A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Enantioselective Dearomative Difunctionalization of Indoles via Palladium-Catalyzed Domino Heck/Sonogashira Sequence

Authors: Yi-xia Jia, Ren-Rong Liu, Yong-Gang Wang, Ying-Long Li, Bing-Bing Huang, and Ren-Xiao Liang

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201703833
Angew. Chem. 10.1002/ange.201703833

Link to VoR: http://dx.doi.org/10.1002/anie.201703833
http://dx.doi.org/10.1002/ange.201703833

WILEY-VCH

10.1002/anie.201703833

COMMUNICATION

WILEY-VCH

Enantioselective Dearomative Difunctionalization of Indoles via Palladium-Catalyzed Domino Heck/Sonogashira Sequence

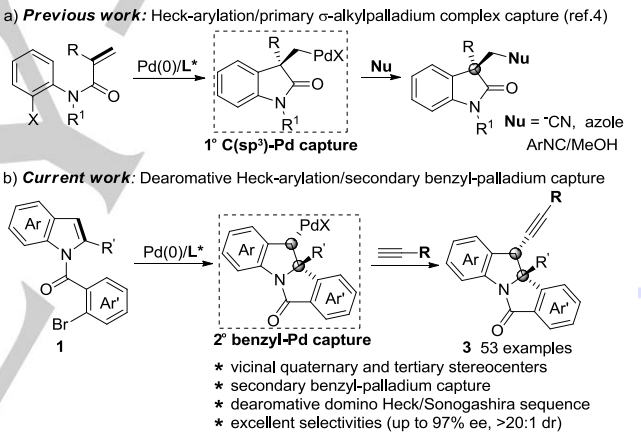
Ren-Rong Liu, Yong-Gang Wang, Ying-Long Li, Bing-Bing Huang, Ren-Xiao Liang, and Yi-Xia Jia*

Dedicated to Professor Qi-Lin Zhou on the occasion of his 60th birthday

Abstract: Pd-catalyzed enantioselective dearomative arylalkynylation of *N*-substituted indoles through a domino Heck/Sonogashira sequence was established with a new BINOL-based phosphoramidite as chiral ligand. A very wide range of 2,3-disubstituted indolines bearing vicinal quaternary and tertiary stereocenters were efficiently constructed in one step with excellent enantioselectivities (up to 97% ee) and diastereoselectivities (>20:1).

Palladium-catalyzed domino Heck/anion capture sequence involving intramolecular carbopalladation of alkene and subsequent trapping of the alkylpalladium intermediates represents an important method for 1,2-difunctionalization of alkene.[1] Numerous transformations, typically initiated by an oxidative addition of Pd(0) to (vinyl)aryl halide, have been developed by employing a variety of trapping agents to terminate the alkyl-Pd species, which evidenced their utilities in organic synthesis.[2] In sharp contrast, the corresponding asymmetric reactions were rather limited. Enantioselective domino Heck/allylic-substitution processes in the reactions with conjugated dienes have showed their efficacy in constructing complex molecules,[3] whereas σ-alkylpalladium capture for enantioselective 1,2-difunctionalization of simple alkenes remained more challenging. Attractive examples involved 1,2-difunctionalization of N-aryl acrylamides reported by Zhu and co-workers with cyanide,[4a] azoles,[4b] and isocyanides/MeOH[4c] as nucleophiles to capture the primary σ-alkylpalladium species, rendering the construction of chiral 3,3'-disubstituted oxindole moieties more efficient (Scheme 1a). Besides, an enantioslective vinylborylation of alkene has been developed recently by Tong and co-workers.[4d] In spite of these progress,[5] one-step construction of vicinal stereocenters by capturing the secondary σ-alkylpalladium species remained underdeveloped as a difficult task.[6] Moreover, the development of other type of trapping agents to terminate asymmetric Heck reaction is highly desirable.

