CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Palladium-Catalyzed Tunable Carbonylative Synthesis of Enones and Benzofulvenes

Authors: Xiao-Feng Wu, Jin-Bao Peng, Fu-Peng Wu, and Anke Spannenberg

To be cited as: *Chem. Eur. J.* 10.1002/chem.201901530

Link to VoR: http://dx.doi.org/10.1002/chem.201901530

Supported by
ACES

WILEY-VCH

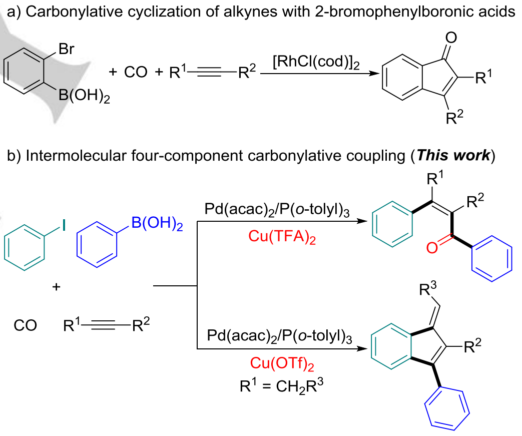
Palladium-Catalyzed Tunable Carbonylative Synthesis of Enones and Benzofulvenes

Jin-Bao Peng, Fu-Peng Wu, Anke Spannenberg, and Xiao-Feng Wu*[a]

Abstract: A palladium-catalyzed four-component carbonylative coupling reaction involving aryl halides, internal alkynes, arylboronic acids, and CO has been developed for the first time. All-carbon substituted α-unsaturated ketones and benzofulvenes can be selectively obtained in a high regio- and stereo-controlled manner. Using $Cu(TFA)_2$ as the additive, a series of tetra-substituted α,β-unsaturated ketones were prepared in moderate to high yields. Using more acidic Lewis acid $Cu(OTf)_2$ as the additive, multi-substituted benzofluvenes were synthesized in moderate yields. This efficient methodology involved the formation of three new C-C bonds, and provided a divergent method for the quick construction of multi-substituted α,β -unsaturated ketones and benzofulvenes from easily available starting materials.

Diversified synthesis is one of the core targets of organic chemistry. On one hand, transformations such as domino reactions and multi-components reactions, can increase the efficiency in new chemical bonds formation significantly.[1-4] On the other hand, selectivity controlled transformations can proliferating the products obtainable from the same substrates.[5-8] It is especially interesting that the selectivity of the products is tuned by slightly modifying the catalyst system.

Among the various transition metal-catalyzed transformations, carbonylative reaction is an efficient method for incorporating C1 synthons into organic compounds to give various carbonyl-containing compounds.[9-13] From the point view of diversity, the transition metal-catalyzed arylcarbonylative coupling of internal alkynes with aryl halides and organometallic compounds should provide an efficient and direct method for the synthesis of tetra-substituted enones and related compounds. Surprisingly, although the synthesis of tetra-substituted olefins via the transition metal catalyzed carbometalation of alkynes has been widely studied,[14-15] the carbonylative version has been scarcely reported and proven to be challenge. In 2007, Chatani and co-workers reported a Rh(I)-catalyzed carbonylation reaction of alkynes with 2-bromophenylboronic acids to prepare multi-substituted indenones (Scheme 1, eq. a).[16] However, to the best of our knowledge, there is no literature for the synthesis of all-carbon substituted α,β-unsaturated ketones been reported to date. One of the most important challenges of this type of reaction is the existence of several competing side-reactions such as the direct cross-coupling or carbonylative cross-coupling of aryl halides and the organometallic compounds. We proposed that the addition of Lewis acid would activate the triple bond and facilitate the intermolecular bifunctionalization of the alkynes (Scheme 1, eq. b). Herein, we report the first palladium-catalyzed intermolecular arylcarbonylative coupling of internal alkynes with aryl halides and arylboronic acids. Using $Cu(TFA)_2$ as the additive, a series of tetra-substituted α,β-unsaturated ketones were prepared in moderate to high yields. The arylcarbonylation reaction proceeds in a high regio- and stereoselective manner and the *syn* adduct of aryl and acyl group to the carbon-carbon triple bond has been obtained. Interestingly, we found that the use of more acidic $Cu(OTf)_2$ as the additive can lead to the production of multi-substituted benzofulvenes. In our control experiments, no interchange between enones and benzofulvenes could be obtained.


