ARTICLE

Redox-neutral rhodium(III)-catalyzed divergent synthesis of tetrasubstituted 1,3-enynes and alkynylated benzofurans†

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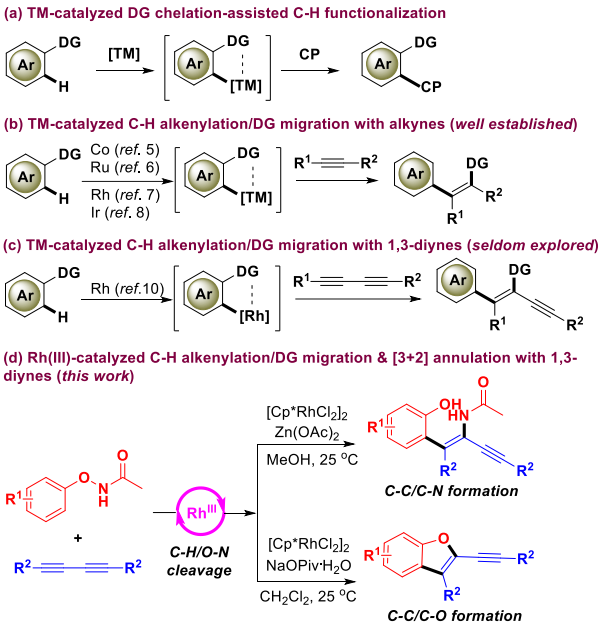
With the assistance of the acetamido directing group (DG), a rhodium-catalyzed C−H alkenylation/DG migration cascade for the synthesis of tetrasubstituted 1,3-enynes from *N*-phenoxyacetamides and 1,3-diynes has been achieved in this work. Alternatively, a rhodium-catalyzed [3+2] annulation for the synthesis of alkynylated benzofurans from the same set of substrates has also been achieved by simply changing the reaction conditions. This work highlights the tunable divergent synthesis of valuable compounds triggered by C−H activation.

Introduction

Transition-metal (TM)-catalyzed C−H functionalization assisted by directing groups (DGs) has become a powerful tool for the efficient and straightforward construction of carbon–carbon/heteroatom bonds in recent decades.[1] Initially, DGs are designed as auxiliary groups, which coordinate with TM and then help to activate the *ortho*-C−H bond to give the active nucleophilic metallacycle that couples with diverse coupling partners (CPs) (Scheme 1a).[2] Thus, DGs usually stay at their original positions when reactions complete in most cases or further undergo intramolecular annulation *in situ* in some cases.[3] However, it should be noted that the chemical traces of DGs may not be desired in the products and may block further transformations, and extra steps are often needed to disconnect them, thus leading to poor atom- and step-economy. Apparently, further synthetic merits and utilities of DGs would be provided if they could play more roles than auxiliary groups, such as migrating functional reagents if they could migrate onto the CPs after the step of C−H functionalization, thus achieving excellent step- and atom-economy and simultaneously increasing the diversity of the products. It is quite fascinating but also challenging to achieve the migration of DGs, mainly because of the challenge in identifying suitable substrates carrying a matching DG which has a dual role of auxiliary group and migrating functional reagent. Nevertheless, the synthetic



Scheme 1 TM-catalyzed C−H alkenylation/DG migration with alkynes or 1,3-diynes.

community has made their pioneering efforts in developing C−H functionalization/DG migration cascades.[4] In particular, the C−H alkenylation/DG migration with alkynes *via* Co(III),[5] Ru(II),[6] Rh(III)[7] and Ir(III)[8] catalysis has been well studied for the synthesis of tetrasubstituted alkenes (Scheme 1b). By contrast, the C−H alkenylation/DG migration with 1,3-diynes, which carry two adjacent carbon–carbon triple bonds, was seldom explored (Scheme 1c). This is mainly because of the inherent challenges of achieving high levels of chemo-, regio- and stereoselectivity in the step of migratory insertion of 1,3-diynes into the nucleophilic metallacycle, as well as the selectivity between mono- and difunctionalization of the two alkyne moieties.[9] To

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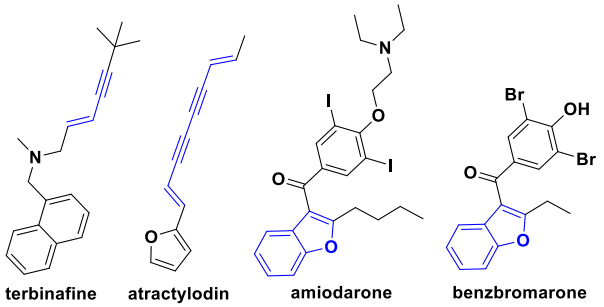