Recently, catalytic asymmetric dearomatization of (hetero)arenes has been intensely developed as an efficient access to produce non-aromatic cyclic molecules.[7] Palladium-catalyzed dearomative Heck-arylation of indoles provides reliable approach to indolines, which are frequently occurring substructures in natural products.[8] Based on dearomative Heck and reductive-Heck reactions, facile construction of C2-substituted indolines bearing one single stereocenter have been realized by Yao and Wu, Fukuyama, and our group.[9] Further, through a domino sequence of Heck/benzyl-Pd species capture, diastereoselective indole dearomative difunctionalization reactions were established by Lautens, Liang, and our group, furnishing a range of 2,3-disubstituted indolines bearing vicinal stereocenters by arylcyanation, diarylation, and arylalkynylation reactions.[10] Nevertheless, enantioselective dearomative Heck arylation of indoles remained much less exploited[9b,9c] and so far no example was reported for the asymmetric dearomative difunctionalization reaction. Here, we communicate a Pd-catalyzed dearomative arylalkynylation of indoles via a domino Heck/Sonogashira sequence using a new BINOL-based phosphoramidite as chiral ligand (Scheme 1b). Indolines bearing vicinal quaternary and tertiary stereocenters at C2-C3 position were efficiently created in one step with excellent enantioselectivities and diastereoselectivities.



Scheme 1. Enantioselective palladium-catalyzed domino Heck-arylation/σ-alkylpalladium species capture process

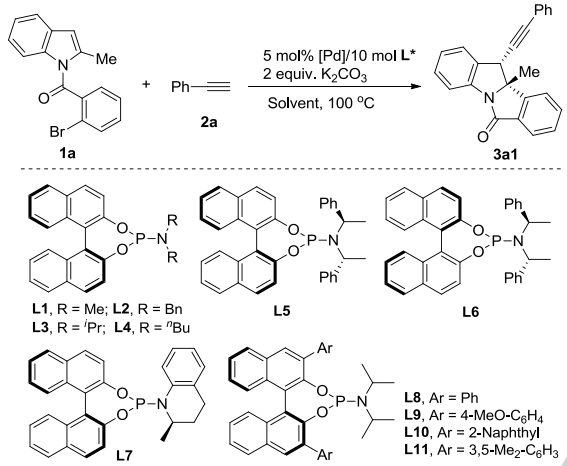
Indole **1a** and phenylacetylene **2a** were chosen as model substrates. Gratifyingly, initial test led to the desired product **3a1** in 70% yield and 29% ee by heating the mixture of **1a** and **2a** in THF (100 °C) with $Pd(dba)_2$ (5 mol%), phosphoramidite **L1** (10 mol%), and K_2CO_3 (2.0 equiv.) (Table 1, entry 1). Surprisingly, the addition of CuI (5 mol%) as a co-catalyst fully suppressed the reaction (entry 2). Slightly lower enantioselectivities were observed when $Pd(dba)_2$ was replaced by $Pd(CH_3CN)_2Cl_2$ or $Pd(OAc)_2$ (entries 3-4). Subsequent ligand examination revealed that the amino substituent of BINOL-based phosphoramidite ligands significantly influenced the enantioselectivity (entries 5-14). Increasing the size of amino substituent could improve the enantioselectivity. Diisopropyl amino ligand **L3** led to 84% yield and 62% ee, while relatively lower ee values were achieved for **L2**, **L4** bearing benzyl and *n*-butyl substituents, respectively (entries 5-7). Comparable results were afforded for MonoPhos-PE (**L5**-**L6**) and Me-THQphos **L7** (entries 8-10). To achieve higher ee, the modified diisopropyl amino ligands **L8**-**L11** bearing 3,3'-diaryl substituents were then examined (entries 11-

[*] Dr. Ren-Rong Liu, Yong-Gang Wang, Ying-Long Li, Bing-Bing Huang, Dr. Ren-Xiao Liang, and Prof. Dr. Yi-Xia Jia
College of Chemical Engineering
Zhejiang University of Technology
Chaowang Road 18#, Hangzhou 310014, China
Supporting information for this article is given via a link at the end of the document.