a) Carbonylative cyclization of alkynes with 2-bromophenylboronic acids

b) Intermolecular four-component carbonylative coupling (***This work***)

Scheme 1. Carbonylative Synthesis of *tetra*-Substituted Enones.

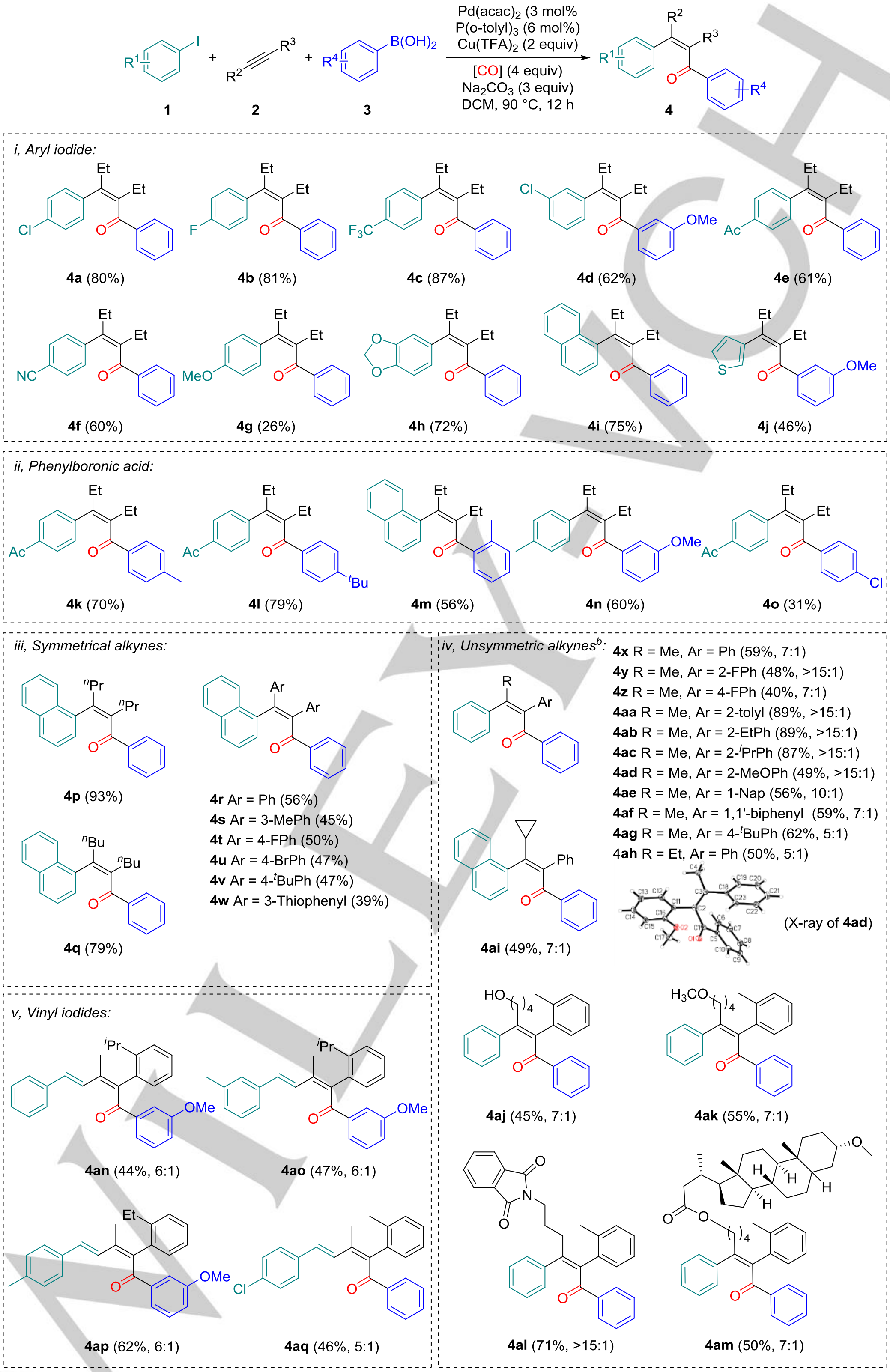
In order to establish this tunable system, 4-chloro-iodobenzene **1a**, 3-hexyne **2a** and phenylboronic acid **3a** were selected as the model substrates. After extensive studies, enones and benzofulvenes can be selectively produced in good yields respectively (For details see Supporting Information). Under the optimized reaction conditions, we investigated the generality of the arylcarbonylative coupling reaction. Firstly, as summarized in Table 1-i, a series of different (hetero)aryl iodides were applied to the optimized conditions and the corresponding conjugated ketones were obtained in moderate to good yields. Aryl halides bearing electron-withdrawing groups (Table 1, **4a-4f**) gave better yields than electron-donating group substituted ones (Table 1, **4g-4h**). Functional groups such as carbonyl (Table 1, **4e**) and cyano group (Table 1, **4f**) were compatible in this transformation.