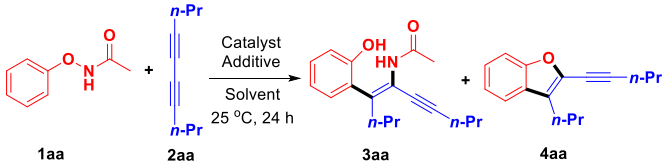
Fig. 1 Representative bioactive molecules carrying the 1,3-enyne or benzofuran scaffolds.

the best of our knowledge, only two examples involving the C–H alkenylation/DG migration with 1,3-diynes have been reported to date. Our group firstly disclosed a rhodium-catalyzed C–H alkenylation/carbamoyl DG migration between *N*-carbamoyl indoles and 1,3-diynes very recently.[10a] Soon afterwards, the group of Kanchupalli reported a similar cascade but focused on aromatic substituted 1,3-diynes.[10b] Based on our experience in functional group migration[11] and interest in C–H functionalization,[12] and inspired by the emerging strategy of DG migration,[4] herein we reveal a C–H alkenylation/acetamido DG migration between *N*-phenoxyacetamides[13] and 1,3-diynes for the synthesis of more challenging tetrasubstituted 1,3-enynes with the catalytic system of $[Cp^*RhCl_2]_2$/$Zn(OAc)_2$/MeOH (Scheme 1d). Of note, the acetamido DG not only works as an auxiliary group, but also acts as an internal amidation reagent that migrates onto the alkene unit of the products after the step of C–H alkenylation. Very interestingly, a [3+2] annulation for the assembly of C2-alkynylated benzofurans occurs instead from the same set of substrates with the catalytic system of $[Cp^*RhCl_2]_2$/$NaOPiv{\cdot}H_2O$/CH_2Cl_2. Considering the large presence of the 1,3-enyne and benzofuran scaffolds in bioactive molecules (Fig. 1),[14] our method is quite appealing as it allows the tunable divergent synthesis of the challenging tetrasubstituted 1,3-enynes and C2-alkynylated benzofurans *via* rhodium catalysis by simply switching the reaction conditions. This protocol features complexity- and diversity-generation and tunable product selectivity.

Results and discussion

N-phenoxyacetamide **1aa** and deca-4,6-diyne **2aa** were used as model substrates to optimize the reaction conditions (Table 1).

Table 1 Optimization of the reaction conditions[a]

