A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Scalable, Stereocontrolled Formal Syntheses of (+)-Isoschizandrin and (+)-Steganone: Development and Applications of Pd(II)-Catalyzed Atroposelective C–H Alkynylation

Authors: Gang Liao, Qi-Jun Yao, Zhuo-Zhuo Zhang, Yong-Jie Wu, Dan-Ying Huang, and Bing-Feng Shi

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201713106
Angew. Chem. 10.1002/ange.201713106

Link to VoR: http://dx.doi.org/10.1002/anie.201713106
http://dx.doi.org/10.1002/ange.201713106

WILEY-VCH

10.1002/anie.201713106

WILEY-VCH

COMMUNICATION

Scalable, Stereocontrolled Formal Syntheses of (+)-Isoschizandrin and (+)-Steganone: Development and Applications of Pd(II)-Catalyzed Atroposelective C–H Alkynylation

Gang Liao,[a] Qi-Jun Yao,[a] Zhuo-Zhuo Zhang,[a] Yong-Jie Wu,[a] Dan-Ying Huang,[c] and Bing-Feng Shi*[a,b]

Abstract: Dibenzocyclooctadiene lignans are an interesting class of molecules for their unique structure of axially chiral biaryls as well as their significant biological activities. Herein, a Pd-catalyzed atroposelective C–H alkynylation was developed for the gram-scale, stereocontrolled formal syntheses of (+)-isoschizandrin and (+)-steganone. *tert*-Leucine was identified as an efficient, catalytic transient chiral auxiliary. The scope of this reaction is also presented and a wide range of enantioenriched biaryls were prepared in good yields (up to 99%) with excellent enantioselectivities (up to >99% ee).

Dibenzocyclooctadiene lignans are a common class of natural products that possess unique structural features and significant biological activities (Figure 1a).[1] For example, (+)-isoschizandrin and its analogues, which originate from *Schizandra chinesis*, a fruit in northern China, were used as an antitussive and a tonic in Chinese and Japanese traditional medicine.[2] And (-)-steganone and its related compounds were isolated from *Steganotaenia araliacea* by Kupchan in 1973, which was reported to have significant activity against P-388 leukemia in mice and excellent bioactivity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB).[3] The key axially chiral biaryl core structures of these dibenzocyclooctadiene lignans, are interesting targets but also represent the bottolenecks for total synthesis.[1a,4] A number of elegant synthetic pathways have been developed for these lignans, whereby some of the approaches require stoichiometric amout of chiral reagents, and suffer from low overall yield, poor step-economy, and/or moderate stereocontrol.[5,6] Furthermore, those synthetic routes are limited to a milligram scale; the ultimate challenge of producing large quantities of these lignans for biological evaluation, has yet to be surmounted. Our goal is to establish a modular, scalable and generally applicable strategy for atroposelective construction of the biaryl core structures, which would provide rapid access to large quantities of related lignans and offer great opportunities to elucidate their biological features.

In recent years, extensive efforts have been expended toward the efficient synthesis of axially chiral biaryl scaffolds.[7] Among these methods, the atroposelective C–H functionalization of biaryls provides an efficient strategy to access these structures.[8-13,16] In 2000, the Rh(I)-catalyzed atroposelective C–H alkylation of biaryls with olefin was achieved by Murai, with moderate stereoinduction (up to 49% ee)[9] In 2010, Miller demonstrated the atroposelective electrophilic bromination enabled by a tripeptide catalytic system.[10] Major breakthroughs in asymmetric C–H functionalizations of biaryls were independently demonstrated by You,[11] Wencel-Delord and Colobert[12] in 2014. You and co-workers reported C–H olefination/dynamic kinetic resolution (DKR) of 1-(naphthalene-1-yl)isoquinolines using chiral [Cp*Rh(III)] catalysts.[11a,11c] Wencel-Delord and Colobert elegantly achieved the synthesis of axially chiral biaryls via chiral sulfoxide-directed Pd-catalyzed C–H olefination,[12a,12c] acetoxylation and iodination.[12b]

