View Article Online

# ChemComm

Chemical Communications

## Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: H. Huang, B. Gao, S. Zou, G. Yang and Y. Ding, *Chem. Commun.*, 2020, DOI: 10.1039/D0CC05362G.



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 <u>Terms & Conditions</u> and the <u>Ethical guidelines</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/chemcomm

### COMMUNICATION

Received 00th January 20xx, Accepted 00th January 20xx Enabled by Reactive Directing Group: Expedite Construction of Bridged Polycyclic Skeletons Bingjian Gao,<sup>a‡</sup> Suchen Zou,<sup>a‡</sup> Guoqing Yang,<sup>a</sup> Yongzheng Ding,<sup>a</sup> and Hanmin Huang<sup>a,b,c\*</sup>

Carbonylative Cycloaddition Between two Different Alkenes

DOI: 10.1039/x0xx00000x

www.rsc.org/

Published on 05 September 2020. Downloaded on 9/7/2020 4:19:49 AM

A novel palladium-catalyzed highly selective hydrocarbonylative cycloaddition reaction with two different alkenes in the presence of CO enabled by reactive direction-group is developed, which offers an efficient and convenient access to the lactone-containing bridged polycyclic compounds in high yield with high chemo- and stereoselectivities.

Olefins and CO are important feedstock chemicals in synthetic organic chemistry. Their abundance from the petrochemical refining and coal chemical industry has spurred the development of new methodologies for the efficient transformation of these simple materials. Transition-metalcatalyzed hydrocarbonylation reactions, transformations that mobilize the CO for elongation of the carbon chain and installing a versatile carbonyl functionality, have allowed for the upcycling of simple olefin feedstock into higher-order valuable carbonyl products.<sup>1,2</sup> In this context, there have been a large number of reports on the hydrocarbonylation of a single alkene with different nucleophiles, resulting in a fertile research field spanning a diverse range of chemical approaches to carbonyl compounds.<sup>2,3</sup> In particular, the direct sequential hydrocarbonylation/Heck reaction process by connecting two molecular of olefins via a carbonyl group represents an attractive approach to enones. Over the last three decades, studies on Pd-catalyzed dimerization various copolymerization of olefins with CO have been reported.<sup>4</sup> However, the carbonylative cross-coupling reaction taken place with two different alkenes and CO remains largely unexplored because of the inherent formidable challenges of controlling the chemoselectivity and regioselectivity (Scheme 1a). Moreover, the intermolecular Heck reaction initiated via the hydropalladation may also take place to compete with the desired carbonylation reaction. Therefore, the development of an efficient strategy to selectively assemble two different alkenes with CO is highly desirable but challenging.

**Scheme 1.** Palladium-catalyzed carbonylative cross-coupling with two alkenes

a: Problem in palladium-catalyzed cabonylative cross-coupling of alkenes



Recently, transition-metal-catalyzed C-H functionalization reactions assisted by chelation-groups have become useful and efficient approaches to delivering highly efficient transformations with high selectivity.<sup>5</sup> Notable progress has been achieved for site-selective reactions by using directing-groups, such as carboxylic acids,<sup>6a</sup> amides,<sup>6b</sup> ethers<sup>6c</sup> and ketones.<sup>6d</sup> Similarly, the chelation-assisted copolymerization of functionalized olefins with non-polar olefins has been successfully established and extensively investigated for the selective synthesis of functionalized polyethylenes (Scheme

<sup>&</sup>lt;sup>a.</sup> Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026, P. R. China. E-mail: <u>hanmin@ustc.edu.cn</u>.