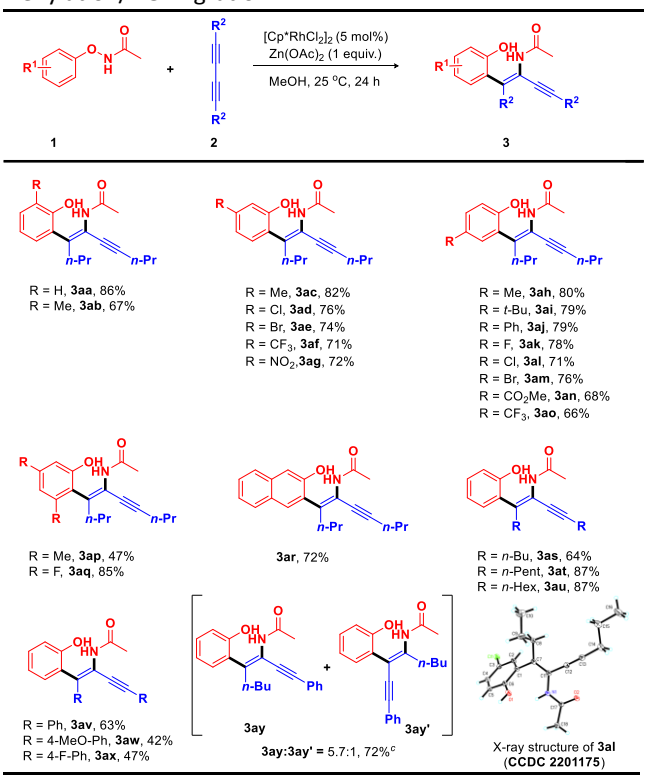


Entry	Catalyst	Additive	Solvent	Yield of **3aa** (%)[b]	Yield of **4aa** (%)[b]
1	$MnBr(CO)_5$	CsOAc	MeOH	0	0
2	$Pd(OAc)_2$	CsOAc	MeOH	0	0
3	$[Cp^*IrCl_2]_2$	CsOAc	MeOH	0	<10
4	$[RuCl_2(p\text{-cym})]_2$	CsOAc	MeOH	0	0
5	$[Cp^*RhCl_2]_2$	CsOAc	MeOH	78	trace
6	$[Cp^*RhCl_2]_2$	CsOAc	Toluene	<10	33
7	$[Cp^*RhCl_2]_2$	CsOAc	CH_2Cl_2	0	40
8	$[Cp^*RhCl_2]_2$	CsOAc	1,4-dioxane	14	32
9	$[Cp^*RhCl_2]_2$	CsOAc	CH_3CN	41	<10
10	$[Cp^*RhCl_2]_2$	CsOAc	DMF	65	0
11	$[Cp^*RhCl_2]_2$	NaOAc	MeOH	71	trace
12	$[Cp^*RhCl_2]_2$	KOAc	MeOH	69	trace
13	**$[Cp^*RhCl_2]_2$**	**$Zn(OAc)_2$**	**MeOH**	**86**	**trace**
14	$[Cp^*RhCl_2]_2$	Na_2CO_3	MeOH	70	0
15	$[Cp^*RhCl_2]_2$	NaOH	MeOH	59	0
16	$[Cp^*RhCl_2]_2$	$NaOPiv{\cdot}H_2O$	MeOH	71	trace
17	$[Cp^*RhCl_2]_2$	KF	MeOH	57	trace
18	$[Cp^*RhCl_2]_2$	NaOAc	CH_2Cl_2	<10	40
19	$[Cp^*RhCl_2]_2$	KOAc	CH_2Cl_2	<10	39
20	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	CH_2Cl_2	21	18
21	$[Cp^*RhCl_2]_2$	$NaHCO_3$	CH_2Cl_2	14	43
22	$[Cp^*RhCl_2]_2$	NaOH	CH_2Cl_2	45	trace
23	**$[Cp^*RhCl_2]_2$**	**$NaOPiv{\cdot}H_2O$**	**CH_2Cl_2**	**trace**	**63**

[a] Reaction conditions: **1aa** (0.25 mmol), **2aa** (0.275 mmol), catalyst (5 mol%), additive (0.25 mmol), solvent (4.0 mL), 25 °C, 24 h. [b] Isolated yields.

At first, substrates **1aa** and **2aa** were treated with various metal catalysts in MeOH at 25 °C for 24 h employing CsOAc as the additive (entries 1-5). To our delight, $[Cp^*RhCl_2]_2$ could catalyze the C–H alkenylation/DG migration highly regio- and stereoselectively (entry 5), providing the *cis*-adduct **3aa** with the phenyl moiety exclusively located at the less hindered position as the only isomer in a good yield (78%). Then, with $[Cp^*RhCl_2]_2$ and CsOAc as the catalyst and additive, respectively, diverse solvents were screened. Very interestingly, the C–H alkenylation/DG migration product **3aa** was found to be preferred in polar solvents such as CH_3CN, MeOH, EtOH and DMF, while the [3+2] annulation product **4aa** was favoured instead in nonpolar or medium polar solvents such as Toluene, CH_2Cl_2, DCE, THF, acetone and 1,4-dioxane (entries 6-10).[15] Of note, MeOH was proved to be the best choice for the exclusive production of **3aa** with 78% yield, while CH_2Cl_2 was found to be the most suitable solvent for the selective preparation of **4aa** with 40% yield. Subsequently, a series of additives were screened in MeOH to further improve the yield of product **3aa** (entries 11-17), and $Zn(OAc)_2$ turned out to be the best additive, with which product **3aa** was isolated in 86% yield exclusively (entry 13).[16] Similarly, an investigation of various additives in CH_2Cl_2 (entries 18-23) revealed that NaOPiv·H_2O was the optimal additive, with which product **4aa** was obtained selectively in 63% yield (entry 23).[17] Finally, blank experiments showed that both the catalyst and additive are crucial for the title C–H alkenylation/DG migration and [3+2] annulation (entries 15-18, Table S1).

Table 2 Substrate scope of the Rh(III)-catalyzed C–H alkenylation/DG migration[a,b]

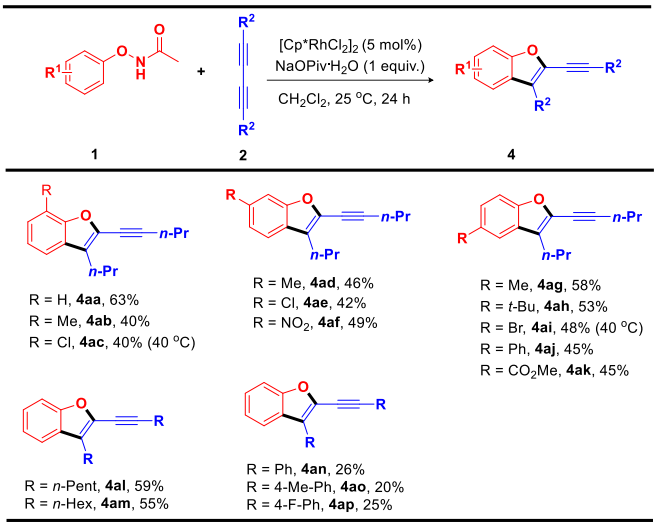


[a] Reaction conditions: **1** (0.25 mmol), **2** (0.275 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $Zn(OAc)_2$ (0.25 mmol), MeOH (4.0 mL), 25 °C, 24 h. [b] Isolated yields. [c] Combined yield.