---

[a] Dr. J.-B. Peng, F.-P. Wu, Prof. Dr. X.-F. Wu
Department of Chemistry, Zhejiang Sci-Tech University, Xiasha Campus, Hangzhou 310018, People's Republic of China
E-mail: Xiao-Feng.Wu@catalysis.de
Dr. A. Spannenberg, Prof. Dr. X.-F. Wu,
Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Straβe 29a, 18059 Rostock, Germany

Supporting information for this article is given via a link at the end of the document.

Table 1. Substrate Scope: Synthesis of *tetra*-Substituted Enones.[a]



4r Ar = Ph (56%)
4s Ar = 3-MePh (45%)
4t Ar = 4-FPh (50%)
4u Ar = 4-BrPh (47%)
4v Ar = 4-^{t}BuPh (47%)
4w Ar = 3-Thiophenyl (39%)

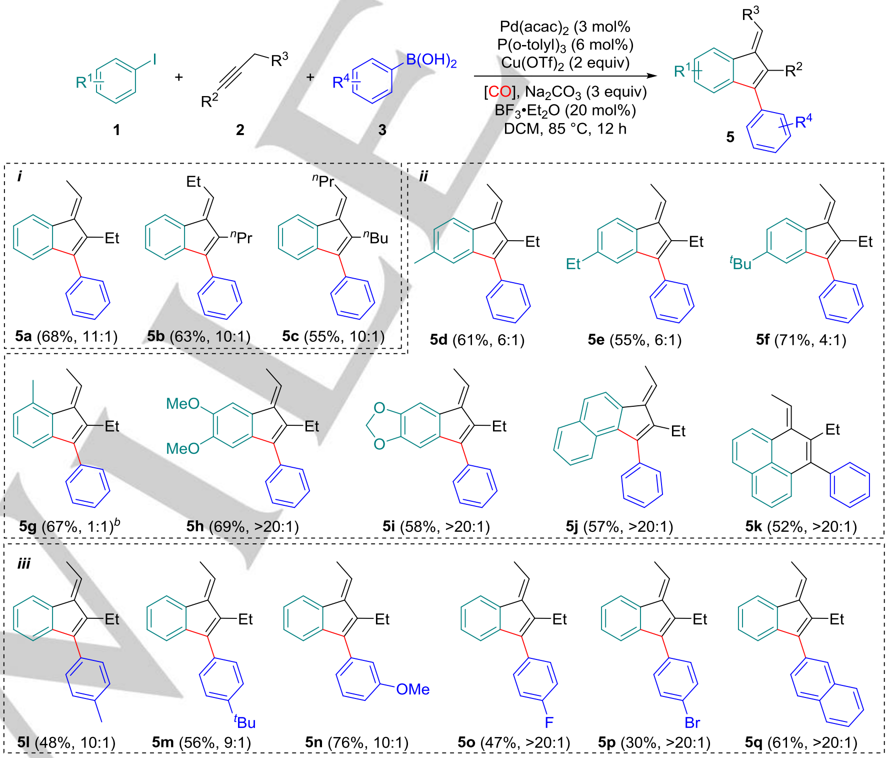
4x R = Me, Ar = Ph (59%, 7:1)
4y R = Me, Ar = 2-FPh (48%, >15:1)
4z R = Me, Ar = 4-FPh (40%, 7:1)
4aa R = Me, Ar = 2-tolyl (89%, >15:1)
4ab R = Me, Ar = 2-EtPh (89%, >15:1)
4ac R = Me, Ar = 2-^{i}PrPh (87%, >15:1)
4ad R = Me, Ar = 2-MeOPh (49%, >15:1)
4ae R = Me, Ar = 1-Nap (56%, 10:1)
4af R = Me, Ar = 1,1'-biphenyl (59%, 7:1)
4ag R = Me, Ar = 4-^{t}BuPh (62%, 5:1)
4ah R = Et, Ar = Ph (50%, 5:1)