<sup>&</sup>lt;sup>b.</sup> Center for Excellence in Molecular Synthesis of CAS, Hefei, 230026, P. R. China

 <sup>&</sup>lt;sup>c.</sup> State Key Laboratory of Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, P. R. China
 †Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x00x0000x

<sup>‡</sup>These authors contributed equally to this work

#### COMMUNICATION

1b).<sup>7</sup> The above results prompted us to envision that the chelation-assisted strategy would be competent for enhancing the selectivity of the transition-metal-catalyzed hydrocarbonylative coupling reactions taking place between two alkenes. However, the directing group itself in most of such C-H functionalization reactions and copolymerization reactions remains intact during the reactions and has to be removed or transformed in some cases, which leads to a lower atom- and step-economy.8 One way to circumvent this drawback is identifying a reactive directing group, which could not only be utilized as a directing group to enhance the selectivity, but also be incorporated into the desired product via a simple transformation. Aldehyde is a class of ubiquitously available and readily interconvertible functional group, which has proved to be a useful directing-group for transition-metal-catalyzed C-H functionalization reactions.9 Inspired by these results and in connection with our interests in hydrocarbonylation reactions,10 we herein report an unprecedented chelationassisted palladium-catalyzed carbonylative cycloaddition reaction with two alkenes and CO, in which the aldehydefunctionality contained in the alkene participated in the carbonylation reaction to form a lactone-containing dienophile, which enabled the following [4+2]-cycloaddition with another alkenes (Scheme 1c). This method offers an efficient solution for the highly selective cross-carbonylative coupling of olefins and the expedient synthesis of bicyclic [2.2.2] lactones, which are common structural motifs in numerous natural products.<sup>11-14</sup>

#### **Results and discussion**

Published on 05 September 2020. Downloaded on 9/7/2020 4:19:49 AM

Our investigation initiated by evaluating the reactivity and product profile of 2-vinylbenzaldehyde (1a) and styrene (2a) under CO atmosphere in the presence of  $[Pd(allyl)Cl]_2$  and NH<sub>4</sub>Cl. Extensive experimentation using this standard substrate (see ESI<sup>+</sup>) revealed a number of critical reaction parameters. In particular, no reaction occurred when bidentate phosphines were utilized as ligands. The observed no reaction may stem from that the palladium-complex ligated with a bidentate ligand cannot provide with coordination site to coordinate with aldehyde-functionality. Among the monophosphines that have been evaluated, the RuPhos exhibited the highest efficiency to provide the desired product 3aa with 84% isolated yield as well as excellent chemoselectivity and stereoselectivity.<sup>15</sup> The exceptionally high reactivity of RuPhos ligated catalyst might be attributed to the unique structure of the ligand which is capable of forming weak dative O-Pd interaction to stabilize the 3coordinate Pd.<sup>16</sup> The inverse electron demand Diels-Alder reaction and steric effect might be responsible for the result that only trace amount of homo-coupling product 3a was detected. In addition, product 3a was obtained in 89% isolated yield with an excellent stereoselectivity under the same reaction conditions when only 1a was utilized as a substrate (see ESI<sup>+</sup>).

With the optimized reaction conditions in hand, the scope of alkenes was studied first (Table 2). It appeared that the electronic nature of the *para* and *meta* substituents on the phenyl ring of the styrenes did not have a strong influence on the reactivity and selectivity. Both electron-rich and electron-

# Journal Name

poor styrenes are competent coupling partners for giving the desired products (3ab-3ak) in moderate to good vields (bip to 81% yield) with excellent selectivities (dr >20:1). With regard to the steric effect, more sterically hindered ortho-substituents generally reduce the yields. In addition, broad functional group compatibility was observed with the tolerance towards halide and alkyl ether. Besides the substituted styrenes, the 1vinylnaphthalene also gave the tandem product 3al in 56% yield. Prop-1-en-2-ylbenzene and (E)-prop-1-en-1-ylbenzene were also tested, giving the corresponding products (3am-3an) in good yields with good selectivities. Further broadening the substrate scope indicated the tandem reaction of 2vinylbenzaldehyde 1a with a series of 1,3-dienes and CO could also be achieved to give the desired adducts (3ao-3aq) in moderate to good yields. Unfortunately, only product 3a was detected when the simple aliphatic alkenes and electrondeficient alkenes, such as ethyl acrylate, diethyl maleate, were tested. It is impressive that cis-cyclooctene could participate in this reaction, in which the cross-coupling cycloaddition reaction occurred and the desired product **3ar** was obtained in 76% yield with excellent diastereoselectivities (dr >20:1). We speculated that the observed high reactivity might be attributed to the ring tension of cyclooctene. Noteworthily, the structures of products of endo-3aa, endo-3am and endo-3an were confirmed by X-ray single-crystal diffraction analysis.<sup>17</sup>