With the optimal reaction conditions identified, we explored the substrate scope of the Rh(III)-catalyzed C–H alkenylation/DG migration (Table 2). In general, a broad range of *N*-phenoxyacetamides bearing diverse substituents at R^1 could react with 1,3-diynes carrying various substituents at R^2 to give the desired tetrasubstituted 1,3-enynes with excellent regio- and stereoselectivity in good to high yields. At first, the scope of *N*-phenoxyacetamides with **2aa** as the model coupling partner was explored. The reaction of *N*-phenoxyacetamide carrying a Me group at the *ortho*-position worked well to provide product **3ab** with a good yield (67%). The reactions of *N*-phenoxyacetamides having electron-donating group (Me), halogens (Cl, Br) or electron-withdrawing groups (CF_3, NO_2) at the *meta*-position took place smoothly at the less hindered position irrespective of the electronic nature of the substituents, affording products **3ac-3ag** in 71-82% yields. Likewise, *N*-phenoxyacetamides possessing electron-donating groups (Me, *t*-Bu), halogens (F, Cl, Br) or electron-withdrawing groups (Ph, CO_2Me, CF_3) at the *para*-position could also undergo this reaction to give products **3ah**-**3ao** in 66-80% yields. Of note, the structure of compound **3al** was unambiguously confirmed by X-ray crystallography.[18] In addition, despite of the steric hindrance, 3,5-*di*-Me and 3,5-*di*-F substituted *N*-phenoxyacetamides were also converted into the corresponding products **3ap** and **3aq** in 47% or 85% yields, respectively. To our delight, this transformation was compatible with *N*-(naphthalen-2-yloxy)acetamide, which underwent the reaction at the less hindered position to produce product **3ar** in 72% yield. Then, the scope of 1,3-diynes was examined with **1aa** as the reaction partner. For example, the reactions of symmetrical 1,3-diynes bearing alkyl groups (*n*-Bu, *n*-Pent, *n*-Hex) happened successfully to assemble products **3as-3au** in 64-87% yields. Similarly, this reaction could also be extended to symmetrical 1,3-diynes carrying aryl groups, which reacted with **1aa** to give products **3av-3ax** in 42-63% yields. A representative unsymmetrical alkyl/aryl 1,3-diyne, namely octa-1,3-diyn-1-ylbenzene, was also converted into the desired product **3ay**, albeit with a slight amount of regioisomer **3ay'**. It is worth noting that products **3aa-3ax** were obtained as single isomers, indicating the exclusive regio- and stereoselectivity of this Rh(III)-catalyzed C–H alkenylation/DG migration.

Next, the scope of the Rh(III)-catalyzed [3+2] annulation was checked (Table 3). Overall, various *N*-phenoxyacetamides bearing substituents at R^1 and 1,3-diynes carrying substituents at R^2 turned out to be suitable substrates, and the desired benzofurans were prepared in moderate to good yields with excellent regioselectivity. For instance, the reactions of non-substituted or *ortho*-substituted *N*-phenoxyacetamides with **2aa** took place smoothly to afford products **4aa**-**4ac** in 40-63% yields. Notably, *meta*-substituted *N*-phenoxyacetamides could undergo this reaction with **2aa** highly regioselectively at the less hindered position irrespective of the electronic nature of the substituents, delivering products **4ad**-**4af** in 42-49% yields. As expected, the reactions of *para*-substituted *N*-phenoxyacetamides with **2aa** occurred smoothly to furnish products **4ag**-**4ak** in 45-58% yields. With respect to 1,3-diynes,

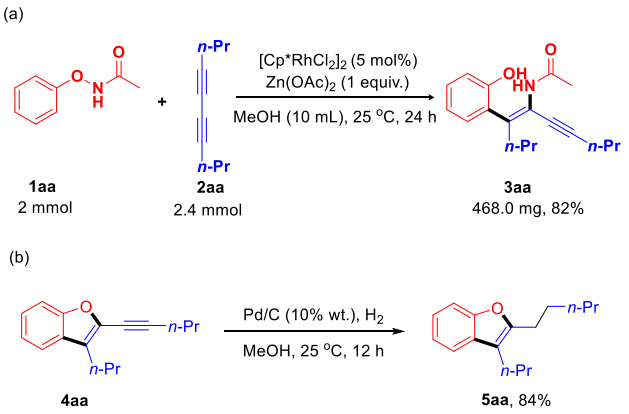
Table 3 Substrate scope of the Rh(III)-catalyzed [3+2] annulation[a,b]