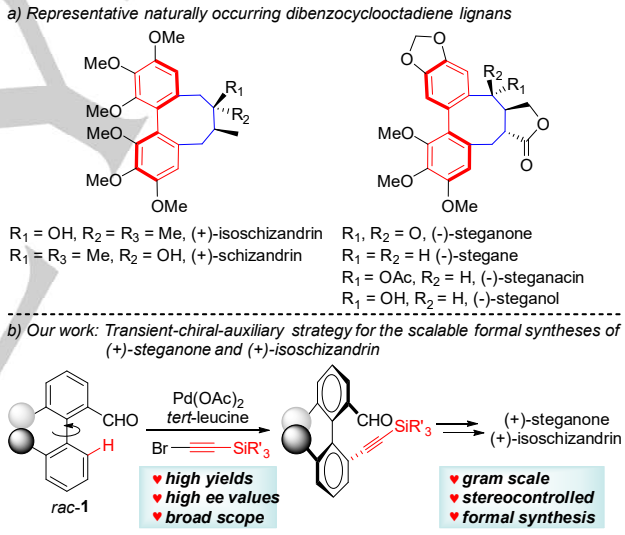


Figure 1. Transient-chiral-auxiliary strategy to axially chiral biaryls.

More recently, Yu and coworkers reported a Pd-catalyzed enantioselective C–H arylation to create a point chirality using a chiral amino acid as a transient directing group.[14] Inspired by this seminal work, we have developed a Pd-catalyzed atroposelective C–H olefination using *tert*-leucine as an inexpensive, catalytic and transient chiral auxiliary.[15] We speculated that a Pd-catalyzed atroposelective C–H alkynylation could streamline the scalable preparation of these dibenzocyclooctadiene lignans in a stereoselective manner, since alkynes can serve as versatile handles for further transformation. However, the extension of atroposelective C–H olefination to the alkynylation version is not straightforward, as alkynylation is expected to involve a Pd(II)/Pd(IV) catalytic cycle, different from a Pd(II)/Pd(0) cycle in olefination. Here we report the highly atroposelective synthesis of axially chiral biaryls by Pd-catalyzed asymmetric C–H alkynylation reaction. This strategy provides efficient access to a wide range of enantioenriched biaryls (up to 99% yields and >99%

[a] G. Liao, Q.-J. Yao, Z.-Z. Zhang, Y.-J. Wu, Prof. Dr. B.-F. Shi
Department of Chemistry, Zhejiang University
Hangzhou 310027 (China)
E-mail: bfshi@zju.edu.cn.
Homepage: http://mypage.zju.edu.cn/en/bfshi/.
[b] Prof. Dr. B.-F. Shi
State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071 (China)
[c] D.-Y. Huang
School of Chemical &Environmental Engineering, Wuyi University, Jiangmen 529020 (China)

