



Enantioselective Palladium-Catalyzed Dearomative Cyclization for the Efficient Synthesis of Terpenes and Steroids**

Kang Du, Pan Guo, Yuan Chen, Zhen Cao, Zheng Wang, and Wenjun Tang*

Abstract: A novel enantioselective palladium-catalyzed dearomative cyclization has been developed for the efficient construction of a series of chiral phenanthrenone derivatives bearing an all-carbon quaternary center. The effectiveness of this method in the synthesis of terpenes and steroids was demonstrated by a highly efficient synthesis of a kaurene intermediate, the facile construction of the skeleton of the anabolic steroid boldenone, and the enantioselective total synthesis of the antimicrobial diterpene natural product (–)-totaradiol.

Tricyclic skeletons bearing chiral all-carbon quaternary centers, such as chiral phenanthrenone derivatives, exist in numerous complex terpenes and steroids with interesting biological activities (Figure 1).^[1] For example, kaurene^[2] is the

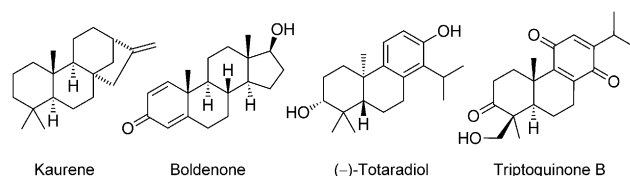
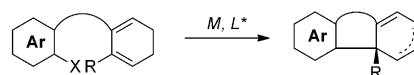


Figure 1. Terpenes and steroids bearing chiral all-carbon quaternary centers.

biosynthetic precursor of the plant hormones gibberellins, boldenone^[3] is an anabolic steroid, totaradiol^[4a–d] is a diterpene natural product that exhibits good antimicrobial properties, and triptocquinone B exhibits a remarkable inhibitory activity against interleukin-1 release.^[4e–f] Their syntheses have attracted a great deal of attention with the emergence of various excellent methods.^[5] Among them, the asymmetric intramolecular Heck reaction^[6] has become a powerful method for constructing chiral polycyclic skeletons bearing all-carbon quaternary centers (Figure 2). However, a number of synthetic steps are often required either in constructing the

Asymmetric Heck reaction



Asymmetric dearomative cyclization (this approach)

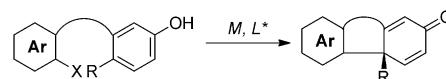


Figure 2. Novel asymmetric dearomative cyclization for the synthesis of terpenes and steroids.

olefin moiety necessary for the Heck cyclization or for the post-modification of the Heck product to the target molecule. Alternatively, asymmetric intramolecular dearomative cyclizations^[7,8] between two aryl systems can offer better synthetic efficiency owing to the availability of aryl systems as well as the convenience in the post-modification of the cyclization product. Herein, we present a powerful asymmetric palladium-catalyzed dearomative cyclization that has led to a series of chiral phenanthrenone derivatives bearing an all-carbon quaternary center in excellent enantioselectivities. The new method has been successfully applied in the highly efficient synthesis of a chiral kaurene intermediate, the facile construction of the skeleton of the anabolic steroid boldenone, and an enantioselective total synthesis of the diterpene natural product (–)-totaradiol.

Although dearomative cyclizations have been frequently applied in natural product synthesis, the asymmetric transition-metal-catalyzed dearomative cyclization has remained underdeveloped, and only a few examples of efficient intramolecular dearomative arylations have been reported thanks to the pioneering work from the Buchwald,^[9] Bedford,^[10] and You^[11] groups. Buchwald^[9] and co-workers developed efficient dearomative cyclizations to form chiral benzocarbazole derivatives and spirocyclohexadienones bearing all-carbon quaternary centers. You^[11e] et al. recently reported an interesting dearomative cyclization to form a tetracyclic spiroamine framework. However, to the best of our knowledge, enantioselective dearomative arylations have not been applied in the synthesis of complex natural products. Asymmetric dearomative cyclizations for the efficient construction of chiral terpenes and steroids remain to be uncovered. We believed that bromine-substituted phenol **1a** could undergo an asymmetric dearomative cyclization in the presence of a chiral palladium catalyst to form chiral phenanthrenone compound **2a** as well as the achiral regioisomeric cyclization product **3a** (Figure 3). Mechanistically, after oxidative addition, compound **1a** would yield Pd^{II} complex **II**. In the presence of a base, nucleophilic substitution could take place