10.1002/anie.201703833

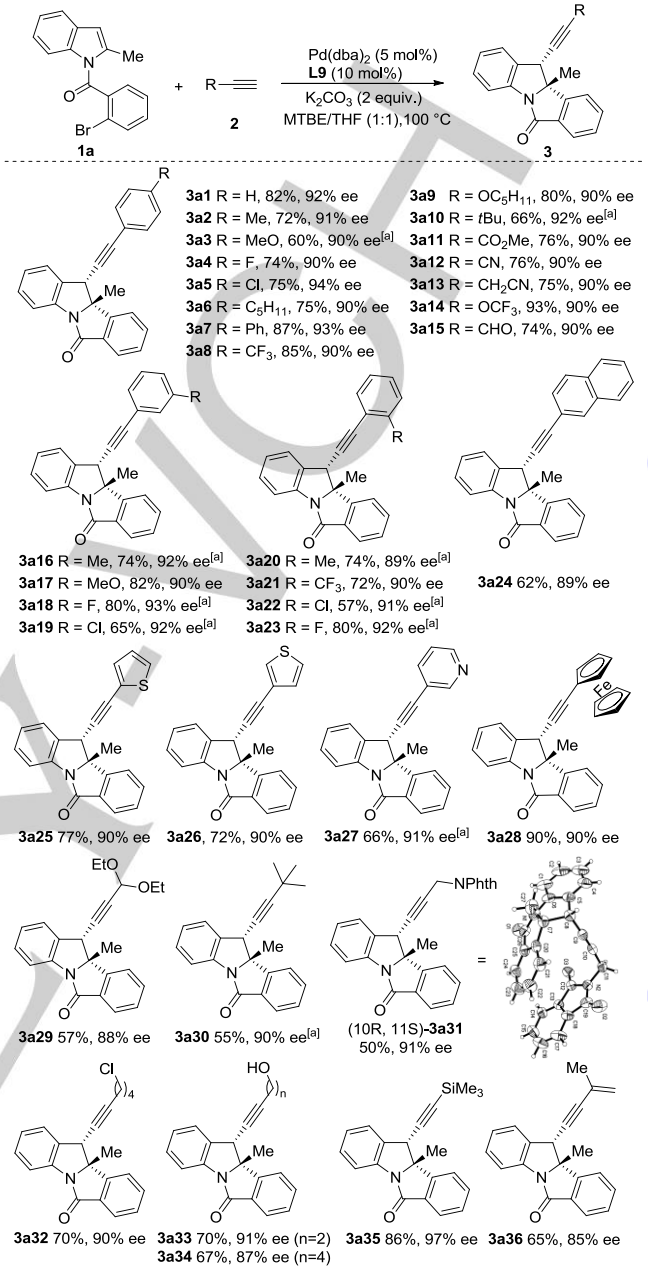
14). As expected, the enantioselectivity of **3a1** was enhanced to 75% for the phenyl-substituted ligand **L8** and to 84% for 4-MeO-phenyl ligand **L9** and 2-naphthyl ligand **L10**. Solvent effect was then investigated (entries 15-17) and the reaction in MTBE delivered **3a1** in 93% ee albeit with a moderate yield (entry 16), while lower ee was observed in toluene (entry 17). Gratefully, the yield was improved to 82% in a mixed solvent of MTBE/THF (1:1) and enantioselectivity was retained (entry 18). It is worth to note that excellent diastereoselectivities (>20:1) were observed for all of the isolated products.

