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Asymmetric Addition of Arylboronic Acids to Cumulene Derivatives Catalyzed by Axially Chiral N-Heterocyclic Carbene–Pd^{2+} Complexes

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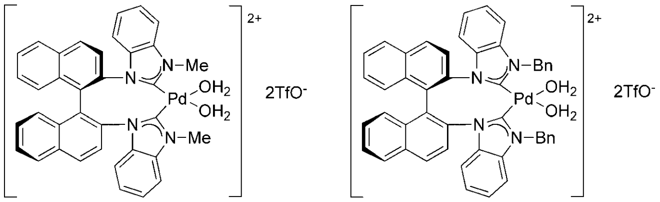
Cumulenes can serve as extremely versatile building blocks for rapid construction of molecular complexity in organic synthesis, because of their unique reactivities in many organic reactions.[1] Moreover, some natural products with a cumulenic structure have been recently discovered.[2,3] Although their novel chemical properties have been extensively explored, thus far, the applications of unsymmetrical cumulene derivatives in asymmetric catalysis have not been reported.[4]

Catalytic, asymmetric, conjugate addition of organoboron reagents to activated alkenes is an efficient method for construction of chiral, enantioenriched compounds by using achiral precursors.[5] To date, several examples on addition of organoboronic acids to allenes catalyzed by palladium have been reported.[6a–d] Moreover, the enantioselective addition of organoboronic reagents to allenic compounds catalyzed by palladium[6e–m] or rhodium[7] has also been successfully developed to provide chiral allylic or allenic products in good yields and good *ee* values. But, to the best of our knowledge, the use of cumulene derivatives as substrates in this asymmetric reaction still remains unexplored. Herein, we report the first examples of asymmetric addition of arylboronic acids to cumulene derivatives catalyzed by axially chiral, N-heterocyclic carbene (NHC)–Pd^{2+}–diaqua complexes **1a** and **1b** (Scheme 1).[8]

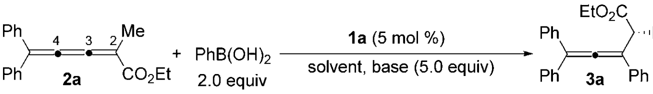
Initially, we utilized ethyl-2-methyl-5,5-diphenylpenta-2,3,4-trienoate **2a** and phenylboronic acid (2.0 equiv) as substrates in the presence of K_3PO_4 (5.0 equiv) as a base with NHC–Pd-complex **1a** (5 mol %) as the catalyst to examine the reaction outcome. It was delightful to find that the insertion of an arylpalladium species into the C2–C3 double bond of **2a** took place smoothly to afford allenic product **3a** in 89 % yield and 18 % *ee* at 80 °C in dioxane along with a trace amount of achiral product derived from the insertion of arylpalladium species at the C3–C4 double bond (Table 1, entry 1 and Scheme 4).[1a,7,9] The examination of various bases and solvents as well as the reaction temperature revealed that this asymmetric addition reaction should be carried out in dioxane with Et_3N (2.0 equiv) at 50 °C, to give **3a** in 96 % yield and 90 % *ee* (Table 1, entries 2–9). The chiral NHC–Pd complex **1b** as the catalyst produced **3a** in 85 % yield and 88 % *ee* under identical conditions (Table 1, entry 10).



(*R*)-[(*N*-Me-NHC)Pd]$^{2+}$ **1a**　(*R*)-[(*N*-Bn-NHC)Pd]$^{2+}$ **1b**

Scheme 1. Chiral, cationic, NHC–Pd^{2+}–diaqua complexes **1a** and **1b**. Bn = benzyl, TfO = triflate.

Table 1. Optimization of the reaction conditions of NHC–Pd-catalyzed, asymmetric addition of phenylboronic acid to **2a**.