[a] Reaction conditions: iodobenzene (0.50 mmol), alkyne (0.60 mmol), arylboronic acid (1.0 mmol), Pd(acac)$_2$ (3 mol %), P(*o*-tolyl)$_3$ (6 mol %), Cu(TFA)$_2$ (2 equiv.), [CO] (Ac$_2$O+HCO$_2$H, 2 mmol), Na$_2$CO$_3$ (3 equiv.), DCM (2 mL), 90 ºC, 12 h, isolated yield. [b] For the unsymmetrical alkynes, the regioisomeric ratio (r.r.) was determined by ^{1}H NMR analysis of the isolated products. [c] (PhBO)$_3$ was used instead of PhB(OH)$_2$. [d] PhBF$_3^-$K$^+$ was used instead of PhB(OH)$_2$

In addition to substituted iodobenzenes, 1-iodonaphthalene and heteroaryl iodides such as 3-iodothiophene were also tolerated and the corresponding products were conveniently generated in 75% and 46% yields, respectively. With respect to arylboronic acids, several phenylboronic acids with different substitution at different positions have been examined (Table 1-ii). Generally, electron-donating group substituted phenylboronic acids delivered the desired tetra-substituted α,β-unsaturated ketones in moderate to high yields (Table 1, **4k-4n**). Poor yield was found when electron-deficient arylboronic acid was used (Table 1, **4o**). Sterically bulky phenylboronic acid resulted in a decreased yield (Table 1, **4m**). In addition to phenylboronic acid, other phenylboron compounds were also tested in this arylcarbonylative coupling reaction. Triphenylboroxin (PhBO)$_3$ was found to be a suitable coupling partner and provided the product **4a** in 86% yield. Potassium phenyltrifluoroborate gave a decreased yield of 32%. However, phenylboronic esters such as pinacol and neopentylglycol ester were ineffective and only trace amount of **4a** was detected.