Table 1. Optimization of the reaction conditions.[a]



Entry	L*	[Pd]	Solvent	Yield [%][b]	Ee [%][c]
1	**L1**	$Pd(dba)_2$	THF	70	29
2[d]	**L1**	$Pd(dba)_2$	THF	Trace	--
3	**L1**	$Pd(OAc)_2$	THF	68	28
4	**L1**	$Pd(CH_3CN)_2Cl_2$	THF	73	23
5	**L2**	$Pd(dba)_2$	THF	78	34
6	**L3**	$Pd(dba)_2$	THF	84	62
7	**L4**	$Pd(dba)_2$	THF	79	45
8	**L5**	$Pd(dba)_2$	THF	74	56
9	**L6**	$Pd(dba)_2$	THF	78	58
10	**L7**	$Pd(dba)_2$	THF	65	60
11	**L8**	$Pd(dba)_2$	THF	80	75
12	**L9**	$Pd(dba)_2$	THF	85	84
13	**L10**	$Pd(dba)_2$	THF	80	84
14	**L11**	$Pd(dba)_2$	THF	82	72
15	**L9**	$Pd(dba)_2$	Et_2O	53	87
16	**L9**	$Pd(dba)_2$	MTBE	67	93
17	**L9**	$Pd(dba)_2$	Toluene	80	75
18[e]	**L9**	$Pd(dba)_2$	MTBE/THF	82	92

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Pd] (5 mol%), **L*** (10 mol%), and K_2CO_3 (2.0 equiv.) in the solvent (3.0 mL) at 100 °C for 18 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] CuI (5 mol%) was added. [e] V_{MTBE}: V_{THF} = 1:1; MTBE: methyl *tert*-butyl ether, THF: tetrahydrofuran.

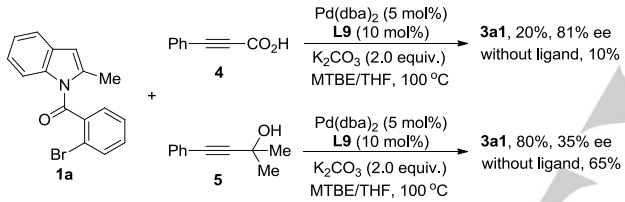


Scheme 2. Scope of the alkynes. Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $Pd(dba)_2$ (5 mol%), **L9** (10 mol%), and K_2CO_3 (2.0 equiv.) in MTBE/THF (3.0 mL, 1:1) at 100 °C; excellent d.r. (>20:1) were observed for all of the products. [a] MTBE (3.0 mL) was used instead.

With the optimal conditions in hand, we investigated the scope of alkyne and the results were listed in Scheme 2. To our delight, a very wide scope of alkynes was observed and all the reactions proceeded smoothly to deliver the desired products in good to excellent enantioselectivities. Arylacetylene bearing a series of *para*-substituents on the phenyl ring, including alkyl (**3a2**, **3a6**, **3a10**, **3a13**), alkoxyl (**3a3**, **3a9**), halide (**3a4**, **3a5**), phenyl (**3a7**), $-CF_3$ (**3a8**), $-OCF_3$ (**3a14**), $-CO_2Me$ (**3a11**), -CN (**3a12**), and formyl group (**3a15**), reacted efficiently with indole **1a** to afford the corresponding products in moderate to good yields with 90-