Entry	*T* [°C]	Base	Solvent	*t* [h]	Yield [%][a]	*ee* [%][b]
1	80	K_3PO_4	dioxane	10	89	18 (*R*)[c]
2	80	K_2CO_3	dioxane	10	92	40 (*R*)
3	80	DIPEA[d]	dioxane	12	93	18 (*R*)
4	80	Et_3N	dioxane	10	96	82 (*R*)
5	50	Et_3N	dioxane	10	95	82 (*R*)
6	50	Et_3N	THF	24	61	18 (*R*)
7	50	Et_3N	toluene	24	91	78 (*R*)
8[e]	50	Et_3N	dioxane	10	96	90 (*R*)
9[f]	50	Et_3N	dioxane	48	81	78 (*R*)
10[e,g]	50	Et_3N	dioxane	48	85	88 (*R*)

[a] Isolated yields. [b] Determined by chiral HPLC. [c] The absolute configuration was determined by X-ray diffraction of **7a**. [d] DIPEA = *N*,*N*-diisopropylethylamine. [e] 2.0 equiv of Et_3N was used. [f] 1.0 equiv of Et_3N was used. [g] NHC–Pd complex **1b** was used as the catalyst.

Having established the optimal reaction conditions, we next investigated the scope and limitations of this asymmetric hydroarylation with a variety of boronic acids and cumulene derivatives **2a–h**. We found that the corresponding ad-

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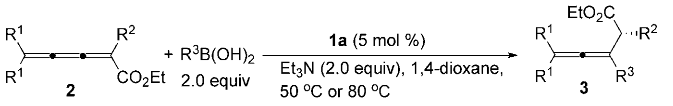
Table 2. NHC–Pd complex **1a**-catalyzed asymmetric hydroarylation of **2a–h** with various boronic acids.



Entry	R^1	R^2	R^3	*t* [h]	Yield [%][a]	*ee* [%][b]
1	C_6H_5	Me (**2a**)	4-MeC_6H_4	10	95 (**3b**)	93 (*R*)
2	C_6H_5	Me (**2a**)	4-$MeOC_6H_4$	10	87 (**3c**)	91[c] (*R*)
3	C_6H_5	Me (**2a**)	4-EtC_6H_4	10	93 (**3d**)	92 (*R*)
4	C_6H_5	Me (**2a**)	4-*t*BuC_6H_4	48	85 (**3e**)	92 (*R*)
5	C_6H_5	Me (**2a**)	4-PhC_6H_4	10	95 (**3f**)	94 (*R*)
6	C_6H_5	Me (**2a**)	4-ClC_6H_4	24	81 (**3g**)	87[c] (*R*)
7	C_6H_5	Me (**2a**)	3-MeC_6H_4	10	88 (**3h**)	92[c] (*R*)
8	C_6H_5	Me (**2a**)	2-naphthyl	10	91 (**3i**)	92[c] (*R*)
9	C_6H_5	Me (**2a**)	3-thienyl	10	91 (**3j**)	88 (*R*)
10	C_6H_5	Me (**2a**)	2-thienyl	48	51 (**3k**)	88 (*R*)
11	C_6H_5	Me (**2a**)	2-*trans*-phenylvinyl	24	67 (**3l**)	50[c] (*R*)
12	C_6H_5	Et (**2b**)	C_6H_5	24	88 (**3m**)	91[c] (*R*)
13	C_6H_5	Et (**2b**)	4-PhC_6H_4	24	89 (**3n**)	88[c] (*R*)
14	C_6H_5	Et (**2b**)	2-naphthyl	12	86 (**3o**)	84[c] (*R*)
15	C_6H_5	Ph (**2c**)	C_6H_5	12	83 (**3p**)	78[c,d] (*R*)
16	4-FC_6H_4	Me (**2d**)	4-$MeOC_6H_4$	12	91 (**3q**)	91[c] (*R*)
17	4-FC_6H_4	Me (**2d**)	3-$MeOC_6H_4$	12	92 (**3r**)	93[c] (*R*)
18	4-ClC_6H_4	Me (**2e**)	C_6H_5	12	93 (**3s**)	91[c] (*R*)
19	4-ClC_6H_4	Me (**2e**)	2-naphthyl	12	92 (**3t**)	93[c] (*R*)
20	4-BrC_6H_4	Me (**2f**)	4-$MeOC_6H_4$	12	69 (**3u**)	92[c] (*R*)
21	4-PhC_6H_4	Me (**2g**)	4-$MeOC_6H_4$	12	89 (**3v**)	86[c] (*R*)
22	3-Br-4-$MeOC_6H_3$	Me (**2h**)	C_6H_5	12	91 (**3w**)	85[c] (*R*)