[*] K. Du, P. Guo, Y. Chen, Z. Cao, Prof. Dr. W. Tang
State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Ling Ling Rd, Shanghai 200032 (China)
E-mail: tangwenjun@sioc.ac.cn
Dr. Z. Wang
Innovation Center China, AstraZeneca Global R&D (China)

[**] We thank the NSFC (21432007, 21272254), STCSM (13J1410900), and the “Thousand Plan” Youth program for financial support and Mettler Toledo for a ReactIR Instrument.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201411817>.

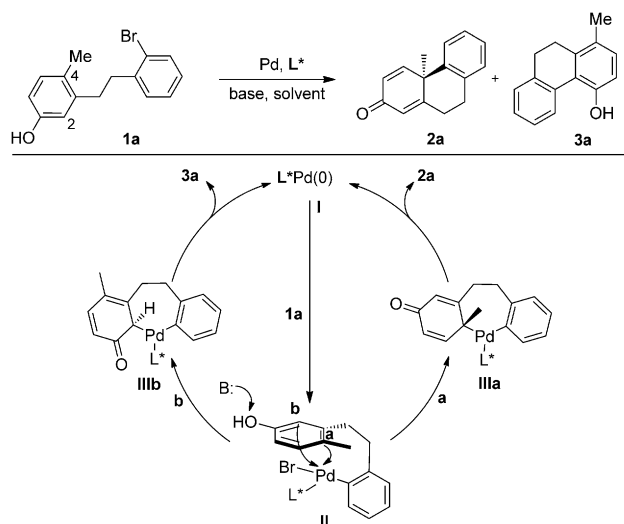


Figure 3. Competitive cyclization pathways of **1a**.

at the 4-position of the phenol moiety (path a) to form **IIIa**, which, after reductive elimination, leads to the formation of chiral phenanthrenone **2a**. In parallel, the cyclization could also occur at the 2-position of the phenol moiety (path b), providing the achiral product **3a**. Although **2a** is thermodynamically less stable than **3a**, the formation of **2a** could be kinetically more favorable. The task is to achieve high reactivity, chemoselectivity, and enantioselectivity for this unprecedented challenging dearomative cyclization.

We first studied the intramolecular cyclization of compound **1a** by employing a chiral palladium catalyst (Table 1). The reactions were performed in toluene at 90 °C for 16 hours with K_2CO_3 as the base at a palladium loading of 2 mol %. A series of chiral bis- or monophosphine ligands were employed. Although cyclization did not occur with BINAP or DuPhos (entries 1 and 2), the reactions with P-chiral biaryl monophosphine ligands **L1–L6**^[12] all proceeded smoothly. Excitingly, good to excellent yields of **2a** were isolated along with **3a** as the minor product. A good *ee* (81 %) was obtained when BI-DIME was employed as the ligand (entry 3). The enantioselectivity (54 % *ee*) decreased when **L2** was employed, which bears a methyl substituent on the upper ring (entry 4). We then modified the ligand structure by changing the second aryl moiety. Ligand **L4**, with two *ortho* aryloxy substituents on the second aryl ring, gave the product with 86 % *ee* (entry 6). AntPhos (**L5**) also gave a similar selectivity (84 % *ee*, entry 7). Gratifyingly, when a new ligand **L6**^[13] bearing a 2,5-diphenylpyrrole moiety was employed, the cyclization product was formed in 94 % yield and 92 % *ee* (entry 8). Further studies on the solvents and catalyst precursors showed that toluene and $[Pd(cinnamyl)Cl]_2$ were most suitable for this cyclization (entries 9–14).