10.1002/anie.201713106

WILEY-VCH

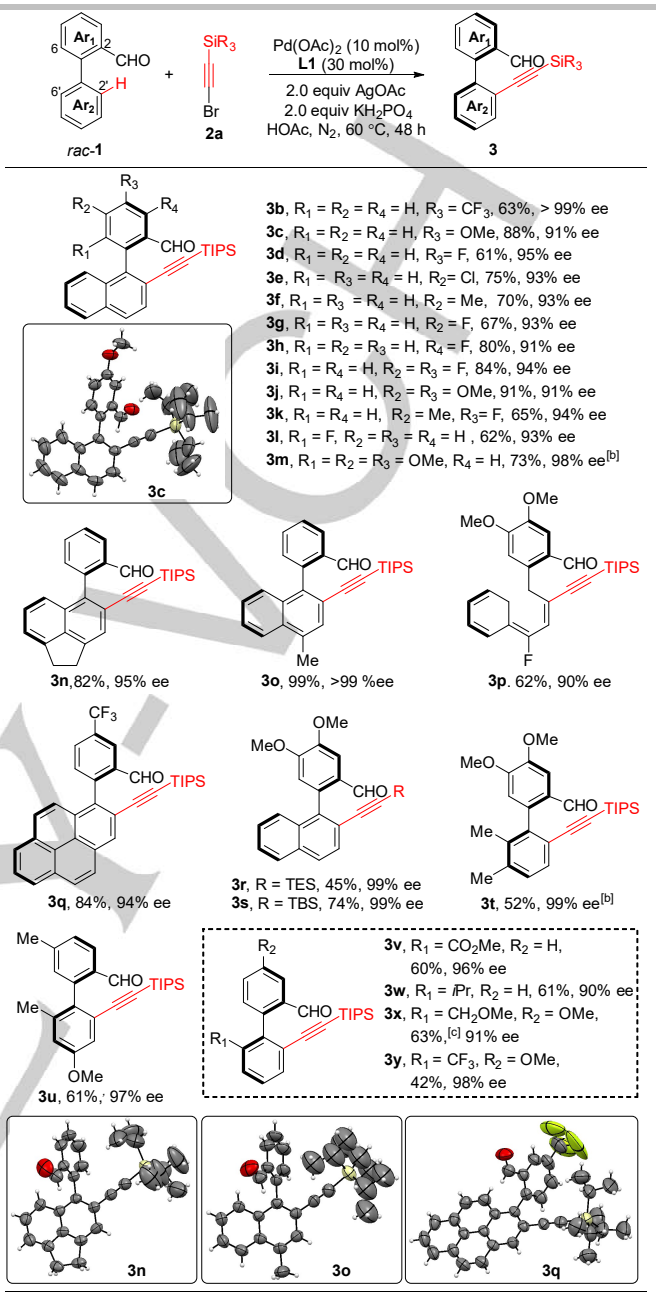
COMMUNICATION

ee). This method also establishes a platform for rapid formal syntheses of (+)-isoschizandrin and (+)-steganone in a gram-scale manner.

To start the designed asymmetric C–H alkynylation, *rac*-**1a** and TIPS-protected alkynyl bromide were chosen as model substrates for optimizing reaction conditions. Derived from the previous olefination, a catalytic combination of $Pd(OAc)_2$ and *L-tert*-leucine **L1** were able to induce high enantioselectivity in the C–H activation step. To our delight, $Pd(OAc)_2$/**L1** together with AgOAc in HOAc afforded the desired axially chiral biary **3a** in a moderate yield and excellent enantioselectivity (Table S1, entry 1, 56% yield, 98% ee). An attempt to perform the reaction without AgOAc resulted in a much lower yield (entry 2, 12%, 98% ee). Non-protic or less acidic solvents gave poor product formation (entries 3-6), which suggests the acidity of reaction system may be crucial to the recycling of the transient auxiliary. This result led us to screen inorganic salts that may buffer the solution to modulate the pH of the reaction solution (entries 7-12). Potassium dihydric phosphate turned out the most efficient, significantly improving the yield of product **3a** to 71% with maintained enantioselectivity (entry 12).

With the optimal conditions in hand, a panel of biaryl substrates were evaluated. Consistent with our previous observation,[15] biaryls containing substituents at either the 6- or 2' positions (**1a-1k**, **1m-1y**) or less bulky substituent at both positions (**1l**) underwent a DKR pathway (Table 1). Various substituted phenylnaphthalenes underwent the desired alkynylation smoothly, indicating that the electronic properties of the substituents on phenyl and naphthalene motiety did not have a significant impact on reactivity and enantioselectivity (**3a-3p**, 61 to 99% yields, 90 to >99% ee). Substrate **3q** bearing a pyrene group could also be tolerated, affording the desired chiral biaryl products in 84% yield and 94% ee. In addition to **2a**, other protected alkynyl bromides were also compatible with the strategy (**3r** and **3s**). Substituted diphenyls also served as good coupling partners with excellent stereocontrol (**3t-3y**). The absolute configurations of products **3c, 3n, 3o** and **3q** were determined by single-crystal X-ray diffraction experiments using Cu Kα radiation[16] and the refinement of Flack's parameters.[17] Other biaryl products were assigned by analogy.[18]

Table 1. Substrate scope for Pd-catalyzed C–H alkynylation /DKR of biaryls[a]



[a] Reaction conditions: *rac*-**1** (0.1 mmol), protected alkynyl bromide **2** (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), **L1** (0.03 mmol), AgOAc (0.2 mmol), KH_2PO_4 (0.2 mmol), HOAc (1 mL), 60 °C, N_2, 48 h. [b] AgTFA instead of AgOAc, 55 °C. [c] 96 h. TIPS = triisopropylsilyl, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, AgTFA = silver trifluoroacetate.