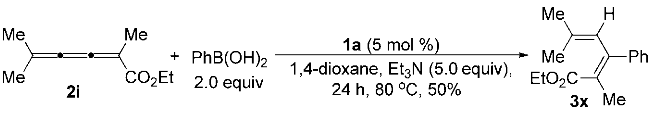
[a] Isolated yields. [b] Determined by chiral HPLC. [c] The reaction was carried out at 80 °C. [d] 1.0 equiv Et_3N was used.

ducts **3b–k** and **3m–w** were produced in good to excellent yields (up to 95 %) and good to excellent *ee* values (up to 94 %) with aromatic boronic acids with diverse substituents on the phenyl ring and heterocyclic 3- or 2-thienylboronic acid (Table 2, entries 1–10 and 12–22). In the case of phenylvinylboronic acid, the desired product **3l** was obtained in 67 % yield and 50 % *ee* at 80 °C, presumably because the in situ generated phenylvinylpalladium species is not stable under the conditions used (Table 2, entry 11). As for 4-*tert*-butylphenyl boronic acid and 2-thienyl boronic acid, the reactions were performed for 48 h, because these boronic acids are not very reactive due to steric and electronic properties (Table 2, entries 4 and 10). In most cases, the reaction was carried out at 80 °C. With 2 mol % of catalyst loading, the reaction became sluggish.

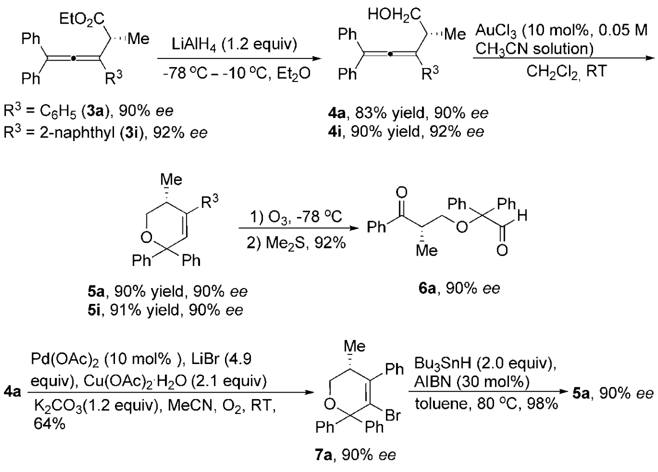
Cumulene **2i** with two aliphatic substituents (R^1 = Me) completely changed regioselectivity to give the achiral product **3x** in 50 % yield (Scheme 2).

The obtained, optically active, allenic products **3a–w** are synthetically useful compounds, which can be easily transformed into interesting chiral building blocks. As shown in Scheme 3, reduction of **3a** and **3i** with $LiAlH_4$ produced **4a** and **4i** in good yields. Products **4a** and **4i** underwent Au^{III}-catalyzed cyclization to give 3,6-dihydropyrans **5a** and **5i** in excellent yields along with retained chirality.[10] The six-membered, cyclic compound **5a** could be further converted to the functionalized, chiral aldehyde **6a** through ozonization to give 92 % yield and 90 % *ee*. These reactions can also be performed on a 2.0 mmol scale, giving **5a** and **5i** in similar yields along with the same *ee* values (see the Supporting Information for details). The asymmetric bromoetherification of **4a** could also be achieved to afford product **7a** in 64 % yield and 90 % *ee* with a Pd/Cu-bimetallic catalytic system in the presence of lithium bromide. The *ee* value of **7a** was determined after debromination (Scheme 3).[11] The absolute configuration of **3** was unequivocally determined by a single-crystal X-ray structural analysis of **7a** (Figure 1, also see the Supporting Information).

A plausible catalytic cycle is outlined in Scheme 4.[1a,7,8,12] The first step is the formation of $[Pd(NHC)(OH)]^+$ (**A**) from the cationic $[Pd(NHC)(H_2O)_2]^{2+}$ (**1**) in the presence of a base. Transmetalation of arylboronic acid with palladium-species **A** gives arylpalladium-complex **B**. The crucial step is the regioselective insertion of **B** into the C2−C3 double



Scheme 2. NHC–Pd complex **1a**-catalyzed hydroarylation of **2i** with phenylboronic acid.