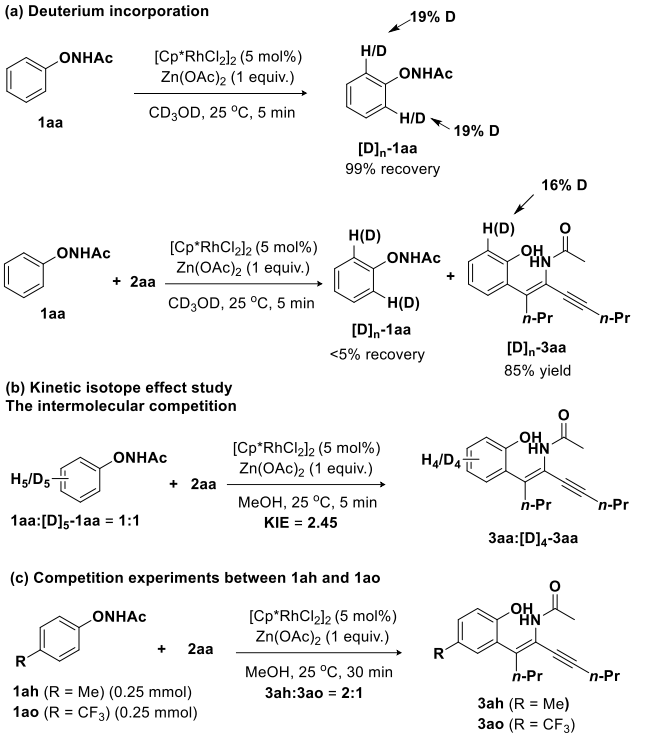
[a] Reaction conditions: **1** (0.25 mmol), **2** (0.275 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $NaOPiv{\cdot}H_2O$ (0.25 mmol), CH_2Cl_2 (4.0 mL), 25 °C, 24 h. [b] Isolated yields.

representative symmetrical 1,3-diynes possessing alkyl groups or aryl groups could be converted into products **4al-4ap** in 20-59% yields. It is noteworthy that all the indicated products showed in Table 3 were observed as single regioisomers, suggesting the excellent regioselectivity of this Rh(III)-catalyzed [3+2] annulation.

To further prove the synthetic application of this methodology, the Rh(III)-catalyzed C–H alkenylation/DG migration between **1aa** and **2aa** was scaled up (Scheme 2a). Impressively, the corresponding product **3aa** was still obtained with a comparable yield (82%) as the small-scale reaction, indicating the potential industrial application of this reaction. In addition, products **3** and **4** could also undergo further downstream transformations. For example, the hydrogenation of the alkyne moiety of product **4aa** afforded compound **5aa** in 84% yield (Scheme 2b). Additionally, a preliminary biological screening of the obtained tetrasubstituted 1,3-enynes **3** and alkynylated benzofurans **4** to evaluate their inhibitory activities against human cancer cell lines A549 and HL-60 was also carried



Scheme 2 Synthetic applications.

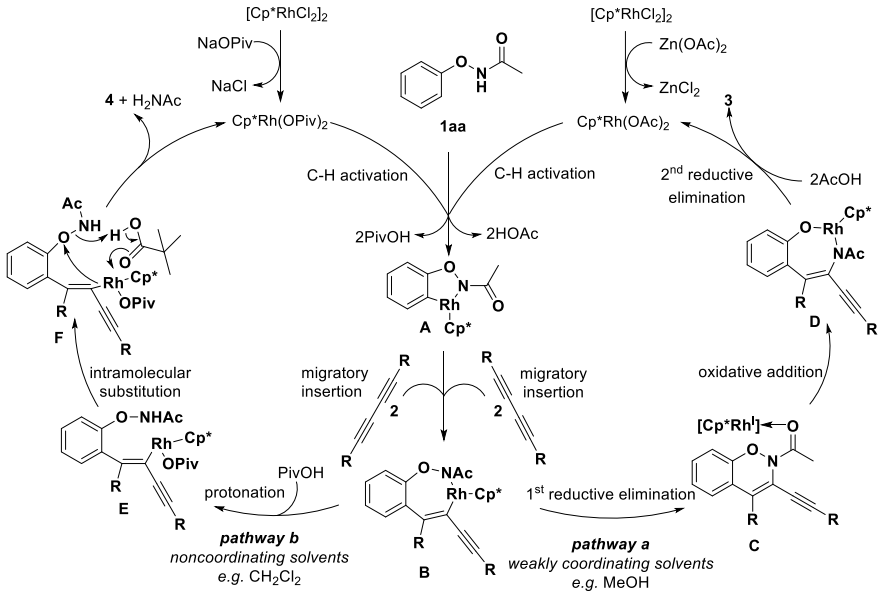


Scheme 3 Mechanistic studies.

out. Unfortunately, most compounds showed poor inhibition rates at the concentration of 10 uM (Table S2 and S3, Supporting Information).