We then studied the substrate scope of this asymmetric cyclization. A series of tricyclic phenanthrenone derivatives (**2a–2l**; Table 2, see also Figure 4) bearing an all-carbon quaternary center were efficiently synthesized in moderate to high yields and in excellent enantioselectivities (83–99 % *ee*). Functional groups, such as fluoro, chloro, and methoxy substituents, were well tolerated (**2b–2d**). Substrates with

Table 1: Palladium-catalyzed asymmetric cyclization of compound **1a**.^[a]

Entry	Ligand	Solvent	Yield [%]	2a/3a	<i>ee</i> of 2a [%] ^[b]
1	(<i>S</i>)-BINAP	toluene	0	—	—
2	(<i>S,S</i>)-DuPhos	toluene	0	—	—
3	(<i>S</i>)- L1	toluene	68	87:13	81
4	(<i>S,S</i>)- L2	toluene	92	94:6	54
5	(<i>S</i>)- L3	toluene	88	91:9	78
6	(<i>S</i>)- L4	toluene	86	91:9	86
7	(<i>S</i>)- L5	toluene	91	97:3	84
8	(<i>S</i>)- L6	toluene	94	96:4	92
9	(<i>S</i>)- L6	toluene/H ₂ O	90	96:4	82
10	(<i>S</i>)- L6	dioxane	94	96:4	88
11	(<i>S</i>)- L6	cyclohexane	95	96:4	87
12	(<i>S</i>)- L6	CF ₃ C ₆ F ₅	64	88:12	86
13 ^[c]	(<i>S</i>)- L6	toluene	94	96:4	90
14 ^[d]	(<i>S</i>)- L6	toluene	95	96:4	88

[a] Unless otherwise specified, the reactions were performed under nitrogen atmosphere at 90 °C for 16 hours with **1a** (0.1 mmol), K_2CO_3 (0.15 mmol), $[Pd(cinnamyl)Cl]_2$ (1 mol %), and the specified ligand (2 mol %). Isolated yields are given. The absolute configuration of **2a** was assigned by comparing the sign of the optical rotation to that of product **2e**. [b] Determined by HPLC analysis on a chiral stationary phase (Chiralcel AD-H). [c] $Pd(OAc)_2$ (2 mol %). [d] $[Pd(allyl)Cl]_2$ (1 mol %).

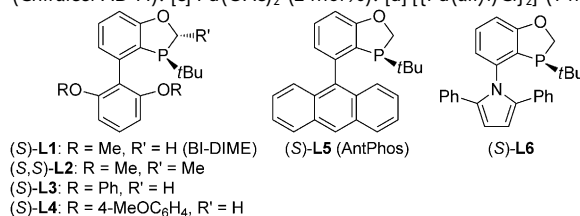


Table 2: Substrate scope of the asymmetric cyclization.^[a]

2b 86% yield 91% <i>ee</i>	2c 74% yield 93% <i>ee</i>	2d 74% yield 90% <i>ee</i>	2e 78% yield 90% <i>ee</i>
2f 54% yield 92% <i>ee</i>	2g 60% yield 99% <i>ee</i>	2h ^[b] 99% yield 99% <i>ee</i>	2i 95% yield 83% <i>ee</i>
2j 35% yield 96% <i>ee</i>	2k 88% yield 91% <i>ee</i>	2l 96% yield 91% <i>ee</i>	2m ^[c] 0% yield

[a] The reactions were performed in toluene under nitrogen atmosphere at 90 °C for 16 hours with **1b–1m** (0.1 mmol), K_2CO_3 (0.15 mmol), $[Pd(cinnamyl)Cl]_2$ (1 mol %), and (*S*)-**L6** (2 mol %). Yields of isolated products are given. The absolute configurations were determined or assigned by analogy on the basis of the X-ray structure of **2e**, the enantioselectivities were determined by HPLC analysis on a chiral stationary phase (Chiralcel AD-H or OJ-H column). [b] Prepared from vinyl triflate **1h**. [c] Cyclization exclusively occurred at the 2-position of the phenol moiety.