Scheme 3. Synthetic manipulations of chiral adducts **3a** and **3i**. AIBN = azobisisobutyronitrile.

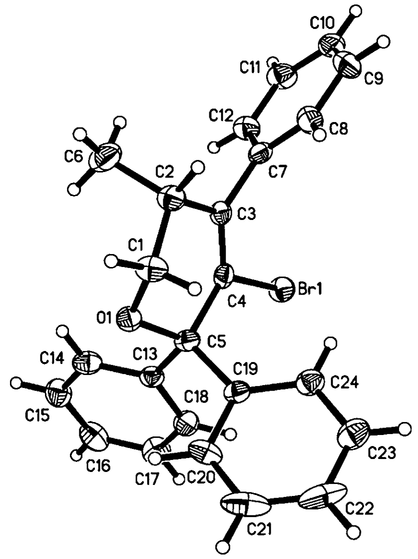
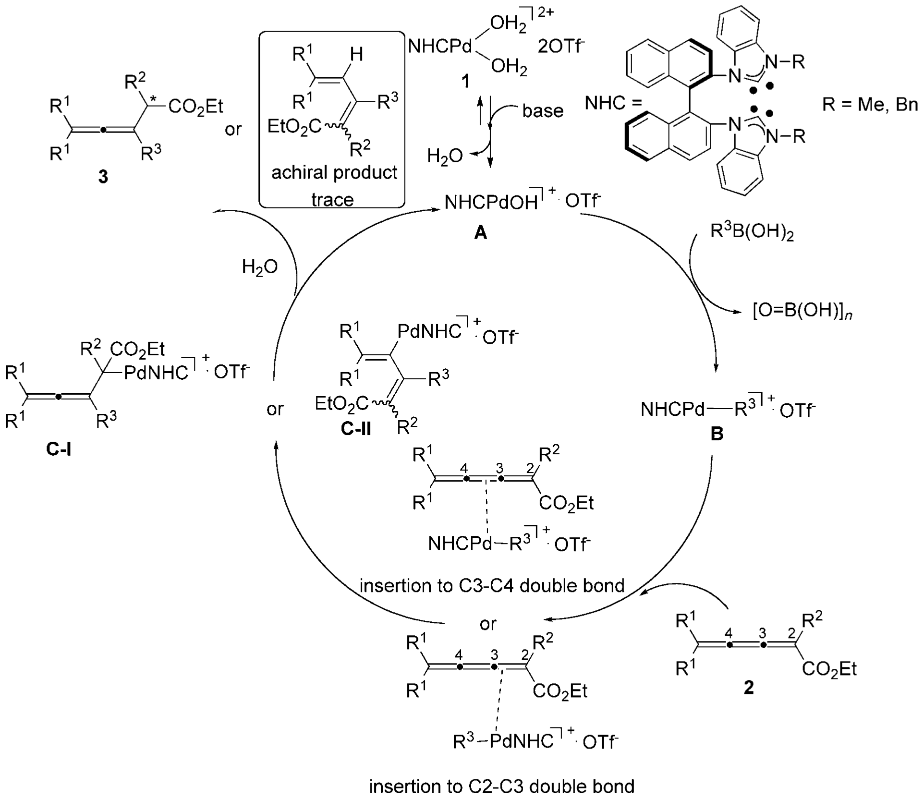


Figure 1. ORTEP drawing of **7a**.



Scheme 4. A plausible reaction mechanism.

bond of diaryl-substituted cumulene-derivatives **2a–i** to give intermediate **C-I**, presumably due to electronic properties. The insertion of **B** into the C3–C4 double bond to give intermediate **C-II** is disfavored in this catalytic system. Finally, the protonation of the chiral palladium-intermediate **C** forms the addition product and regenerates the active species **A** to continue the catalytic cycle.