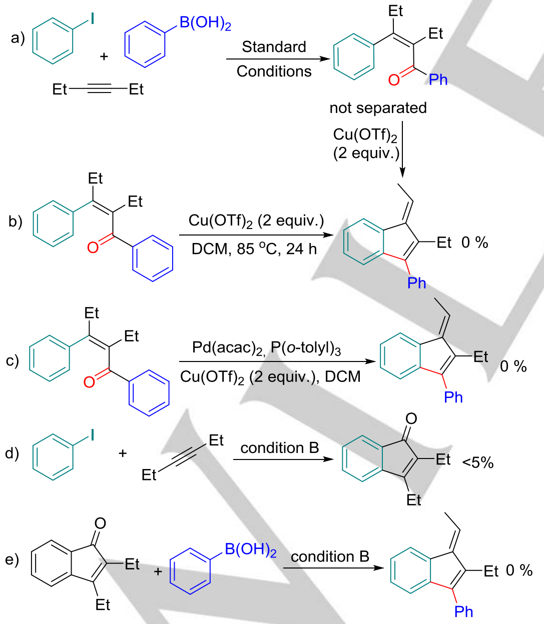
Subsequently, we turned our attention to test the generality of the alkynes. Symmetrical dialkylethynes such as 4-octyne and 5-decyne were well tolerated and produced the corresponding enones in 93% and 79% yields, respectively (Table 1, **4p** and **4q**). However, moderate yields (39%-56%) were obtained when symmetrical diarylethynes were used (Table 1, **4r-4w**). The decrease in yields might result from the lower electron density and higher steric hindrance of the diarylethynes. For unsymmetrical alkynes with two similar substituents, two unseparable regioisomers were formed in this reaction. However, when unsymmetrical alkynes with one alkyl and one aryl substituents were used in this reaction, the desired products were obtained in moderate to good yields with acceptable regioselectivity (Table 1-iv, **4x-4ai**). Steric difference of the two substituents on the carbon-carbon triple bond affected the regioselectivity significantly. For example, when 1-phenyl-1-propyne were used to the standard conditions, **4x** was obtained in 59% yield with 7:1 regioselectivity. Similar regioselectivities were obtained when 1-(*p*-substituted-phenyl)-1-propynes were used as the substrates (Table 1-iv, **4z, 4af** and **4ag**). However, when 1-(*o*-substituted-phenyl)-1-propynes were used in this reaction, excellent regioselectivities (>15:1) were obtained (Table 1-iv, **4y**, **4aa-4ag**). The stereochemistry and configuration of the products were assigned based on X-ray crystal structure analysis of **4ad** (CCDC: 1869004) as a representative example (Table 1-iv).[17] The aryl segments from aryl halides were attached at the carbon atom having the alkyl substituents, while the aryl segments from the arylboronic acids were carbonylated at the carbon atom having the aryl groups. Then several alcohol, ether, ester and amino substituted unsymmetrical alkynes were prepared and tested as well (Table 1-iv, **4aj-4am**). To our delight, moderate to good yields can be isolated under our standard conditions. Additionally, four examples of vinyl iodides were transformed successfully and gave the desired products in moderate yields (Table 1-v, **4an-4aq**).

Table 2. Substrate Scope: Synthesis of multi-Substituted Benzofulvenes.[a]



[a] Reaction conditions: iodobenzene (0.50 mmol), alkyne (0.60 mmol), arylboronic acid (1.5 mmol), Pd(acac)$_2$ (3 mol %), P(*o*-tolyl)$_3$ (6 mol %), Cu(OTf)$_2$ (2 equiv.), BF$_3$•Et$_2$O (20 mol %), [CO] (Ac$_2$O+HCO$_2$H, 2 mmol), Na$_2$CO$_3$ (3 equiv), DCM (2 mL), 85 ºC, 12 h, isolated yield. Z/E ratio was determined by GC using dodecane as internal standard.

During the investigation of the effect of the additives, small amount of indene derivative **5a** was obtained when more acidic Cu(OTf)$_2$ was used as the additive. It is generally known that indene derivative, including methyleneindene (benzofulvene), is one of the most important carbocycles in organic chemistry. This framework present frequently in many natural products and biologically active compounds.[18-21] Indenes have also been widely used in materials[22-26] as well as ligands for metal complexes.[27-29] Several strategies have been developed for the synthesis of 1*H*-indenes and benzofulvenes.[30] Owing to the importance of this structure, we optimized the reaction conditions for the formation of **5a** (see details in SI). Using Cu(OTf)$_2$ as the additive and $BF_3 \cdot Et_2O$ as a co-catalyst (Slightly decreased yield was obtained in the absence of $BF_3 \cdot Et_2O$, see details in SI), multi-substituted benzofulvene **5a** was obtained in 68% yield with Pd(OAc)$_2$/P(*o*-tolyl)$_3$ catalyst system at 85 ℃ (Table 2, **5a**). As summarized in Table 2-i, 4-octyne and 5-decyne afforded the corresponding indene products **5b** and **5c** in 63% and 55% yields, respectively. A range of electron-donating group substituted iodobenzenes were applied to the optimized condition and the corresponding products were successfully produced in moderate yields (Table 2-ii, **5d-5i**). It should be noted that for the reaction of iodonaphthalene, the cyclization prefers to take place at the α-position (Table 2-ii, **5j** and **5k**). For example, a 6-6-5 tricyclic compound **5j** was obtained in 57% yield when 2-iodonaphthalene was used in this reaction. While the reaction of 1-iodonaphthalene provided phenalene derivative **5k** where the cyclization occurred at the 1'-position. On the other hand, a range of substituted arylboronic acids were also tested in this transformation. The corresponding products were obtained in moderate yields (Table 2-iii, **5l-5q**).