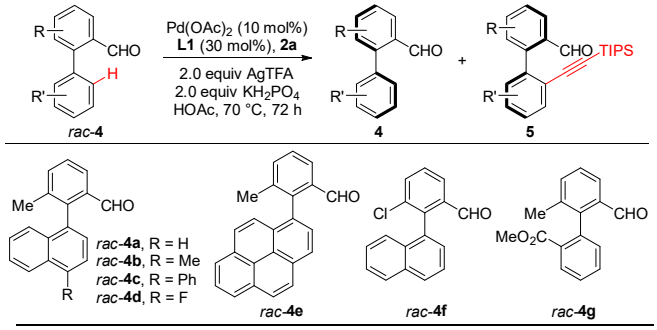
We next asked whether the asymmetric C–H alkynylation of biarys could be applicable to kinetic resolution (KR) of biaryls bearing sterically more bulky substituents at both the 6- and 2'-positions.[11b,12b,15,18] Gratifyingly, excellent selectivities were observed under slightly modified conditions as shown in Table 2. With this method, substrates with different steric properties were examined. The alkynylated products **5** were obtained in 35%-47% yield with 92 to 98% ee, and the starting materials were recovered in 41%-53% yield with 68 to 97% ee (entries 1-7, *s*-factor = 100-600). Notably, 3-chloro-biaryl **4f** was found to be compatible with this reaction affording excellent yield and selectivity (entry 6, *s*-factor = 600). Biaryl **4g** could also be converted to the corresponding alkynylation product with good selectivity (entry 7, *s*-factor = 190).

10.1002/anie.201713106

WILEY-VCH

COMMUNICATION

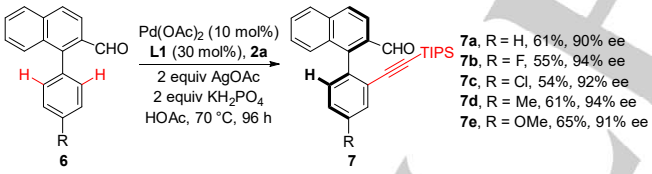
Table 2. Substrate scope for Pd-catalyzed C–H alkynylation/KR of biaryls



entry	4	5	4 yield (%)[a]	4 ee (%)[b]	5 yield (%)[a]	5 ee (%)[b]	s[c]
1	**4a**	**5a**	49	90	42	96	152
2	**4b**	**5b**	53	68	40	96	100
3	**4c**	**5c**	50	95	43	96	183
4	**4d**	**5d**	44	97	43	93	116
5	**4e**	**5e**	53	75	35	98	224
6	**4f**	**5f**	46	89	46	99	600
7	**4g**	**5g**	61	63	31	98	190

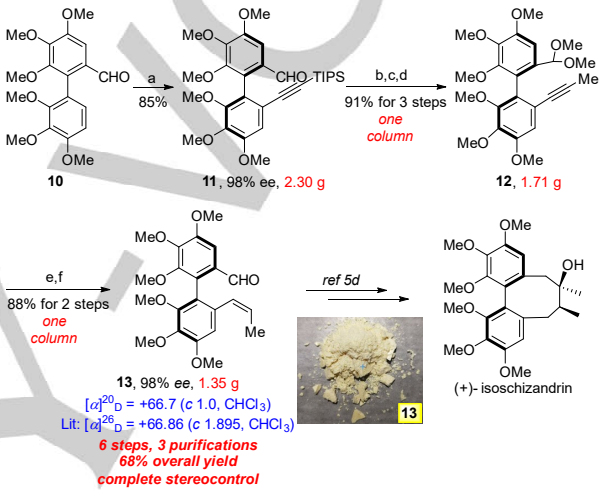
[a] Isolated yield. [b] The ee value was determined by HPLC. The absolute configurations of the enantioenriched products and starting materials were assigned by analogy to **3**. [c] s = ln[(1-C)(1-ee$_4$)]/ln[(1-C)(1+ee$_4$)], C = ee$_4$/(ee$_4$+ee$_5$).

Further, we sought to expand the potential of this methodology by performing the reaction on desymmetrization of proaixally biaryls. Fortunately, the desired axially chiral biaryls were produced in synthetically useful yields with excellent enantioselectivties (Scheme 1, **7a**-**7e**, 48-65% yield, 90-96% ee). The absolute configurations of **7** were similarly assigned according to biaryls **3** since they had the same mode of stereoinduction.



Scheme 1. Pd-catalyzed C–H alkynylation/desymmetrization of proaxially biaryls.