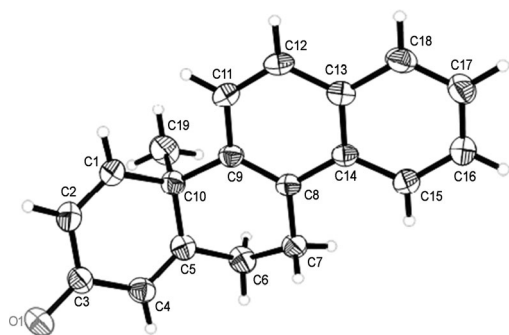


Figure 4. X-ray structure of cyclization product **2e**.^[14] Ellipsoids set at 30% probability. The absolute configuration at the C10 position is *R*.

naphthalene, quinone, and furan rings were also compatible with the reaction conditions (**2e–2g**). A vinyl triflate **1h** was also successfully employed to provide the desired product **2h** in 99% yield and 99% *ee*. Aside from six-membered rings, five- and seven-membered rings were also constructed efficiently (**2i–2j**). The alkyl substituent at the 4*a*-position was not limited to a methyl group, as longer aliphatic substituents, such as ethyl and butyl groups, were also tolerated (**2k** and **2l**). However, the cyclization failed to form compound **2m**, which bears a phenyl substituent at the 4*a*-position.

The high rigidity of (*S*)-**L6** allowed us to propose a stereochemical model for this cyclization, where the enantioselectivity should be determined during the reductive elimination. As shown in Figure 5, the 2,5-diphenylpyrrole

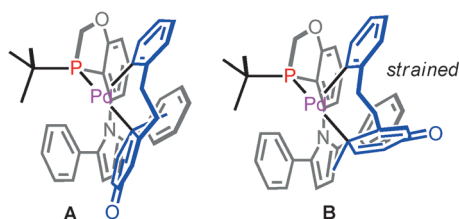
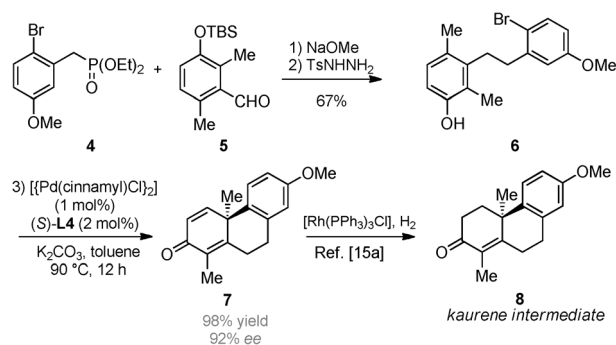


Figure 5. Proposed stereochemical model for the reductive elimination step of the cyclization of **1a** with Pd/(*S*)-**L6** as the catalyst.

moiety of (*S*)-**L6** blocks the backside of the complex, and its bulky *tert*-butyl group can well dictate the orientation of substrate coordination. We believe that substrate **1a**, after oxidative addition and nucleophilic substitution, could adopt two major conformers, **A** and **B**, when coordinated to the Pd/(*S*)-**L6** complex.^[15] Conformer **B** appears to be more strained whereas the more favorable conformer **A** undergoes reductive elimination to provide the cyclization product **2a** with the observed *R* configuration.

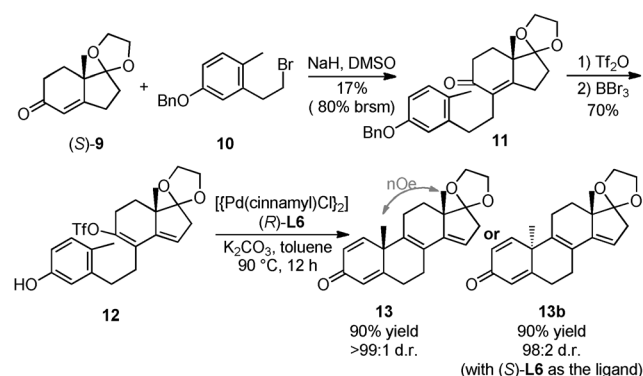
The cyclization was applied in the efficient synthesis of enone **8**, a key chiral intermediate^[16] for the synthesis of kaurene, abietic acid, and a bruceantin analogue (Scheme 1). Horner–Wadsworth–Emmons reaction between phosphonate **4** and aldehyde **5**^[17] followed by reduction of the double bond with TsNHNH₂ provided bromide **6** in 67% overall yield. The cyclization of **6** with Pd/(*S*)-**L4** (2 mol %) proceeded smoothly