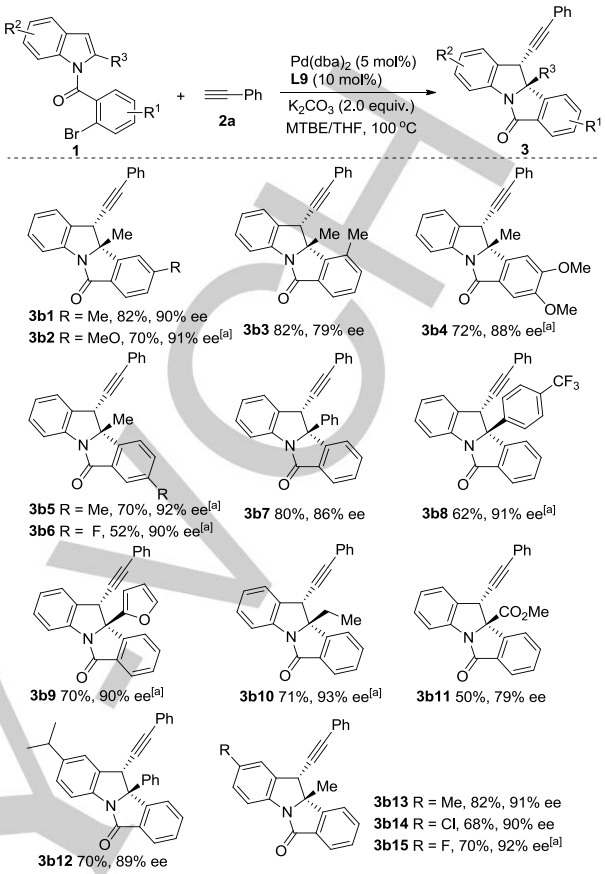
10.1002/anie.201703833

94% ee. *Ortho*- and *meta*-substituents of arylacetylene, such as methyl, methoxyl, trifluoromethyl, and halides, were also well tolerated to give products **3a16**-**3a23** in 89-93% ee and no steric effect was observed for those *ortho*-substituted products **3a20**-**3a23**. In addition, 2-naphthylethyne, ferrocenylethyne, and heteroarylethynes were successfully employed as substrates in the reactions to furnish indolines **3a24**-**3a28** in excellent enantioselectivities. Furthermore, a range of aliphatic alkynes were tested in this reaction. Excellent enantioselectivities for products **3a30** and **3a35** were achieved with 3,3-dimethylbut-1-yne and ethynyltrimethylsilane as substrates. Gratifyingly, indolines bearing acetal (**3a29**), chloride (**3a32**), alcohol (**3a33**, **3a34**), and propene (**3a36**) were isolated in moderate yields and good to excellent enantioselectivities in the reactions with the corresponding aliphatic alkynes. The reaction of a propargylic imide with **1a** led to product **3a31** in 50% yield and 91% ee, of which the absolute configuration was determined to be 10*R*/11*S* based on its single crystal X-ray analysis.[11] Finally, non-terminal alkynes (3-phenylpropiolic acid **4** and 2-methyl-4-phenylbut-3-yn-2-ol **5**) were also tested in the reaction (Scheme 3). Product **3a1** was obtained in either lower yield or lower ee, probably due to poor solubility of acid **4** in the solvent and the backgroud reactions without chiral ligand in both cases.

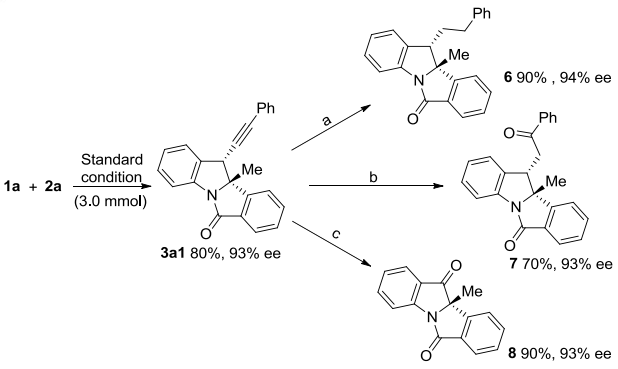


Scheme 3. Dearomative arylalkynylation reaction of non-terminal alkynes

The substrates scope with regard to indoles was then examined. As summarized in Scheme 4, substituent effect on the phenyl ring of the 2-bromobenzoyl moiety (R^1) was first investigated. Either electron-donating or electron-withdrawing substituents were well tolerated in the reactions to yield products **3b1**-**3b6** in good to excellent ees, while lower ee was observed for product **3b3** bearing an *ortho*-methyl substituent and lower yield was obtained for product **3b6** having a fluoro group. Next, a range of substituents attached on the indole ring were screened. Indoles bearing aryl, ethyl, and ester groups at C2 position reacted efficiently with **2a** and afforded products **3b7**-**3b11** in good results. It's worth to note that excellent enantioselectivity was achieved for **3b9** bearing a C2-furyl group, while lower ee was detected for **3b11** containing a ester substituent at C2 position. Moreover, the isopropyl, methyl, chloro, and fluoro substituents at C5 position of indole were well compatible in the reactions to yield products **3b12**-**3b15** in 89-92% ee with moderate to good yields.