Table 2. Substrate Scope of Alkenes for Cross-annulation<sup>a</sup>



 $^a$  Reaction conditions: 1 (0.5 mmol), 2 (0.6 mmol), CO (20 atm), [Pd(allyl)Cl]\_2 (2.5 mol%), RuPhos (5.5 mol%), NH\_4Cl (5 mol%), anisole (1.0 mL), 120 °C, 12 h, isolated yield and in all case dr > 20:1.

To extend the applications of this reaction, a variety of substituted 2-vinylbenzaldehydes were then subjected to the standard reaction conditions by using styrene **2a** in the presence of CO (20 atm). Under the optimized reaction conditions, a series of 2-vinyl aryl aldehydes with electron-donating or -withdrawing substituents on the phenyl ring could react with styrene to give the corresponding products **3ba-3ia** in good yields with excellent diastereoselectivities (Table 3). Typical functional groups such as chloride, fluoride, methoxyl and alkyl were well-tolerated under the optimized reaction

Published on 05 September 2020. Downloaded on 9/7/2020 4:19:49 AM

#### Journal Name

conditions. Notably, no apparent steric effect or electronic effect was observed in these reactions. After successfully examining the tandem cross-coupling annulation reaction, the substrate scope of homo-annulation reactions was then explored. The corresponding *endo*-type bicyclo[2,2,2] lactones **3a-j** were obtained in good to excellent yields with excellent diastereoselectivities in all cases. The reaction was found to be marginally affected by the electronics and sterics of the substituents on the aromatic aldehydes as shown by the reaction of **1d** and **1j**, both of which gave relatively lower yields. Typical substituents such as the halide, alkyl, alkoxyl were tolerated. Additionally, 2-vinyl-1-naphthaldehyde afforded the product **3j** in 48% yield with excellent diastereoselectivities (dr >20:1). The solid structures of *endo*-**3a** and *exo*-**3a** were confirmed by X-ray single-crystal diffraction analysis.<sup>17</sup>

**Table 3.** Substrate Scope of 2-vinylbenzaldehydes for Crossannulation and Homo-annulation



<sup>*o*</sup> Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), CO (20 atm),  $[Pd(allyl)CI]_2$  (2.5 mol%), RuPhos (5.5 mol%), NH<sub>4</sub>Cl (5 mol%), anisole (1.0 mL), 120 °C, 12 h, isolated yield and in all case dr > 20:1. <sup>*b*</sup> **1** (0.8 mmol), **2** (0 mmol), isolated yield and in all case dr > 20:1.



Scheme 2. Synthetic utility

To demonstrate the synthetic potential of this reaction, a gram-scale reaction has been conducted to afford **3aa** and **3a** in 70% and 82% yields, respectively (see ESI<sup>+</sup>). The synthetic utility of the bridged polycyclic compounds was demonstrated by simple transformations (Scheme 2). Under the catalysis of Fe(OTf)<sub>3</sub>, the 1-methyl-2-phenylnaphthalene **4** could be obtained in 84% yield by heating of **3aa** in chlorobenzene at 130 °C via extrusion of CO<sub>2</sub> and aromatization. It is interesting to find that the product **3a** was converted to the 5-methyl-11H-