Scheme 1. Efficient synthesis of kaurene intermediate **8**. TBS = *tert*-butyldimethylsilyl, Ts = *para*-toluenesulfonyl.

to provide tricyclic compound **7** in 98% yield and 92% *ee*. Hydrogenation of **7** using a reported procedure^[16a] led to the formation of **8** in four steps from aldehyde **5**. This synthetic route by a palladium-catalyzed dearomative cyclization provides significant advantages over a reported fourteen-step synthesis featuring an asymmetric Heck reaction.^[16a]

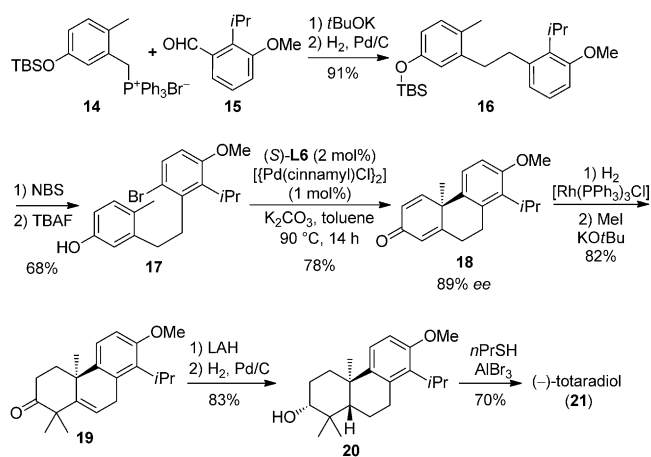
The method was also applied to the construction of the skeleton of the anabolic steroid boldenone (Scheme 2).^[3]



Scheme 2. Efficient synthesis of boldenone skeleton **13**. brsm = based on recovered starting material, Tf = trifluoromethylsulfonyl.

Thus, ketal **9**,^[18] which was readily prepared from the Hajos–Parrish ketone, was reacted with bromide **10** in the presence of NaH to form **11** in an unoptimized yield of 17%. Conversion of **11** into the vinyl triflate with Tf₂O as the reagent followed by treatment with BBr₃ provided **12** in 70% overall yield. Cyclization of triflate **12** in the presence of the Pd/(*R*)-**L6** catalyst led to boldenone skeleton **13** in 90% yield and a diastereomeric ratio of >99:1. Notably, its diastereoisomer **13b** could also be prepared efficiently by cyclization with a Pd/(*S*)-**L6** catalyst in 90% yield and 98:2 d.r. The catalyst-controlled preparation of both **13** and **13b** demonstrates the high compatibility of this asymmetric cyclization with other chiral elements that might be present in the substrate and its potential synthetic utilities in steroid synthesis.

Finally, this asymmetric cyclization was applied to the total synthesis of (–)-totaradiol (Scheme 3). Thus, a Wittig reaction with compound **14** and the known aldehyde^[4d] **15**



Scheme 3. Total synthesis of (–)-totaradiol (**21**). LAH = lithium aluminum hydride, NBS = *N*-bromosuccinimide, TBAF = tetrabutylammonium fluoride.

followed by hydrogenation provided the saturated coupling product **16** in 91% overall yield. Bromination with NBS and subsequent treatment with TBAF provided phenol **17** in 68% overall yield. Asymmetric cyclization of **17** with Pd/(*S*)-**L6** as the catalyst provided the desired product **18** in 78% yield and 89% *ee*. A simple crystallization of **18** from hexane elevated its optical purity to >99% *ee*. Hydrogenation and methylation^[19] of **18** provided ketone **19** in 82% overall yield. Reduction of **19** with LAH followed by hydrogenation formed compound **20** in 83% overall yield. Methoxy deprotection of **20** with AlBr₃/*n*PrSH^[4d] completed the enantioselective synthesis of (–)-totaradiol (**21**) in 23% overall yield over ten steps from the known aldehyde **15** by using our newly developed cyclization method. We believe that this asymmetric cyclization can offer rapid access to various other diterpenoids, such as triptonequinone B.