To probe the reaction mechanism, a series of mechanistic studies were performed. Deuterium incorporation experiments were conducted at first (Scheme 3a). Treating **1aa** in CD_3OD under standard conditions for 5 minutes resulted in 19% deuteration at the *ortho*-position. Additionally, the reaction of **1aa** and **2aa** in CD_3OD under the same reaction conditions gave deuterated **3aa** with 16% deuteration at the *ortho*-position of the hydroxyl group. These results suggested the step of C–H bond cleavage is reversible. Besides, the kinetic isotope effect (KIE) study through intermolecular competition experiments gave a KIE value of 2.45, suggesting the step of the C–H bond cleavage could be the rate-limiting step (Scheme 3b). At last, intermolecular competition experiments between electron-rich *N*-phenoxyacetamide **1ah** and electron-deficient *N*-phenoxyacetamide **1ao** resulted in a ratio of 2/1 of the corresponding products **3ah/3ao** (Scheme 3c), indicating electron-rich *N*-phenoxyacetamides were favoured.

Based on the preliminary mechanistic studies and literature reports,[13a,19] a plausible reaction mechanism was proposed in Scheme 4. At first, DG-assisted C–H activation at the *ortho*-position occurs to give rhodacycle **A**. The following regioselective migratory insertion of the 1,3-diynes into the Rh–C bond of rhodacycle **A** gives intermediate **B**. The product selectivity in different solvents could be explained by the coordinating ability of the solvents. On the one hand, intermediate **B** could be stabilized by weakly coordinating solvents (*e.g.* MeOH), which may coordinate with the rhodium to form an 18-electron species. In this case, intermediate **B** undergoes a sequential 1st reductive elimination/oxidative



Scheme 4 Proposed reaction mechanism.

addition/2nd reductive elimination to provide tetrasubstituted 1,3-enynes **3** with the regeneration of the rhodium catalyst (pathway a). On the other hand, when the reaction is performed in noncoordinating solvents (*e.g*. CH_2Cl_2), intermediate **B** prefers to undergo protonation to provide intermediate **E**, which subsequently undergoes an intramolecular substitution to deliver C2-alkynylated benzofurans **4** with the release of the rhodium catalyst (pathway b).

Conclusions

In conclusion, we have developed the tunable divergent synthesis of tetrasubstituted 1,3-enynes and alkynylated benzofurans *via* rhodium-catalyzed C−H alkenylation/DG migration and [3+2] annulation, respectively. This protocol is characterized by excellent regio- and stereoselectivity, excellent monofunctionalization over difunctionalization, broad substrate scope, good functional group tolerance, moderate to high yields, and mild redox-neutral conditions. The features of complexity- and diversity-generation and tunable product selectivity highlight the potential of this methodology in the synthesis of tetrasubstituted 1,3-enynes and alkynylated benzofurans. Further biological studies of these compounds are currently undergoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 For selected reviews, see: (*a*) F. Collet, R. H. Dodd and P. Dauban, *Chem. Commun.*, 2009, 5061−5074; (*b*) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev*., 2011, **40**, 5068−5083; (*c*) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res*., 2012, **45**, 814−825; (*d*) T. A. Ramirez, B. Zhao and Y. Shi, *Chem. Soc. Rev*., 2012, **41**, 931−942; (*e*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev*., 2012, **112**, 5879−5918; (*f*) J. Wencel-Delord and F. Glorius, *Nat. Chem*., 2013, **5**, 369−375; (*g*) A. Ros, R. Fernández and J. M. Lassaletta, *Chem. Soc. Rev*., 2014, **43**, 3229−3243; (*h*) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front*., 2015, **2**, 1107−1295; (*i*) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev*., 2017, **117**, 8754−8786; (*j*) Y. Park, Y. Kim and S. Chang, *Chem. Rev*., 2017, **117**, 9247−9301; (*k*) M. T. Mihai, G. R. Genov and R. J. Phipps, *Chem. Soc. Rev*., 2018, **47**, 149−171; (*l*) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, *Chem. Rev*., 2019, **119**, 2192–2452.

2 For selected reviews, see: (*a*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev*., 2010, **110**, 624−655; (*b*) N. Yoshikai, *Synlett* 2011, 1047–1051; (*c*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev*., 2012, **41**, 3651−3678; (*d*) L. Ackermann, *Acc. Chem. Res*., 2014, **47**, 281−295; (*e*) B. Zhao, Z. Shi and Y. Yuan, *Chem. Rec*., 2016, **16**, 886–896; (*f*) D. D. Subhedar, A. A. Mishra and B. M. Bhanage, *Adv. Synth. Catal*., 2019, **361**, 4149−4195; (*g*) G. Kuang, G. Liu, X. Zhang, N. Lu, Y. Peng, Q. Xiao and Y. Zhou, *Synthesis* 2020, **52**, 993–1006; (*h*) J. Zhang, X. Lu, C. Shen, L. Xu, L. Ding and G. Zhong, *Chem. Soc. Rev*., 2021, **50**, 3263–3314.