#### COMMUNICATION

benzo[b]fluorene via 7 the View Arttandem addition DOI/de Avar at 660538Ad decarboxylation/nucleophilic aromatization process under the same reaction conditions. These new transformations provide an alternative synthetic approach to biaryl compounds and polycyclic aromatic hydrocarbons (PAHs), which are important building blocks in material chemistry.<sup>18a</sup> Reducing the **3aa** with Et<sub>3</sub>SiH in the presence of the catalytic amount of InBr<sub>3</sub> afforded the bridged cyclic ether 5 in 70% yield.<sup>18b</sup> The aldehyde functionality could be facilely reduced to alcohol by NaBH<sub>4</sub>, providing product **8** in 92% yield. In addition, the lactone could be hydrolysed in the acidic condition to afford product 6 in 84% yield.<sup>18c</sup> Moreover, the product 3aa could be transferred to the product 9 in 90% yield by conventional Wittig reaction.<sup>18d</sup>

To get some insight into the reaction mechanism, a series of mechanism experiments were conducted. No product 3aa was obtained when 3a served as the substrate to react with 2a under the standard conditions. This result excluded the possibility that the adduct 3aa was generated from product 3a and suggested that the cycloaddition reaction was irreversible (see ESI<sup>+</sup>). The observed kinetic isotope effects ( $k_H/k_D = 1.04$ ) indicated that the carbon-hybridization change from sp<sup>2</sup> to sp<sup>3</sup> event of CH=O was most unlikely involved in the ratedetermining step (see ESI<sup>+</sup>). Further competition reaction with 1a, 2a, and MeOH under the standard reaction condition disclosed that the product 3aa was obtained as the major product, suggesting that aldehyde-functionality facilitated the hydrocarbonylation and enabled the high chemoselectivity (see ESI<sup>+</sup>). Kinetic analysis of the standard homo-annulation reaction of 1a under standard conditions was conducted. The reaction profile showed that producing the adduct 3a paralleled the consumption of 1a (see ESI<sup>+</sup>), which indicated that the intermediate produced from the hydrocarbonylation was quickly consumed in the catalytic system. The initial reaction rate investigation shows an induction period of ~35 min. We assumed that the induction period may originate from the generation of HPdCl species from the palladium precursor. Further kinetic experiments demonstrated a zero-order dependence on the pressure of CO and a first-order dependence on the concentration of both 1a and palladium catalyst (see ESI<sup>+</sup>). The kinetic results for each factor suggested that the hydropalladation of the alkene with palladium-hydride species is the rate-determining step of the tandem reaction, which is consistent with the KIE experiment.



Fig. 1. Plausible Reaction Mechanism

emcomm Accepted Manusc

#### Journal Name

On the basis of the above results and previous studies,<sup>10</sup> a tentative reaction pathway for this carbonylative cycloaddition reaction was proposed (Fig. 1). Initially, palladium hydride species II is formed via oxidative addition of NH<sub>4</sub>Cl to (RuPhos)Pd(0) I, which is formed in situ via reduction of Pd(II) with CO or phosphine ligand. The selective hydropalladation of 2-vinylbenzaldehyde with II under the assistance of aldehyde affords the benzylpalladium species III, which further reacts with CO to produce the intermediate IV. The subsequent reductive elimination of IV gives the intermediate V and regenerates the Pd(0) species. The transient benzopyran-2-one VI is then generated by deprotonation under the assistance of base, which undergoes [4+2]-cycloaddition with an alkene to give the desired product 3. Huckel calculations showed that the LUMO of VI has much larger coefficients at C-1 than at C-4, which lead to highly regioselectivity.15b, 18c

COMMUNICATION

In summary, we have designed and implemented a new and efficient strategy to realize an efficient palladium-catalyzed carbonylative cross-coupling reaction with two different alkenes and CO. With commercially available catalyst components, a variety of 2-vinyl aryl aldehydes and simple alkenes could be directly carbonylated to complex bridged polycyclic compounds in good to excellent yields. Remarkable chemo- and stereoselectivity were observed by using the aldehyde-functionality as the reactive directing group. The resulting bridged polycyclic products could be derivatized to useful synthons. Notably, this transformation proceeds in a 100% atom economy and builds a connection between a palladium-catalyzed hydrocarbonylation and cycloaddition. Mechanism studies suggest that the reactive aldehydefunctionality facilitates the hydrocarbonylation and enables the high chemoselectivity. We expect that these controllable hydrocarbonylation/cycloaddition processes will provide new routes to upcycle the simple olefin and CO feedstock into valuable carbonyl products with versatile uses. Further studies on substrate scope and mechanism are currently underway and will be reported in due course.