In summary, we have developed a novel and efficient palladium-catalyzed dearomative cyclization, which enabled the synthesis of a series of chiral tricyclic phenanthrene derivatives bearing all-carbon quaternary centers in excellent enantioselectivities. This method, which is complementary to the traditional Heck reaction, has provided a new strategy for the efficient synthesis of terpenes and steroids. The effectiveness of this method has been demonstrated by the efficient syntheses of a chiral kaurene intermediate, the boldenone skeleton, and of the antimicrobial diterpene totaradiol.

Received: December 8, 2014

Published online: February 4, 2015

Keywords: asymmetric cyclization · palladium · phosphine ligands · total synthesis · transition-metal catalysis

- [1] a) T. J. Maimone, P. S. Baran, *Nat. Chem. Biol.* **2007**, *3*, 396; b) J. Gershenzon, N. Dudareva, *Nat. Chem. Biol.* **2007**, *3*, 408; L. Velluz, J. Valls, G. Nominé, *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 181; *Angew. Chem.* **1965**, *77*, 185; c) R. A. Yoder, J. N. Johnston, *Chem. Rev.* **2005**, *105*, 4730; d) A.-S. Chapelon, D. Moraleda, R. Rodriguez, C. Ollivier, M. Santelli, *Tetrahedron* **2007**, *63*, 11511.