3 For selected reviews, see: (*a*) G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed*., 2013, **52**, 11726−11743; (*b*) M. Corbet and F. D. Campo, *Angew. Chem. Int. Ed*., 2013, **52**, 9896–9898; (*c*) X. Yang, G. Shan, L. Wang and Y. Rao, *Tetrahedron Lett*., 2016, **57**, 819−836; (*d*) J. Liu, G. Chen and Z. Tan, *Adv. Synth.*

Catal., 2016, **358**, 1174−1194; (*e*) Y. Kommagalla and N. Chatani, *Coord. Chem. Rev*., 2017, **350**, 117–135; (*f*) W. Ma, P. Gandeepan, J. Li and L. Ackermann, *Org. Chem. Front*., 2017, **4**, 1435−1467; (*g*) L. D. Caspers and B. J. Nachtsheim, *Chem. Asian J*., 2018, **13**, 1231–1247; (*h*) K. Ghosh, R. K. Rit, M. Shankar, K. Mukherjee and A. K. Sahoo, *Chem. Rec*., 2020, **20**, 1017–1042; (*i*) M. Kapoor, A. Singh, K. Sharma and M. H. Hsu, *Adv. Synth. Catal*., 2020, **362**, 4513–4542; (*j*) S. Rej, Y. Ano and N. Chatani, *Chem. Rev*., 2020, **120**, 1788–1887; (*k*) L. S. Fitzgerald and M. L. O'Duill, *Chem. Eur. J*., 2021, **27**, 8411–8436.

4 For a recent review and examples on C−H functionalization/DG migration, see: Y. Wu, C. Pi, Y. Wu and X. Cui, *Chem. Soc. Rev.*, 2021, **50**, 3677–3689, and references cited therein.

5 (*a*) H. Ikemoto, R. Tanaka, K. Sakata, M. Kanai, T. Yoshino and S. Matsunaga, *Angew. Chem. Int. Ed.*, 2017, **56**, 7156–7160; (*b*) K. Sakata, M. Eda, Y. Kitaoka, T. Yoshino and S. Matsunaga, *J. Org. Chem*., 2017, **82**, 7379–7387; (*c*) C. Zhu, R. Kuniyil, B. B. Jei and L. Ackermann, *ACS Catal*., 2020, **10**, 4444–4450; (*d*) X. Xu, L. Zhang, H. Zhao, Y. Pan, J. Li, Z. Luo, J. Han, L. Xu and M. Lei, *Org. Lett*., 2021, **23**, 4624–4629.

6 (*a*) M. Li, T.-Y. Yao, S.-Z. Sun, T.-X. Yan, L.-R. Wen and L.-B. Zhang, *Org. Biomol. Chem*., 2020, **18**, 3158–3163; (*b*) H. Mao, J. Chen, X. Zhang, N. Yu, Y. Lu and F. Zhao, *ChemistrySelect* 2022, **7**, e202200292.

7 (*a*) Y. Chen, D. Wang, P. Duan, R. Ben, L. Dai, X. Shao, M. Hong, J. Zhao and Y. Huang, *Nat. Commun*., 2014, **5**, 4610; (*b*) J.-L. Pan, P. Xie, C. Chen, Y. Hao, C. Liu, H.-Y. Bai, J. Ding, L.-R. Wang, Y. Xia and S.-Y. Zhang, *Org. Lett*., 2018, **20**, 7131–7136; (*c*) X. Wu, Y. Lu, J. Qiao, W. Dai, X. Jia, H. Ni, X. Zhang, H. Liu and F. Zhao, *Org. Lett*., 2020, **22**, 9163–9168; (*d*) F. Zhao, J. Qiao, Y. Lu, X. Zhang, L. Dai, X. Gong, H. Mao, S. Lu, X. Wu and S. Liu, *Org. Lett*., 2021, **23**, 5766−5771; (*e*) F. Zhao, Z. Zhou, Y. Lu, J. Qiao, X. Zhang, X. Gong, S. Liu, S. Lin, X. Wu and W. Yi, *ACS Catal*., 2021, **11**, 13921–13934; (*f*) X. Xu, C. Luo, H. Zhao, Y. Pan, X. Zhang, J. Li, L. Xu, M. Lei and P. J. Walsh, *Chem. Eur. J*., 2021, **27**, 8811–8821; (*g*) R. Mi, H. Chen, X. Zhou, N. Li, D. Ji, F. Wang, Y. Lan and X. Li, *Angew. Chem. Int. Ed*. 2022, **61**, e202111860.