This research was supported by the National Natural Science Foundation of China (21790333, 21925111, 21672199 and 21702197).

#### **Conflicts of interest**

There are no conflicts to declare

#### Notes and references

- 1 S. Zhang, H. Neumann and M. Beller, *Chem. Soc. Rev.* 2020, **49**, 3187.
- 2 (a) P. Kalck and M. Urrutigoity, *Chem. Rev.*, 2018, 118, 3833;
  (b) X.-F. Wu, X. Fang, L. Wu, R. Jackstell, H. Neumann and M. Beller, *Acc. Chem. Res.* 2014, 47, 1041;
  (c) T. Kégl, Carbonylation of Alkenes and Dienes. In Modern Carbonylation Methods; pp. 161-198 (Wiley, 2008).
- (a) J. Yang, J. Liu, H. Neumann, R. Franke, R. Jackstell and M. Beller, *Science*, 2019, **366**, 1514; (b) D. Ding, G. Zhu, and X. Jiang, *Angew. Chem., Int. Ed.*, 2018, **57**, 9028; (c) A. Acerbi, C. Carfagna, M. Costa, R. Mancuso, B. Gabriele, and N. Della Ca', *Chem. Eur. J.* 2018, **24**, 4835.

- 4 (a) C. Pisano, G. Consiglio, A. Sironi and M. Moret, J. Chem. Soc., Chem. Commun., 1991, 421; (b) Mol Brookbarb Cr. Grammer, J. M. DeSimone and J. C. Barborak, J. Am. Chem. Soc., 1992, 114, 5894; (c) A. Nakamura, K. Munakata, S. Ito, T. Kochi, L. W. Chung, K. Morokuma and K. Nozaki, J. Am. Chem. Soc., 2011, 133, 6761; (d) X. F. Wu, H. Neumann and M. Beller, Chem. -Asian J., 2012, 7, 1199; (e) H. Heeres, A. J. Minnaard, B. Hessen and H. J. Heeres, Org. Process Res. Dev., 2012, 16, 400; (f) W. Chang, J. Dai, J. Li, Y. Shi, W. Ren and Y. Shi, Org. Chem. Front., 2017, 4, 1074; (g) H. Wang and X-F. Wu, J. Organomet. Chem., 2020, 910, 121134.
- 5 (a) J. R. Hummel, J. A. Boerth and J. A. Ellman, *Chem. Rev.*, 2017, **117**, 9163; (b) C. Sambiagio, D. Schonbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnurch, *Chem. Soc. Rev.*, 2018, **47**, 6603; (c) P.Gandeepan and L. Ackermann, *Chem*, 2018, **4**, 199
- 6 (a) R. Giri and J.-Q. Yu, J. Am. Chem. Soc., 2008, 130, 14082;
  (b) M. Wasa, K. M. Engle and J.-Q. Yu, J. Am. Chem. Soc., 2010, 132, 3680;
  (c) A. Iglesias, R. Alvarez, A. R. de Lera and K. Muniz, Angew. Chem., Int. Ed., 2012, 51, 2225;
  (d) C. P. Lenges and M. Brookhart, J. Am. Chem. Soc., 1993, 121, 6616.
- 7 (a) H. Yasuda, R. Nakano, S. Ito and K. Nozaki, *J. Am. Chem. Soc.*, 2018, 140, 1876; (b) C. Tan and C. Chen, *Angew. Chem., Int. Ed.*, 2019, 131, 7268.
- 8 F. Zhang and D. R. Spring, *Chem. Soc. Rev.*, 2014, **43**, 6906.