The application of a synthetic strategy to streamline the synthesis of complex natural products is considered as an important validation of its potential and usefulness. To apply this strategy to the total syntheses of (+)-isoschizandrin and (+)-steganone, there are still several challenges lying ahead: (i) This transformation would be required to take place in electron-rich substrates (*e.g.* **10** and **14**) and with perfect site-selectivity when confronting two possible C–H bonds (*e.g.* **14**). (ii) The multiple substituents would need to be tolerated, especially in gram-scale preparation. As shown in Scheme 2, our synthesis commenced with the atroposelective C –H alkynylation of aldehyde **10** on 5 mmol scale, to give aldehyde **11** in good yield and high enantiopurity (85%, 98% ee, 2.30 g). Protection of aldehyde **11** by treatment with *p*-TsOH and trimethyl orthoformate, TIPS removal with TBAF, and subsequent methylation of the resulting terminal alkyne occurred smoothly to produce **12** in 91% yield over three steps with only one chromatographic purification (1.71 g). Attempts to reduce **12** with Lindlar catalysis were not fruitful due to competing side reactions involving the over-reduction or/and formation of Z/E-isomer mixture. We circumvented this problem by the use of a previous reported Ti(OiPr)$_4$/*i*PrMgCl system.[20] Treatment of **12** with aqueous HCl produced alkenyl ketone **13** in 88% yield with excellent enantioselectivity and stereoselectivity (98% ee, 1.35 g). It is worth mentioning that biaryl precursor **13**, a known precursor to (+)-isoschizandrin in Molander's synthesis,[5d] was prepared in *a total of six steps with only three chromatographic purifications and in 68% overall yield* from **10**. By comparison to previous syntheses of **13**,[5d,e] this route is practical and robust—all steps are conducted on a gram scale with complete stereocontrol.



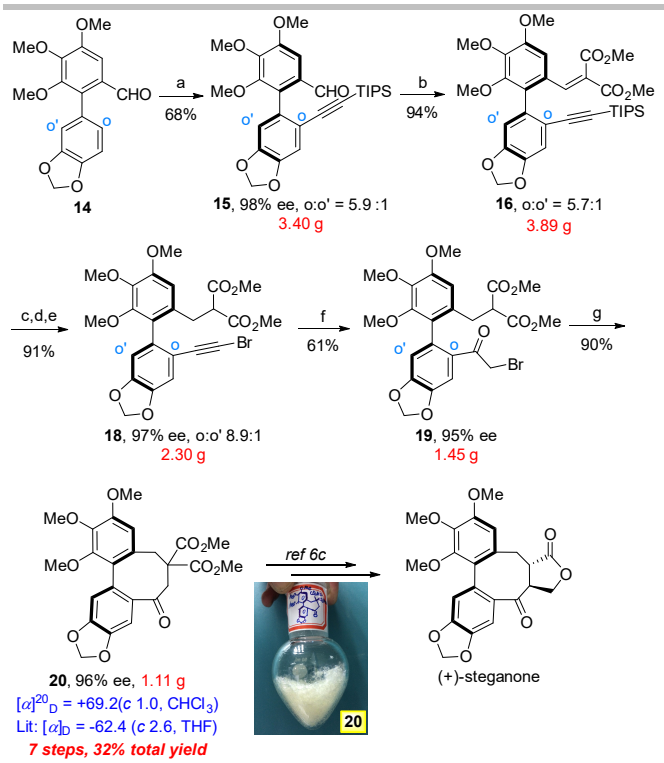
Scheme 2. Formal synthesis of (+)-isoschizandrin. (a) Pd(OAc)$_2$, **L1**, AgTFA, KH_2PO_4, **2a**, HOAc, 55 °C, 58 h, N_2, 85%; (b) TsOH, trimethyl orthoformate; (c) TBAF, THF, rt; (d) *n*-BuLi, MeI, THF, -78 °C, 91% for 3 steps; (e) Ti(*i*OPr)$_4$, *i*PrMgCl, Et_2O, -78 °C to -45 °C; (f) H_2O, 1M HCl, rt, 88% for 2 steps. DME = dimethoxyethane.