Scheme 4. Scope of the indoles. Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $Pd(dba)_2$ (5 mol%), **L9** (10 mol%), and K_2CO_3 (2.0 equiv.) in MTBE/THF (3.0 mL, 1:1) at 100 °C; excellent d.r. (>20:1) were observed for all of the products. [a] MTBE (3.0 mL) was used instead.



Scheme 5. Gram-scale reaction and synthetic transformations of **3a1**: [a] Pd/C (10 mol%), H_2 (1 atm) in MeOH at 25 °C for 12 h; [b] $Pd(OAc)_2$ (5 mol%), in TFA/DCM (1:1, 0.1 M) for 72 h; [c] $KMnO_4$ (3.0 equiv.), $NaHCO_3$ (1.2 equiv.), Bu_4NBr, in DCM/H_2O at 45 °C for 12 h.

A gram-scale reaction of indole **1a** with phenylacetylene **2a** was carried out, which afforded product **3a1** in 80% yield and 93% ee, showing good reliability of the reaction (Scheme 5). Synthetic transformations of **3a1** were then performed. A Pd/C-

catalyzed hydrogenation reaction under H_2 atmosphere easily converted **3a1** to compound **6** in 90% yield. The hydrolysis of the alkyne moiety in TFA/DCM with $Pd(OAc)_2$ as a catalyst led to ketone **7** in 70% yield. Moreover, indolin-3-one **8** bearing a C2-quaternary stereocenter, an intriguing structural unit in natural products, was formed in 90% yield and 93% ee in the presence of $KMnO_4$.

In conclusion, enantioselective dearomative difunctionalization of indoles has been developed through intramolecular Heck-arylation and the following intermolecular capture of secondary benzyl-palladium species by alkynes with $Pd(dba)_2$/phosphoramidite complex as a chiral catalyst. Based on this domino sequence, a very wide range of chiral indolines bearing vicinal quaternary and tertiary stereocenters at C2-C3 position were efficiently constructed in one step with moderate to good yields, excellent enantioselectivities and diastereoselectivities.

Acknowledgements

We are grateful for the generous support by the National Natural Science Foundation of China (21372202, 21502169, 21522207) and the Natural Science Foundation of Zhejiang Province (LR14B020001, LQ15B020003).

Keywords: Dearomatization · Palladium · Heck reaction · Alkynes · Asymmetric catalysis

[1] For reviews, see a) R. Grigg, V. Sridharan, *J. Organomet. Chem.* **1999**, *576*, 65; b) G. Poli, G. Giambastiani, A. Heumann, *Tetrahedron* **2000**, *56*, 5959; c) T. Vlaar, E. Ruijter, R. V. A. Orru, *Adv. Synth. Catal.* **2011**, *353*, 809; d) J. Muzart, *Tetrahedron* **2013**, *69*, 6735.

