H-D exchange between the desired product **3aa** and CD_3OD. Subsequently, kinetic isotope effect (KIE) study was also conducted (Scheme 5b). Two low KIE values of 0.82 and 0.80 obtained by intermolecular competition experiments and two parallel reactions, respectively, indicate that the C–H bond cleavage step is unlikely to be rate-limiting. Additionally, no crossover products of the carbamoyl DGs were observed when we mixed equimolar **1ab** and **1ay** with **2aa** under the standard reaction conditions (Scheme 5c), indicating that the migration of the DG is likely to proceed in an intramolecular manner.



Scheme 5. Mechanistic studies.

On the basis of mechanistic studies and literature reports,[10-13] a plausible reaction mechanism was proposed in Scheme 6. At first, the ligand exchange between $[RuCl_2(p\text{-cymene})]_2$ and NaOAc yields the active catalyst $Ru(OAc)_2(p\text{-cymene})$, which activates indole **1aa** to form the five-membered ruthenacycle **A**. The following regioselective coordination and migratory insertion of the alkyne into the Ru–C bond of ruthenacycle **A** give intermediate **B**. Then, the intramolecular nucleophilic addition of Ru–C bond to the carbonyl group occurs to afford intermediate **C**, which undergoes C–N bond cleavage and protonation to deliver the desired tetrasubstituted alkenes with the regeneration of the active ruthenium catalyst.



Scheme 6. Proposed reaction mechanism.

Conclusion

In conclusion, we have achieved an efficient ruthenium(II)-catalyzed C–H alkenylation/DG migration between *N*-carbamoyl indoles and alkynes for the synthesis of tetrasubstituted alkenes. Notably, the carbamoyl DG is endowed with a dual role of auxiliary group and internal acylation reagent via C–N bond cleavage at room temperature. This protocol shows broad substrate scope, excellent regio- and stereoselectivity, good to excellent yields, high atom- and step-economy, good tolerance of functional groups, mild redox-neutral conditions and chromatography-free work-up in most cases. Further pharmacological studies of the tetrasubstituted alkenes bearing the privileged indole moiety are currently undergoing in our laboratory.

Acknowledgements

This research was supported by Zhejiang Provincial Natural Science Foundation of China (Grant No. LQ19B020003, LY21B020003), Jinhua Science and Technology Bureau (Grant No. 2021-3-150), Natural Science Foundation of Ningxia Province (Grant No. 2021AAC03389), State Key Laboratory of Drug Research (Grant No. SIMM2105KF-09), Start-up Funding from Jinhua Branch of Sichuan Industrial Institute of Antibiotics (Grant No. 1003), and Developing Funding from Jinhua Branch of Sichuan Industrial Institute of Antibiotics (Grant No. SIIAJH-202002, SIIAJH-202006).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: ruthenium • C–H alkenylation • directing group migration • cascade reaction • tetrasubstituted alkene

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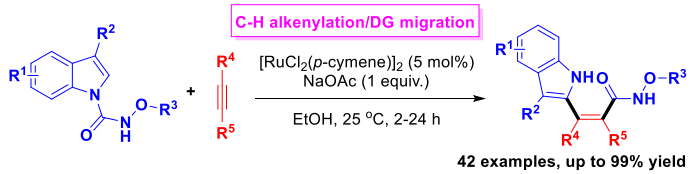

We have achieved the regio- and stereoselective synthesis of tetrasubstituted alkenes via ruthenium(II)-catalyzed C–H alkenylation/directing group migration between *N*-carbamoyl indoles and alkynes. This method shows broad substrate scope, excellent regio- and stereoselectivity, good to excellent yields, high atom- and step-economy, good tolerance of functional groups, mild redox-neutral conditions and chromatography-free work-up in most cases.