Finally, the more challenging stegane family natural products, such as steganone,[6] were selected as targets to showcase the synthetic potential (Scheme 3). Thus, the asymmetric C–H alkynylation of biaryl aldehyde **14** led to the preparation of **15** in a gram scale with good enantioselectivity and regioselectivity (68% yield, 3.40 g, 98% ee, o:o' = 5.9: 1). Knoevenagel condensation of **15** utilizing proline as catalyst afforded the arylidene malonate **16** in 94% yield.[21] Reduction of **16** proceeded smoothly with Raney-Ni catalyst to access **17** quantitatively. Upon the treatment with TBAF followed by bromination, **17** was successfully converted to alkynyl bromide **18** in 91% yield (2.30 g, 97% ee, o:o' = 8.9 : 1). While initial trials of hydration under harsh conditions led to partial racemization (aryl-aryl bond rotation), it was found that a mercuric triflate-AgSbF$_6$-mediated hydration successfully furnished **19** in 61% yield without loss of the axial chirality (1.45 g, 95% ee).[22,23] The resulting α-bromo ketone **19** was treated with DBU to give the cyclic ketone **20** in 90% yield with high enantiopurity (1.11 g, 96% ee). The optical rotation of our synthetic cyclic ketone **20** ($[\alpha]^{20}_D$ = +69.2(c 1.0, $CHCl_3$)) was nearly identical, but of an opposite sign to that of previously reported by Meyers ($[\alpha]_D$ = -62.4 (c 2.6, THF)).[6c] The enantiomer of the cyclic ketone **20** was an established precursur to (-)-steganone.[6c] Thus, a gram-scale formal synthesis of *ent*-(+)-steganone is achieved.

10.1002/anie.201713106

WILEY-VCH

COMMUNICATION



Scheme 3. Formal synthesis of (+)-steganone. (a) $Pd(OAc)_2$, **L1**, AgTFA, KH_2PO_4, **2a**, HOAc, 55 °C, 48 h, N_2, 68%; (b) *L*-Proline, DMM, DMSO, Et_3N, rt, 94%; (c) Raney-Ni, H_2, THF, rt, 100%; (d) TBAF, THF 0 °C; (e) $AgNO_3$, NBS, acetone, 0 °C 91% for 3 steps; (f) $Hg(OTf)_2$, $AgSbF_6$, CH_3OH, DCM, H_2O, rt, 61%; (g) DBU, THF, rt, 90%. DMM = dimethyl malonate, DCM = dichloromethane, DMSO = dimethyl sulfoxide, NBS = *N*-bromosuccinimide, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

In conclusion, we have demonstrated the remarkable synthetic potential of a Pd-catalyzed atroposelective C–H alkynylation strategy in natural product syntheses. *tert*-Leucine was used as a key catalytic transient chiral auxiliary. A broad range of enantioenriched biaryls were obtained in good yields (up to 99%) with excellent enantioselectivities (up to > 99% ee). The gram-scale, stereocontrolled formal syntheses of (+)-isoschizandrin and (+)-steganone were achieved based on this method. These syntheses compare very favorably with previous syntheses in terms of step-economy, overall yields and stereocontrol. Further applications of this method in the synthesis of other dibenzocyclooctadiene lignan analogues and axially chiral biaryls are in progress.

Acknowledgements

Financial support from the NSFC (21772170, 21422206, 21572201), the National Basic Research Program of China (2015CB856600), the Fundamental Research Funds for the Central Universities and Zhejiang Provincial NSFC (LR17B020001) is gratefully acknowledged.

Keywords: atroposelective • C–H alkynylation • formal synthesis • (+)-isoschizandrin • steganone

[1] For selected reviews, see: a) J. Chang, J. Reiner, J. Xie, *Chem. Rev.* **2005**, *105*, 4581; b) D. D. Ayres, J. D. Loike, *Lignans: Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, U.K., 1990; c) D. A. Whiting, *Nat. Prod. Rep.* **1985**, *2*, 191; d) D. A. Whiting, *Nat. Prod. Rep.* **1987**, *4*, 499.

[2] Y. Ikeya, H. Taguchi, H. Mitsuhashi, S. Takeda, Y. Kase, M. Aburada, *Phytochemistry* **1988**, *27*, 569.

[3] S. M. Kupchan, R. W. Britton, M. F. Zeigler, C. J. Gilmore, R. J. Restivo, R. F. Bryan, *J. Am. Chem. Soc.* **1973**, *95*, 1335.