- [2] a) K.-i. Hayashi, K. Horie, Y. Hiwatashi, H. Kawaide, S. Yamaguchi, A. Hanada, T. Nakashima, M. Nakajima, L. N. Mander, H. Yamane, M. Hasebe, H. Nozaki, *Plant Physiol.* **2010**, *153*, 1085; b) K. Nakanishi, T. Goto, G. Ito, S. Natori, S. Nozoe, *Natural Products Chemistry*, Academic Press, New York, **1974**, 1983.
- [3] F. Le Bideau, S. Dagorne, *Chem. Rev.* **2013**, *113*, 7793.
- [4] a) J. G. Bendall, R. C. Cambie, *Aust. J. Chem.* **1995**, *48*, 883; b) J. A. Barltrop, N. A. J. Rogers, *J. Chem. Soc.* **1958**, 2566; c) M. Tada, J. Kurabe, H. Yasue, T. Ikuta, *Chem. Pharm. Bull.* **2008**, *56*, 287; d) M. B. Kim, J. T. Shaw, *Org. Lett.* **2010**, *12*, 3324; e) I. Yamamura, Y. Fujiwara, T. Yamato, O. Irie, K. Shishido, *Tetrahedron Lett.* **1997**, *38*, 4121; f) K. Shishido, K. Goto, S. Miyoshi, Y. Takaishi, M. Shibuya, *Tetrahedron Lett.* **1993**, *34*, 339.
- [5] For an asymmetric iridium-catalyzed cyclization, see: a) M. A. Schafroth, D. Sarlah, S. Krautwald, E. M. Carreira, *J. Am. Chem. Soc.* **2012**, *134*, 20276; for asymmetric Brønsted/Lewis acid catalyzed cyclizations, see: b) K. Ishihara, S. Nakamura, H. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 4906; c) K. Ishihara, H. Ishibashi, H. Yamamoto, *J. Am. Chem. Soc.* **2001**, *123*, 1505; d) H. Ishibashi, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 11122; e) Y.-J. Li, B. Zhao, L.-J. S. Tan, Z.-L. Shen, T.-P. Loh, *J. Am. Chem. Soc.* **2010**, *132*, 10242; f) K. Surendra, E. J. Corey, *J. Am. Chem. Soc.* **2012**, *134*, 11992; for organocatalyzed cyclizations, see: g) A. Sakakura, A. Ukai, K. Ishihara, *Nature* **2007**, *445*, 900; h) S. Rendler, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 5027; i) R. R. Knowles, S. Lin, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 5030; for a platinum-catalyzed cyclization, see: j) C. A. Mullen, A. N. Campbell, M. R. Gagné, *Angew. Chem. Int. Ed.* **2008**, *47*, 6011; *Angew. Chem.* **2008**, *120*, 6100; for a gold-catalyzed cyclization, see: k) S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8276; for recent syntheses of complex *ent*-kaurenes, see: l) E. C. Cherney, J. C. Green, P. S. Baran, *Angew. Chem. Int. Ed.* **2013**, *52*, 9019; *Angew. Chem.* **2013**, *125*, 9189; m) P. Lu, Z.-H. Gu, A. Zakarian, *J. Am. Chem. Soc.* **2013**, *135*, 14552; n) P. Lu, A. Mailyan, Z.-H. Gu, D. M. Guptill, H.-B. Wang, H. M. L. Davies, A. Zakarian, *J. Am. Chem. Soc.* **2014**, *136*, 17738; o) B. J. Moritz, D. J. Mack, L.-C. Tong, R. J. Thomson, *Angew. Chem. Int. Ed.* **2014**, *53*, 2988; *Angew. Chem.* **2014**, *126*, 3032; p) K. E. Lazarski, B. J. Moritz, R. J. Thomson, *Angew. Chem. Int. Ed.* **2014**, *53*, 10588; *Angew. Chem.* **2014**, *126*, 10762.
- [6] a) M. Mori, K. Chiba, Y. Ban, *Tetrahedron Lett.* **1977**, *18*, 1037; b) Y. Sato, M. Soeoka, M. Shibasaki, *J. Org. Chem.* **1989**, *54*, 4738; c) N. E. Carpenter, D. J. Kucera, L. E. Overman, *J. Org. Chem.* **1989**, *54*, 5846; d) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945; e) S. P. Maddaford, N. G. Andersen, W. A. Cristofoli, B. A. Keay, *J. Am. Chem. Soc.* **1996**, *118*, 10766.
- [7] For reviews, see: a) A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917; b) S. Quideau, L. Pouységu, D. Deffieux, *Synlett* **2008**, 467; c) L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235; d) L. Pouységu, T. Sylla, T. Garnier, L. B. Rojas, J. Charris, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 5908; e) S. P. Roche, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068; *Angew. Chem.* **2011**, *123*, 4154; f) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; *Angew. Chem.* **2012**, *124*, 12834; g) Q. Ding, Y. Ye, R. Fan, *Synthesis* **2013**, 1.
- [8] For recent examples, see: a) T. Yakura, M. Omoto, Y. Yamauchi, Y. Tian, A. Ozono, *Tetrahedron* **2010**, *66*, 5833; b) T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, Y. Hamada, *Org. Lett.* **2010**, *12*, 5020; c) A. Rudolph, P. H. Bos, A. Meetsma, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2011**, *50*, 5834; *Angew. Chem.* **2011**, *123*, 5956; d) T. Oguma, T. Katsuki, *J. Am. Chem. Soc.* **2012**, *134*, 20017; e) T. Nemoto, Z. Zhao, T. Yokosaka, Y. Suzuki, R. Wu, Y. Hamada, *Angew. Chem. Int.*