Scheme 2. Control Experiments.

In order to get some insight of the reaction pathway, control experiments were designed and performed as well (Scheme 2). However, no interchange between enone and benzofulvene could be observed under our experiments (Scheme 2, a-c). Additionally, under conditions B and in the absence of phenylboronic acid, only trace amount of indenone could be detected (Scheme 2, d). No benzofulvene could be formed from indenone and phenylboronic acid neither (Scheme 2, e). It's important to mention that by-products including benzophenone which from carbonylative coupling between iodobenzene and phenylboronic acid, and alkyne hydration could be detected during the optimization process.

In summary, we have developed the first palladium catalyzed intermolecular arylcarbonylative coupling of internal alkynes with aryl halides and arylboronic acids. Using Cu(TFA)$_2$ as the additive, a series of tetra-substituted α,β-unsaturated ketones were prepared in moderate to high yields. The arylcarbonylation reaction proceeds in a high regio- and stereoselective manner and the syn adduct of aryl and acyl group to the carbon-carbon triple bond has been obtained. In addition, we found that when more acidic Lewis acid Cu(OTf)$_2$ been used as the additive, multi-substituted benzofluvenes can be produced selectively. This efficient methodology involved the formation of three new C−C bonds, and provided a divergent method for the quick construction of multi-substituted α,-unsaturated ketones and benzofulvenes from easily available starting materials.[31]

Acknowledgements

The authors thank the financial supports from NSFC (21772177, 21801225).

Keywords: palladium catalyst • carbonylation • cascade reaction • selectivity control • cyclization

[1] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115-136.
[2] E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234-6246.
[3] D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095-1108.
[4] L. F. Tietze, *Domino Reactions: Concepts for Efficient Organic Synthesis*. Wiley-VCH, **2014**.
[5] J. Peng, X. F. Wu, *Angew. Chem. Int. Ed.* **2018**, *57*, 1152-1160.
[6] V. Kumar Tiwari, M. Kapur, *Org. Biomol. Chem.* **2019**, *17*, 1007-1026.
[7] J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 10954-10990.
[8] Z. Huang, G. Dong, *Acc. Chem. Res.* **2017**, *50*, 465-471.
[9] B. Gabriele, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.* **2012**, 6825-6839.
[10] a) J.-B. Peng, X. Qi, X.-F. Wu, *Synlett* **2017**, *28*, 175-194; b) X.-F. Wu, *RSC Adv.* **2016**, *6*, 83831-83837; c) J.-B. Peng, H. Q. Geng, X.-F. Wu, *Chem* **2019**, *5*, 526-552.
[11] D. U. Nielsen, K. T. Neumann, T. Skrydstrup, *Chimia* **2018**, *72*, 606-609.
[12] P. H. Gehrtz, V. Hirschbeck, B. Ciszek, I. Fleischer, *Synthesis* **2016**, *48*, 1573−1596.
[13] Y. Bai, D. C. Davis, M. Dai, *J. Org. Chem.* **2017**, *82*, 2319-2328.
[14] a) L. F. Tietze, T. Hungerland, T. Eichhorst, A. Düfert, C. Maaß, D. Stalke, *Angew. Chem. Int. Ed.* **2013**, *52*, 3668-3671; b) B. M. Monks, S. P. Cook, *J. Am. Chem. Soc.* **2012**, *134*, 15297-15300.
[15] a) C. Zhou, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 3765-3777; b) C. Zhou, D. E. Emrich, R. C. Larock, *Org. Lett.* **2003**, *5*, 1579-1582; c) R.