[2] For selected leading examples, see: a) B. Burns, R. Grigg, V. Santhakumar, V. Sridharan, P. Stevenson, T. Worakun, *Tetrahedron* **1992**, *48*, 7297; b) S. Jaegli, J.-P. Vors, L. Neuville, J. Zhu, *Synlett*, **2009**, *18*, 2997; c) S. Jaegli, J.-P. Vors, L. Neuville, J. Zhu, *Tetrahedron* **2010**, *66*, 8911; d) S. G. Newman, M. Lautens, *J. Am. Chem. Soc.* **2011**, *133*, 1778; e) S. Jaegli, W. Erb, P. Retailleau, J.-P. Vors, L. Neuville, J. Zhu, *Chem. Eur. J.* **2010**, *16*, 5863; f) S. Hayashi, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* **2009**, *48*, 7224; *Angew. Chem.* **2009**, *121*, 7360; g) S. G. Newman, J. K. Howell, N. Nicolaus, M. Lautens, *J. Am. Chem. Soc.* **2011**, *133*, 14916; h) X. Jia, D. A. Petrone, M. Lautens, *Angew. Chem. Int. Ed.* **2012**, *51*, 9870; *Angew. Chem.* **2012**, *124*, 10008; i) X. Liu, X. Ma, Y. Huang, Z. Gu, *Org. Lett.* **2013**, *15*, 4814; j) H. Yoon, D. A. Petrone, M. Lautens, *Org. Lett.* **2014**, *16*, 6420; k) M.-B. Zhou, X.-C. Huang, Y.-Y. Liu, R.-J. Song, J.-H. Li, *Chem. Eur. J.* **2014**, *20*, 1843; l) M.S. McCammant, L. Liao, M. S. Sigman, *J. Am. Chem. Soc.* **2013**, *135*, 4167; m) D. A. Petrone, H. Yoon, H. Weinstabl, M. Lautens, *Angew. Chem. Int. Ed.* **2014**, *53*, 7908; *Angew. Chem.* **2014**, *126*, 8042; n) H. Liu, C. Li, D. Qiu, X. Tong, *J. Am. Chem. Soc.* **2011**, *133*, 6187; o) D. D. Vachhani, H. H. Butani, N. Sharma, U. C. Bhoya, A. K. Shah, E. V. V. Eycken, *Chem. Commun*. **2015**, *51*, 14862; p) C. M. Le, P. J. C. Menzies, D. A. Petrone, M. Lautens, *Angew. Chem. Int. Ed.* **2015**, *54*, 254; *Angew. Chem.* **2015**, *127*, 256.

[3] a) T. Ohshima, K. Kagechika, M. Adachi, M. Sodeoka, M. Shibasaki, *J. Am. Chem. Soc*. **1996**, *118*, 7108; b) K. Kagechika, M. Shibasaki, *J. Org. Chem*. **1991**, *56*, 4093; c) D. Flubacher, G. Helmchen, *Tetrahedron Lett.* **1999**, *40*, 3867; d) B. J. Stokes, L. Liao, A. M. de Andrade, Q. Wang, M. S. Sigman, *Org. Lett.* **2014**, *16*, 4666; e) X. Wu, H.-C. Lin, M.-L. Li, L.-L. Li, Z.-Y. Han, L.-Z. Gong, *J. Am. Chem. Soc*. **2015**, *137*, 13476.

[4] a) A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. Eur. J.* **2007**, 13, 961; b) W. Kong, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 16028; c) W. Kong, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 9714; *Angew. Chem.* **2016**, *128*, 9866; d) Z. Jiang, L. Hou, C. Ni, J. Chen, D. Wang, X. Tong, *Chem. Commun.* **2017**, DOI: 10.1039/C7CC01488K.

[5] For asymmetric reductive-Heck reactions, see: a) A. Minatti, X. Zheng, S. L Buchwald, *J. Org. Chem*. **2007**, *72*, 9253; b) S. Liu, J. Zhou, *Chem. Commun.* **2013**, *49*, 11758; c) G. Yue, K. Lei, H. Hirao, J. Zhou, *Angew. Chem. Int. Ed.* **2015**, *54*, 6531; *Angew. Chem.* **2015**, *127*, 6631; d) W. Kong, Q. Wang, J. Zhu *Angew. Chem. Int. Ed.* **2017**, DOI: 10.1002/anie.201700195.

[6] J. Hu, H. Hirao, Y. Li, J. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 8676; *Angew. Chem.* **2013**, *125*, 8838.

[7] For reviews, see: a) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; b) C.-X. Zhuo, C. Zheng, S.-L. You, *Acc. Chem. Res*. **2014**, *47*, 2558; c) W.-T. Wu, L. Zhang, S.-L. You, *Chem. Soc. Rev.* **2016**, *45*, 1570.