[4] a) Y. Liu, J. Chang, J. Xie, *Chin. J. Org. Chem.* **2012**, *32*, 2040; b) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563; c) M. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193; d) L. Xie, L. H. Chen, J. X. Xie, *Chin. J. Org. Chem.* **1991**, *11*, 371.

[5] For stereoselective synthesis of (+)-isoschizandrin, see: a) A. M. Warshawsky, A. I. Meyers, *J. Am. Chem. Soc.* **1990**, *112*, 8090; b) M. Tanaka, H. Itoh, H. Mitsuhashi, M. Maruno, T. Wakamatsu, *Tetrahedron: Asymmetry* **1993**, *4*, 605; c) M. Tanaka, C. Mukaiyama, H. Mitsuhashi, M. Maruno, T. Wakamatsu, *J. Org. Chem.* **1995**, *60*, 4339; d) G. A. Molander, K. M. George, L. G. Monovich *J. Org. Chem.* **2003**, *68*, 9533; e) W.-W. Chen, Q. Zhao, M.-H. Xu, G.-Q. Lin, *Org. Lett.* **2010**, *12*, 1072.

[6] For stereoselective synthesis of (-)-steganone, see: a) J. P. Robin, O. Gringore, E. Brown, *Tetrahedron Lett.* **1980**, *21*, 2709; b) K. Tomioka, T. Ishiguro, Y. Iitaka, K. Koga, *Tetrahedron* **1984**, *40*, 1303; c) A. I. Meyers, J. R. Flisak, R. A. Aitken, *J. Am. Chem. Soc.* **1987**,*109*, 5446; d) M. Uemura, A. Daimon, Y. Hayashi, *J. Chem. Soc., Chem. Commun.* **1995**, *19*, 1943; e) L. G. Monovich, Y. L. Hue´rou, M. Rönn, G. A. Molander, *J. Am. Chem. Soc.* **2000,** *122,* 52; f) K. Kamikawa, T. Watanabe, A. Daimon, M. Uemura, *Tetrahedron* **2000**, *56*, 2325; g) A. Joncour, A. Décor, S. Thoret, A. Chiaroni, O. Baudoin, *Angew. Chem. Int. Ed.* **2006**, *45*, 4149; h) S. Takeda, H. Abe, Y. Takeuchi, T. Harayama, *Tetrahedron* **2007**, *63*, 396; i) B. Yalcouye, C. Sabine, A. Panossian, F. R. Leroux, F. Colobert, *Eur. J. Org. Chem.* **2014**, 6285; j) Q. Dherbassy, J. Wencel-Delord, F. Colobert, *Tetrahedron* **2016**, *72*, 5238.

[7] For recent reviews on the synthesis of axially chiral biaryls, see: a) O. Baudoin, *Eur. J. Org. Chem.* **2005**, 4223; b) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384; c) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, *Chem. Soc. Rev.* **2015**, *44*, 3418; d) G. Ma, M. P. Sibi, *Chem. Eur. J.* **2015**, *21*, 11644; e) P. Loxq, E. Manoury, R. Poli, E. Deydier, A. Labande, *Coord. Chem. Rev.* **2016**, *308*, 131; f) H. Yang, X. Yang, W. Tang, *Tetrahedron* **2016**, *72*, 6143.

[8] For representative reviews on asymmetric C-H activation, see: a) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242; b) H. M. Peng, L.-X. Dai, S.-L. You, *Angew. Chem. Int. Ed.* **2010**, *49*, 5826; c) L. Yang, H. Huang, *Catal. Sci. Technol.* **2012**, *2*, 1099; d) K. M. Engle, J.-Q. Yu, *J. Org. Chem.* **2013**, *78*, 8927; e) J. Wencel-Delord, F. Colobert, *Chem. Eur. J.* **2013**, *19*, 14010; f) J. Pedroni, N. Cramer, *Chem. Commun.* **2015**, *51*, 17647; g) C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908; h) D.-W. Gao, Q. Gu, C. Zheng, S.-L. You, *Acc. Chem. Res.* **2017**, *50*, 351.

[9] F. Kakiuchi, P. L. Gendre, A. Yamada, H. Ohtaki, S. Murai, *Tetrahedron: Asymmetry* **2000**, *11*, 2647.