Yanada, S. Obika, T. Inokuma, K. Yanada, M. Yamashita, S. Ohta, Y. Takemoto, *J. Org. Chem.* **2005**, *70*, 6972-6975.

[16] Y. Harada, J. Nakanishi, H. Fujihara, M. Tobisu, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 5766-5771.

[17] The relative configuration was confirmed by X-ray crystallography. CCDC 1869004 (**4ad**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] H. H. Seltzman, C. Shiner, E. E. Hirt, A. F. Gilliam, B. F. Thomas, R. Maitra, R. Snyder, S. L. Black, P. R. Patel, Y. Mulpuri, I. Spigelman, *J. Med. Chem.* **2016**, *59*, 7525-7543.

[19] A. J. Liedtke, B. C. Crews, C. M. Daniel, A. L. Blobaum, P. J. Kingsley, K. Ghebreselasie, L. J. Marnett, *J. Med. Chem.* **2012**, *55*, 2287-2300.

[20] E. Alcalde, N. Mesquida, S. López-Pérez, J. Frigola, R. Mercè, *J. Med. Chem.* **2009**, *52*, 675-687.

[21] J. W. Huffman, L. W. Padgett, *Curr. Med. Chem.* **2005**, *12*, 1395-1411.

[22] X. Gu, W. A. Luhman, E. Yagodkin, R. J. Holmes, C. J. Douglas, *Org. Lett.* **2012**, *14*, 1390-1393.

[23] J.-I. Nishida, S. Tsukaguchi, Y. Yamashita, *Chem. Eur. J.* **2012**, *18*, 8964-8970.

[24] Z. U. Levi, T. D. Tilley, *J. Am. Chem. Soc.* **2010**, *132*, 11012-11014.

[25] J. Yang, M. V. Lakshmikantham, M. P. Cava, D. Lorcy, J. R. Bethelot, *J. Org. Chem.* **2000**, *65*, 6739-6742.

[26] J. Barbera, O. A. Rakitin, M. B. Ros, T. Torroba, *Angew. Chem., Int. Ed.* **1998**, *37*, 296-299.

[27] H. G. Alt, A. Köppl, *Chem. Rev.* **2000**, *100*, 1205-1222.

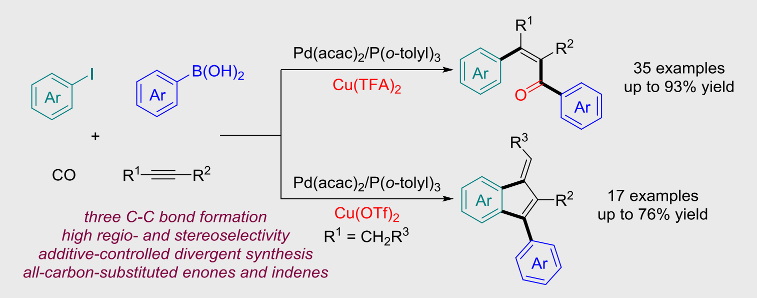
[28] J. G. M. Morton, H. Al-Shammari, Y. Sun, J. Zhu, D. W. Stephan, *Dalton Trans.* **2014**, *43*, 13219-13231.

[29] M. Enders, R. W. Baker, *Curr. Org. Chem.* **2006**, *10*, 937-953.

[30] B. Gabriele, R. Mancuso, L. Veltri, *Chem. Eur. J.* **2016**, *22*, 5056-5094.

[31] Z. Yin, X.-F. Wu, *Org. Process Res. Dev.* **2017**, *21*, 1869-1871.

COMMUNICATION



*Jin-Bao Peng, Fu-Peng Wu, Anke Spannenberg, and Xiao-Feng Wu**

Page No. – Page No.

Palladium-Catalyzed Tunable Carbonylative Synthesis of Enones and Benzofulvenes