[8] For Pd-catalyzed dearomative arylation reactions, see: a) J. García-Fortanet, F. Kessler, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 6676; b) R. B. Bedford, C. P. Butts, M. F. Haddow, R. Osborne, R. F. Sankey, *Chem. Commun.* **2009**, *45*, 4832; c) S. Rousseaux, J. García-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald, *J. Am. Chem. Soc*. **2011**, *133*, 9282; d) K.-J. Wu, L.-X. Dai, S.-L. You, *Org. Lett*. **2012**, *14*, 3772; e) K.-J. Wu, L.-X. Dai, S.-L. You, *Chem. Commun.* **2013**, *49*, 8620; f) R.-Q. Xu, Q. Gu, W.-T. Wu, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2014**, *136*, 15469 g) K. Du, P. Guo, Y. Chen, Z. Cao, Z. Wang, W. Tang, *Angew. Chem. Int. Ed.* **2015**, *54*, 3033; *Angew. Chem.* **2015**, *127*, 3076; h) R.-Q. Xu, P. Yang, H.-F. Tu, S.-G. Wang, S.-L. You, *Angew. Chem. Int. Ed.* **2016**, *55*, 15137; *Angew. Chem.* **2016**, *128*, 15361.

[9] a) L. Zhao, Z. Li, L. Chang, J. Xu, H. Yao, X. Wu, *Org. Lett*. **2012**, *14*, 2066; b) C. Shen, R.-R. Liu, R.-J. Fan, Y.-L. Li, T.-F. Xu, J.-R. Gao, Y.-X. Jia, *J. Am. Chem. Soc*. **2015**, *137*, 4936; c) K. Douki, H. Ono, T. Taniguchi, J. Shimokawa M. Kitamura, T. Fukuyama, *J. Am. Chem. Soc.* **2016**, *138*, 14578.

[10] a) D. A. Petrone, A. Yen, N. Zeidan, M. Lautens, *Org. Lett*. **2015**, *17*, 4838 b) D. A. Petrone, M. Kondo, N. Zeidan, M. Lautens, *Chem. Eur. J.* **2016**, *22*, 5684; c) S. Chen, X.-X. Wu, J. Wang, X.-H. Hao, Y. Xia, Y. Shen, H. Jing, Y.-M. Liang, *Org. Lett*. **2016**, *18*, 4016; d) R.-R. Liu, T.-F. Xu, Y.-G. Wang, B. Xiang, J.-R. Gao, Y.-X. Jia, *Chem. Commun.* **2016**, *52*, 13664.

[11] CCDC 1543558 (**3a31**) containing the supplementary crystallographic data could be obtained free of charge from The Cambridge Crystallographic Data Centre.

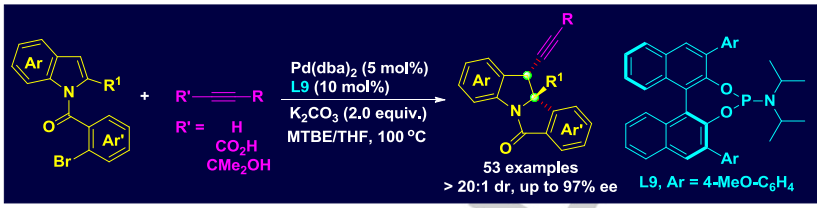
10.1002/anie.201703833

WILEY-VCH

Asymmetric Catalysis

*Ren-Rong Liu, Yong-Gang Wang, Ying-Long Li, Bing-Bing Huang, Ren-Xiao Liang, and Yi-Xia Jia**_____ ***Page – Page***

Enantioselective Dearomative Difunctionalization of Indoles via Palladium-Catalyzed Domino Heck/Sonogashira Sequence



Dearomative difunctionalization: A Pd-catalyzed highly enantioselective dearomative arylalkynylation of *N*-substituted indoles with alkynes has been established by using a BINOL-based phosphoramidite as chiral ligand. A wide range of 2,3-disubstitute indolines bearing vicinal tertiary and quaternary stereocenters were efficientl constructed in one step with excellent enantioselectivities and diastereoselectivities.