- Ed.* **2013**, 52, 2217; *Angew. Chem.* **2013**, 125, 2273; f) Q. Xiao, J. J. Jackson, A. Basak, J. M. Bowler, B. G. Miller, A. Zakarian, *Nat. Chem.* **2013**, 5, 410; g) T. Nemoto, N. Matsuo, Y. Hamada, *Adv. Synth. Catal.* **2014**, 356, 2417.
- [9] a) J. García-Fortanet, F. Kessler, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, 131, 6676; b) S. Rousseaux, J. García-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, 133, 9282.
- [10] a) R. B. Bedford, C. P. Butts, M. F. Haddow, R. Osborne, R. F. Sankey, *Chem. Commun.* **2009**, 4832; b) R. B. Bedford, N. Fey, M. F. Haddow, R. F. Sankey, *Chem. Commun.* **2011**, 47, 3649.
- [11] a) Q.-F. Wu, W.-B. Liu, C.-X. Zhou, Z.-Q. Rong, K.-Y. Ye, S.-L. You, *Angew. Chem. Int. Ed.* **2011**, 50, 4455; *Angew. Chem.* **2011**, 123, 4547; b) K.-J. Wu, L.-X. Dai, S.-L. You, *Org. Lett.* **2012**, 14, 3772; c) C.-X. Zhuo, S.-L. You, *Angew. Chem. Int. Ed.* **2013**, 52, 10056; *Angew. Chem.* **2013**, 125, 10240; d) K.-J. Wu, L.-X. Dai, S.-L. You, *Chem. Commun.* **2013**, 49, 8620; during the preparation of this manuscript, You et al. reported an interesting dearomative cyclization to form a tetracyclic spiroamine framework; see: e) R.-Q. Xu, Q. Gu, W.-T. Wu, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2014**, 136, 15469.
- [12] a) W. Tang, A. G. Capacci, X. Wei, W. Li, A. White, N. D. Patel, J. Savoie, J. J. Gao, S. Rodriguez, B. Qu, N. Haddad, B. Z. Lu, S. Krishnamurthy, N. K. Yee, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2010**, 49, 5879; *Angew. Chem.* **2010**, 122, 6015; b) W. Tang, S. Keshipeddy, Y. Zhang, X. Wei, J. Savoie, N. D. Patel, N. K. Yee, C. H. Senanayake, *Org. Lett.* **2011**, 13, 1366; c) Q. Zhao, C. Li, C. H. Senanayake, W. Tang, *Chem. Eur. J.* **2013**, 19, 2261; d) W. Tang, N. D. Patel, G. Xu, X. Xu, J. Savoie, S. Ma, M. Hao, S. Keshipeddy, A. G. Capacci, X. Wei, Y. Zhang, J. J. Gao, W. Li, S. Rodriguez, B. Z. Lu, N. K. Yee, C. H. Senanayake, *Org. Lett.* **2012**, 14, 2258; e) G. Xu, W. Fu, G. Liu, C. H. Senanayake, W. Tang, *J. Am. Chem. Soc.* **2014**, 136, 570; f) G. Xu, Q. Zhao, W. Tang, *Chin. J. Org. Chem.* **2014**, 34, 1919.
- [13] See the Supporting Information for details.
- [14] CCDC 1033016 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.
- [15] A T-shaped conformation is proposed for the three-coordinate Pd^{II} complex. For examples of T-shaped monophosphine-coordinated Pd^{II} complexes, see: a) J. P. Stambuli, C. D. Incarvito, M. Bühl, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, 126, 1184; b) J. P. Stambuli, Z. Weng, C. D. Incarvito, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2007**, 46, 7674; *Angew. Chem.* **2007**, 119, 7818; c) S. E. Denmark, R. C. Smith, *J. Am. Chem. Soc.* **2010**, 132, 1243; d) P. J. Milner, T. J. Maimone, M. Su, J. Chen, P. Müller, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, 134, 19922.
- [16] a) K. Kondo, M. Sodeoka, M. Shibasaki, *J. Org. Chem.* **1995**, 60, 4322; b) M. E. Kuehne, J. A. Nelson, *J. Org. Chem.* **1970**, 35, 161; c) R. A. Bell, R. E. Ireland, R. A. Partyka, *J. Org. Chem.* **1970**, 35, 161; d) C. K.-F. Chiu, S. V. Govindan, P. L. Fuchs, *J. Org. Chem.* **1994**, 59, 311; e) W. Nerinckx, W. Vandewalle, *Tetrahedron: Asymmetry* **1990**, 1, 265.
- [17] W. Chen, K. Kobayashi, K. Takahashi, T. Honda, *Synth. Commun.* **2011**, 41, 3385.
- [18] a) P. Ciceri, F. W. J. Demnitz, *Tetrahedron Lett.* **1997**, 38, 389; b) G. A. Molander, M. S. Quirmbach, L. F. Silva, Jr., K. C. Spencer, J. Balsells, *Org. Lett.* **2001**, 3, 2257.
- [19] D. A. Siler, J. D. Mighion, E. J. Sorensen, *Angew. Chem. Int. Ed.* **2014**, 53, 5332; *Angew. Chem.* **2014**, 126, 5436.