- 9 (a) K. Padala and M. Jeganmohan, Org. Lett., 2012, 14, 1134;
  (b) C. Liu, M. Liu, J. Sun, C. Li and L. Dong, Org. Chem. Front., 2018, 5, 2115; (c) J. Yin, M. Tan, D. Wu, R. Jiang, C. Li and J. You, Angew. Chem., Int. Ed., 2017, 56, 13094; (d) X. Liu, G. Li, F. Song and J. You, Nat Commun., 2014, 5, 5030; (e) R. Santhoshkuma, S. Mannathan and C. H. Cheng, J. Am. Chem. Soc., 2015, 137, 16116.
- 10 (a) B. Gao, G. Zhang, X. Zhou and H. Huang, *Chem. Sci.*, 2018, 9, 380; (b) G. Zhang, B. Gao and H. Huang, *Angew. Chem., Int. Ed.*, 2015, 54, 7657; (c) X. Zhou, A. Chen, W. Du, Y. Wang, Y. Peng and H. Huang, *Org. Lett.*, 2019, 21, 9114; (d) S. Zou, B. Gao, Y. Huang, T. Zhang and H. Huang, *Org. Lett.*, 2019, 21, 6333; (e) J. Li, S. Wang, S. Zou and H. Huang, *Commun. Chem*, 2019, 2, 14; (f) Y. Hu and H. Huang, *ACS Catal.*, 2016, 6, 6785.
- 11 N. Uchiyama, F. Kiuchi, M. Ito, G. Honda, Y. Takeda, O. K. Khodzhimatov and O. A. Ashurmetov, *Tetrahedron*, 2006, 6, 4355.
- 12 Y. Y. Fan, J. B. Xu, H. C. Liu, L. S. Gan, J. Ding, and J. M. Yue, *J. Nat. Prod.*, 2017, **80**, 3159.
- 13 K.-C. Hsu, J.-M. Fang and Y.-S. Cheng, J. Nat. Prod., 1995, 58, 1592.
- 14 C. H. Brieskorn, A. Fuchs, J. B. Bredenberg, J. D. McChesney and E. Wenkert, *J. Org. Chem.*, 1964, **29**, 2293.
- 15 (a) K. Afarinkia, M. J. Bearpark and A. Ndibwami, J. Org. Chem., 2005, **70**, 1122; (b) D. A. Bleasdale and D. W. Jones, J. Chem. Soc., Perkin Trans., 1991, **1**, 1683.
- 16 (a) F. Pan, G. B. Boursalian and T. Ritter, *Angew. Chem., Int. Ed.*, 2018, **57**, 16871; (b) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461.
- 17 CCDC 1990497 (**3a**), 1991852 (*exo*-**3a**) 1990498 (**3aa**), 1990499 (**3am**) and 1990501 (**3an**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data\_request/cif.
- 18 (a) D. Wu, H. J. Ge, S. H. Liu and J. Yin, *RSC Adv.*, 2013, 3, 22727; (b) N. Sakai, T. Moriya and T. Konakahara, *J. Org. Chem.*, 2007, 72, 5920; (c) D. A. Bleasdale and D. W. Jones, *J. Chem. Soc., Chem. Commun.*, 1985, 1027; (d) A. Abengózar, P. García-García, D. Sucunza, A. Pérez-Redondo and J. J. Vaquero, *Chem. Commun.*, 2018, 54, 2467.

4 | J. Name., 2012, 00, 1-3

This journal is © The Royal Society of Chemistry 20xx

ChemComm

View Article Online DOI: 10.1039/D0CC05362G

 $R^2$ R<sup>2</sup> cat. [Pd] R<sup>'</sup> R<sup>3</sup> 120 °C, anisole Ar 36 examples up to 95% yield bicyclo[2,2,2] structure