[10] J. Gustafson, D. Lim, S. J. Miller, *Science* **2010**, *328*, 1251.

[11] a) J. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2014**, *53*, 13244; b) D.-W. Gao, Q. Gu, S.-L. You, *ACS Catal.* **2014**, *4*, 2741; c) J. Zheng, W.-J. Cui, C. Zheng, S.-L. You, *J. Am. Chem. Soc.* **2016**, *138*, 5242.

[12] a) T. Wesch, F. R. Leroux, F. Colobert, *Adv. Synth. Catal.* **2013**, *355*, 2139; b) C. K. Hazra, Q. Dherbassy, J. Wencel-Delord, F. Colobert, *Angew. Chem. Int. Ed.* **2014**, *53*, 13871; c) Q. Dherbassy, G. Schwertz, M. Chessé, C. K, Hazra, J. Wencel-Delord, F. Colobert, *Chem. Eur. J.* **2016**, *22*, 1735;

[13] a) Y.-N. Ma, H.-Y. Zhang, S.-D. Yang, *Org. Lett.* **2015**, *17*, 2034; b) S.-X. Li, Y.-N. Ma, S.-D. Yang, *Org. Lett.* **2017**, *19*, 1842; c) C. He, M. Hou, Z. Zhu, Z. Gu, *ACS Catal.* **2017**, *7*, 5316.

[14] F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science* **2016**, *351*, 252.

[15] Q.-J. Yao, S. Zhang, B.-B. Zhan, B.-F. Shi, *Angew. Chem. Int. Ed.* **2017**, *56*, 6617.

[16] Suitable crystals were selected for measurement on an Oxford Diffraction Gemini A Ultra diffractometer with Cu Kα radiation (λ = 1.54178 Å). Crystallographic data have been deposited with the Cambridge

10.1002/anie.201713106

Crystallographic Data Centre [CCDC 1587156 (**3c**), 1587155 (**3n**), 1587158 (**3o**), 1587157 (**3q**)].

[17] H. D. Flack, *Acta Crystallogr. A.* **1983**, *39*, 876.

[18] The absolute configuration of biaryl products were further established as *Ra* by comparing the optical rotations of **13** and **20** (see SI for details) with that documented in ref 5h and 6c.

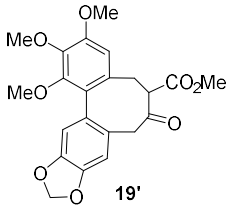
[19] For an example of Pd-catalyzed enantioselective C-H iodination via kinetic resolution, see: L. Chu, K.-J. Xiao, J.-Q. Yu, *Science* **2014**, *346*, 451.

[20] a) C. Oger, L. Balas, T. Durand, J. –M. Galano, *Chem. Rev.* **2013**, *113*, 1313; b) K. Harada, H. Urabe, F. Sato, *Tetrahedron Lett.* **1995**, *36*, 3203; c) N. L. Hungerford, W. Kitching, *Chem. Commun.* **1996**, 1697.

[21] G. Cardillo, S. Fabbroni, L. Gentilucci, M. Gianotti, A. Tolomeklli, *Synth. Commun.* **2003**, *33*, 1587.

[22] M. Nishizawa, M. Skwarczynski, H. Imagawa, T. Sugihara, *Chem. Lett.* **2002**, *31*, 12.

[23] A side product **19'** was formed in 12% yield, probably through a hydration/hydrolysis/decarboxylation sequence.



19'

10.1002/anie.201713106

WILEY-VCH

COMMUNICATION

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

*Gang Liao, Qi-Jun Yao, Zhuo-Zhuo Zhang, Yong-Jie Wu, Dan-Ying Huang, and Bing-Feng Shi**

Page No. – Page No.

Scalable, Stereocontrolled Formal Syntheses of (+)-Isoschizandrin and (+)-Steganone: Development and Applications of Pd(II)-Catalyzed Atroposelective C–H Alkynylation

A Pd-catalyzed atroposelective C–H alkynylation was developed and applied to the gram-scale, stereocontrolled formal syntheses of (+)-isoschizandrin and (+)-steganone. *tert*-Leucine was identified as an efficient, catalytic transient chiral auxiliary. The scope of this reaction is also presented and a wide range of enantioenriched biaryls were prepared in good yields (up to 99%) with excellent enantioselectivities (up to >99% ee).