Concerning the formation of the achiral **3x** in the case of cumulene **2l**, with two aliphatic substituents (R^1=Me), it seems to us that the β-allenic ester is formed first, which then suffers isomerization to the more stable conjugate diene under the basic reaction conditions. This isomerization is facilitated by the presence of the rather small methyl groups at the allene terminus.[13]

In conclusion, we have developed the first examples of asymmetric addition of arylboronic acids to cumulene derivatives catalyzed by chiral, cationic, C_2-symmetric, NHC–Pd^{2+}–diaqua complexes, affording allenic esters in good to excellent yields and moderate to good enantioselectivities. Further transformation of these optically active, allenic adducts to useful chiral products, with good yields and retained chirality, have also been demonstrated. Further optimization of this interesting catalytic system and elucidation of the detailed mechanism are in progress in our group.

Experimental Section

General procedure: In a dried Schlenk tube, catalyst (0.005 mmol), arylboronic acids (0.2 mmol), cumulene derivatives (0.1 mmol), and Et_3N (27.7 μL, 0.2 mmol) were dissolved in 1,4-dioxane (1.0 mL) in an argon atmosphere. The reaction solution was stirred at the appointed temperature. After the reaction had run to completion (monitored by TLC), the solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel eluted with ethyl acetate/petroleum ether (1:200 v/v) to afford the products.

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Keywords: allenic compounds · boronic acids · carbenes · cumulene derivatives · palladium

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[1] a) T. Furuta, T. Asakawa, M. Iinuma, S. Fujii, K. Tanaka, T. Kan, *Chem. Commun.* **2006**, 3648; b) N. Tokitoh, H. Hayakawa, M. Goto, W. Ando, *Tetrahedron Lett.* **1988**, *29*, 1935, and references cited therein; c) H. Uno, K. Kasahara, N. Nibu, S. Nagaoka, N. Ono, *J. Org. Chem.* **2000**, *65*, 1615; d) M. Iyoda, S. Tanaka, H. Otani, M. Nose, M. Oda, *J. Am. Chem. Soc.* **1988**, *110*, 8494; e) T. Kusukawa, Y. Kabe, B. Nestler, W. Ando, *Organometallics* **1995**, *14*, 2556; f) T.

Kusumoto, T. Hiyama, *Tetrahedron Lett.* **1987**, *28*, 1811; g) W. M. Schubert, T. H. Liddicoet, W. A. Lanka, *J. Am. Chem. Soc.* **1954**, *76*, 1929; h) C. B. Ziegler Jr. , *J. Org. Chem.* **1990**, *55*, 2983; i) A. Roedig, G. Zaby, *Chem. Ber.* **1980**, *113*, 3342; j) J. K. Crandall, D. M. Coppert, T. Schuster, F. Lin, *J. Am. Chem. Soc.* **1992**, *114*, 5998; k) N. Suzuki, M. Nishiura, Y. Wakatsuki, *Science* **2002**, *295*, 660; l) N. Suzuki, Y. Fukuda, C. E. Kim, H. Takahara, M. Iwasaki, M. Saburi, M. Nishiura, Y. Wakatsuki, *Chem. Lett.* **2003**, *32*, 16; m) P.-H. Liu, L. Li, J. A. Webb, Y. Zhang, N. S. Goroff, *Org. Lett.* **2004**, *6*, 2081.

[2] A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196.

[3] a) F. Bohlmann, H. Bornowski, C. Arndt, *Chem. Ber.* **1965**, *98*, 2236; b) F. Bohlmann, K.-M. Kleine, C. Arndt, *Justus Liebigs Ann. Chem.* **1966**, *694*, 149; c) F. Bohlmann, C. Zdero, *Tetrahedron Lett.* **1970**, *11*, 2465; d) F. Bohlmann, C. Zdero, *Chem. Ber.* **1971**, *104*, 1329.

[4] a) T. Asakawa, M. Iinuma, T. Furuta, S. Fujii, T. Kan, K. Tanaka, *Chem. Lett.* **2006**, *35*, 512; b) F. Toda, M. Yamamoto, K. Tanaka, T. C. W. Mak, *Tetrahedron Lett.* **1985**, *26*, 631; c) L. Vo-Quang, P. Battioni, Y. Vo-Quang, *Tetrahedron* **1980**, *36*, 1331; d) R. W. Saalfrank, A. Welch, M. Haubner, *Angew. Chem.* **1995**, *107*, 2937; *Angew. Chem. Int. Ed. Engl.* **1996**, *34*, 2709; e) W. Li, M. Shi, *Org. Biomol. Chem.* **2009**, *7*, 1775; f) X. Y. Guan, M. Shi, *J. Org. Chem.* **2009**, *74*, 1977; g) J. G. Garcia, B. Ramos, L. M.; Pratt, A. Rodríguez, *Tetrahedron Lett.* **1995**, *36*, 7391; Pratt, A. Rodríguez, *Tetrahedron Lett.* **1995**, *36*, 7391; h) J. M. Aurrecoechea, E. Pérez, M. Solay, *J. Org. Chem.* **2001**, *66*, 564; i) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795.