8 S. Liu, H. Mao, J. Qiao, X. Zhang, Y. Lu, X. Gong, A. Jia, L. Gu, X. Wu and F. Zhao, *Asian J. Org. Chem*., 2021, **10**, 3308–3320.

9 D.-G. Yu, F. de Azambuja, T. Gensch, C. G. Daniliuc and F. Glorius, *Angew. Chem. Int. Ed*., 2014, **53**, 9650−9654.

10 (*a*) F. Zhao, X. Gong, Y. Lu, J. Qiao, X. Jia, H. Ni, X. Wu and X. Zhang, *Org. Lett*., 2021, **23**, 727−733; (*b*) S. Kumar, S. Nunewar, K. M. Usama, V. Kanchupalli, *Eur. J. Org. Chem*., 2021, 2223–2229.

11 F. Zhao, D. Zhang, Y. Nian, L. Zhang, W. Yang and H. Liu, *Org. Lett*., 2014, **16**, 5124–5127.

12 (*a*) F. Zhao, X. Jia, J. Zhao, C. Fei, L. Liu, G. Liu, D. Wang and F. Chen, *RSC Adv*., 2017, **7**, 25031–25040; (*b*) X. Jia, P. Li, X. Liu, J. Lin, Y. Chu, J. Yu, J. Wang, H. Liu and F. Zhao, *Molecules* 2019, **24**, 988; (*c*) H. Ni, X. Shi, Y. Li, X. Zhang, J. Zhao and F. Zhao, *Org. Biomol. Chem*., 2020, **18**, 6558–6563; (*d*) X. Wu, P. Li, Y. Lu, J. Qiao, J. Zhao, X. Jia, H. Ni, L. Kong, X. Zhang and F. Zhao, *Adv. Synth. Catal*., 2020, **362**, 2953–2960; (*e*) F. Zhao, J. Chen, J. Qiao, Y. Lu, X. Zhang, H. Mao, S. Lu, X. Gong, S. Liu, X. Wu and L. Dai, *Adv. Synth. Catal*., 2021, **363**, 4380−4389; (*f*) F. Zhao, J. Qiao, Y. Lu, X. Zhang, L. Dai, S. Liu, H. Ni, X. Jia, X. Wu and S. Lu, *J. Org. Chem*., 2021, **86**, 10591−10607; (*g*) H. Ni, Y. Li, X. Shi, Y. Pang, C. Jin and F. Zhao, *Tetrahedron Lett*., 2021, **68**, 152915.

13 For selected examples on TM-catalyzed C−H functionalization of *N*-phenoxyacetamides, see: (*a*) G. Liu, Y. Shen, Z. Zhou and X. Lu, *Angew. Chem. Int. Ed*., 2013, **52**, 6033–6037; (*b*) J. Zhou, J. Shi, Z. Qi, X. Li, H. E. Xu and W. Yi, *ACS Catal*., 2015, **5**, 6999–7003; (*c*) Z. Hu, X. Tong and G. Liu, *Org. Lett*., 2016, **18**, 1702–1705; (*d*) G. Zheng, Z. Zhou, G. Zhu, S. Zhai, H. Xu, X. Duan, W. Yi and X. Li, *Angew. Chem. Int. Ed*., 2020, **59**, 2890–2896; (e) L. Wu, L. Li, H. Zhang, H. Gao, Z. Zhou and W. Yi, *Org. Lett*., **2021**, *23*, 3844–3849.

14 (*a*) S. L. Iverson and J. P. Uetrecht, *Chem. Res. Toxicol*., 2001, **14**, 175–181; (*b*) A. L. K. Shi Shun and R. R. Tykwinski, *J. Org. Chem*., 2003, **68**, 6810–6813; (*c*) Z. Xu, S. Zhao, Z. Lv, L. Feng, Y. Wang, F. Zhang, L. Bai and J. Deng, *Eur. J. Med. Chem*., 2019, **162**, 266–276.

15 For information on the screening of more solvents, see entries 2-5 in Table S1 in Supporting Information.

16 For information on the screening of more additives in MeOH, see entries 6-9 in Table S1 in Supporting Information.

17 For information on the screening of more additives in CH_2Cl_2, see entries 10-14 in Table S1 in Supporting Information.

18 **CCDC 2201175** contains the supplementary crystallographic data for compound **3al**. These data can be also obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

19 (*a*) Y.-F. Yang, K. N. Houk and Y.-D. Wu, *J. Am. Chem. Soc*., 2016, **138**, 6861–6868; (*b*) X. Wang, A. Lerchen, T. Gensch, T. Knecht, C. G. Daniliuc and F. Glorius, *Angew. Chem. Int. Ed*., 2017, **56**, 1381–1384; (*c*) W. Yi, W. Chen, F.-X. Liu, Y. Zhong, D. Wu, Z. Zhou and H. Gao, *ACS Catal*., 2018, **8**, 9508–9519.