[5] a) *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**; b) *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*, 2nd ed. (Eds.: M.; Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**; c) *Comprehensive Asymmetric Catalysis I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; d) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 0171; e) N. Miyaura, *ACS Symp. Ser.* **2001**, *783*, 94–107; for reviews, see: f) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; g) T. Hayashi, *Pure Appl. Chem.* **2004**, *76*, 465; h) T. Hayashi, *Synlett* **2001**, 0879. For selected examples, see: i) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579; j) T. Zhang, M. Shi, *Chem. Eur. J.* **2008**, *14*, 3759.

[6] a) C. H. Oh, T. W. Ahn, R. V. Reddy, *Chem. Commun.* **2003**, 2622; b) A. K. Gupta, C. Y. Rhim, C. H. Oh, *Tetrahedron Lett.* **2005**, *46*, 2247; c) S. Ma, N. Jiao, L. Ye, *Chem. Eur. J.* **2003**, *9*, 6049; d) M. Yoshida, T. Gotou, M. Ihara, *Chem. Commun.* **2004**, 1124; e) C. D. Hopkins, H. C. Malinakova, *Org. Lett.* **2004**, *6*, 2221; f) C. D. Hopkins, L. Guan, H. C. Malinakova, *J. Org. Chem.* **2005**, *70*, 6848; g) T. Ohmura, H. Taniguchi, M. Suginome, *J. Am. Chem. Soc.* **2006**, *128*, 13682; h) J. D. Sieber, J. P. Morken, *J. Am. Chem. Soc.* **2006**, *128*, 74; i) A. R. Woodward, H. E. Burks, L. M. Chan, J. P. Morken, *Org. Lett.* **2005**, *7*, 5505; j) M. Yoshida, Y. Shoji, K. Shishido, *Org. Lett.* **2009**, *11*, 1441; k) B. M. Trost, C. Jäkel, B. Plietker, *J. Am. Chem. Soc.* **2003**, *125*, 4438; l) M. Ogasawara, T. Nagano, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 5764.

[7] a) T. Nishimura, S. Hirabayashi, Y. Yasuhara, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 2556; b) T. Nishimura, H. Makino, M. Nagaosa, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 12865.

[8] a) T. Chen, J. J. Jiang, Q. Xu, M. Shi, *Org. Lett.* **2007**, *9*, 865; b) G. N. Ma, T. Zhang, M. Shi, *Org. Lett.* **2009**, *11*, 875; c) Z. Liu, M. Shi, *Tetrahedron* **2010**, *66*, 2619.

[9] a) M. T. Reetz, D. Moulin, A. Gosberg, *Org. Lett.* **2001**, *3*, 4083; b) C. J. Chapman, K. J. Wadsworth, C. G. Frost, *J. Organomet. Chem.* **2003**, *680*, 206; c) R. J. Moss, K. J. Wadsworth, C. J. Chapman, C. G. Frost, *Chem. Commun.* **2004**, 1984; d) L. Navarre, S. Darses, J.-P. Genet, *Angew. Chem.* **2004**, *116*, 737; *Angew. Chem. Int. Ed.* **2004**, *43*, 719; e) M. P. Sibi, H. Tadamidani, K. Patil, *Org. Lett.* **2005**, *7*, 2571.

[10] a) B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485; b) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537.

[11] B. Alcaide, P. Almendros, R. Carrascosa, T. Martínez del Campo, *Chem. Eur. J.* **2009**, *15*, 2496.

[12] For the application of chiral diaquo palladium complexes in asymmetric catalysis, please see: a) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240; b) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, *120*, 2474; c) A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 5450.

[13] N. Krause, A. Gerold, *Angew. Chem.* **1997**, *109*, 194; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186, and references therein.

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