Asymmetric Catalysis

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Palladium-Catalyzed Asymmetric Amination of Allenyl Phosphates: Enantioselective Synthesis of Allenes with an Additional Unsaturated Unit**

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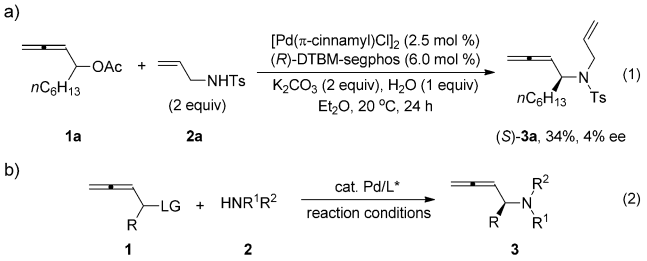
Abstract: *A highly enantioselective Pd-catalyzed amination of allenyl phosphates generating 2,3-allenyl amines with central chirality has been developed. Under the optimized conditions, chiral 2,3-allenyl amines with or without (an) additional C–C double or triple bond(s) have been prepared at 0°C with up to 90% yield and 94% ee by identifying (R)-3,4,5-(MeO)$_3$-MeOBIPHEP as the ligand.*

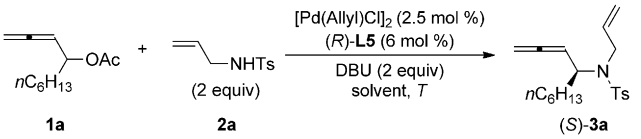
The unique reactivity of allenes and their occurrence in many natural products, pharmaceuticals,[1] and chiral ligands in asymmetric organic reactions[2] make the enantioselective synthesis of optically active allenes with both axial and/or central chirality a hot topic in chemistry.[3] 2,3-Allenyl amines have been widely used in organic synthesis to construct heterocyclic compounds,[4,5] and efficient, enantioselective approaches to optically active 2,3-allenyl amines are highly desirable. The Pd-catalyzed asymmetric synthesis of axially chiral allenyl amines has been reported for some cases,[6] but a catalytic asymmetric approach to optically active 2,3-allenyl amines with α-central chirality has never been realized. The challenge in such a case is the differentiation between the propadienyl and R groups, which are very similar [see Scheme 1, Eq. (2)]. As far as we know, most of these asymmetric reactions are relatively limited in terms of scope, and we observed that the asymmetric substitution of *N*-allyl-4-methylbenzenesulfonamide (**2a**) and the racemic allenylic acetate **1a** under the standard conditions developed for the corresponding reaction with diethyl malonate[7] led to compound (*S*)-**3a** in 34% yield and an *ee* value of merely 4% [Scheme 1, Eq. (1)]. Thus, we sought to identify a new leaving group, a different, more suitable ligand, and a new set of reaction conditions for the highly enantioselective asymmetric Pd-catalyzed amination of racemic allenylic derivatives to generate central chirality. Herein, we describe the realization of this transformation with high enantioselectivity [Scheme 1, Eq. (2)].



Scheme 1. Approaches to optically active allenyl amines with central chirality. a) Result of under the conditions reported in Ref. [7]. b) The current approach. L = Ligand, LG = leaving group, Ts = 4-toluenesulfonyl.

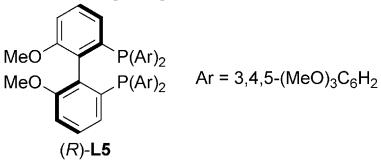
Considering the importance of allenes with an additional unsaturated C–C bond and the nature of the amine,[4,5] **2a** was chosen as the amine substrate for this catalyzed substitution. By conducting the reaction of 2,3-allenol acetate **1a** with **2a** using [Pd(Allyl)Cl]$_2$, different ligands ((*R*)-**L1**–**L5**, see Figure S1 in the Supporting Information), and DBU as the base, we observed that (*R*)-**L5** gave the best *ee* value (86% *ee*), although the yield was not satisfactory (Table 1, entry 1).

Table 1: Effects of solvent and temperature.[a]



Entry	Solvent	*T* [°C]	*t* [h]	(*S*)-**3a** [%] Yield	*ee*[b]	**1a**[c] [%]
1	*p*-xylene	50	5	40	86	0
2	*p*-xylene	30	40	45	90	0
3	*p*-xylene	10	48	66	92	10
4	*m*-xylene	0	48	62	93	31
5	*o*-xylene	0	48	68	93	18
6	*o*-xylene	−10	48	59	93	31

[a] Reaction conducted with 0.3 mmol of **1a**, 2.0 equiv of **2a**, 2.5 mol% of [Pd(Allyl)Cl]$_2$, 6.0 mol% of (*R*)-**L5**, and 2 equiv of DBU in 3 mL of solvent. [b] Determined by HPLC analysis using a chiral stationary phase. [c] Recovered starting material **1a**. Determined by ^{1}H NMR analysis of the crude product with mesitylene as the internal standard. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



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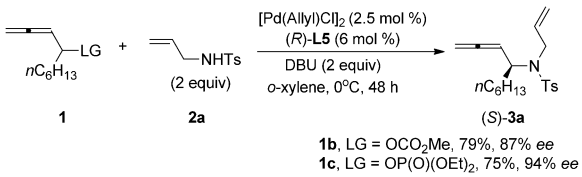
In studies on the effects of the base, DBU turned out to be superior (Table S2). Solvents such as TBME, THF, $CHCl_3$, toluene, and mesitylene were screened but the enantioselectivity of the reaction was lower (Table S3). As expected, when we conducted the reaction in *p*-xylene at a lower temperature, the yield and *ee* value were both much higher, but some of the starting material **1a** was recovered (Table 1, entries 1–3). As the melting point of *p*-xylene is 13 °C, *m*-xylene and *o*-xylene were tested as solvents for the reaction at 0 °C, and *o*-xylene turned out to be superior, affording product (*S*)-**3a** in 68 % yield and 93 % *ee*, with 18 % of **1a** (determined by NMR spectroscopy) being recovered after 48 h (Table 1, entry 5). The reaction at −10 °C gave a similar *ee* value, but a much lower yield (Table 1, entry 6).

Finally, we observed that the leaving group also played a very important role. Compared to acetate **1a** and carbonate **1b**, phosphate **1c** showed the highest reactivity and was completely converted, giving product (*S*)-**3a** in 75 % yield and slightly better enantioselectivity (94 % *ee*) [Eq. (3)]. We thus selected the conditions shown in Equation (3) with phosphate **1c** for further study.

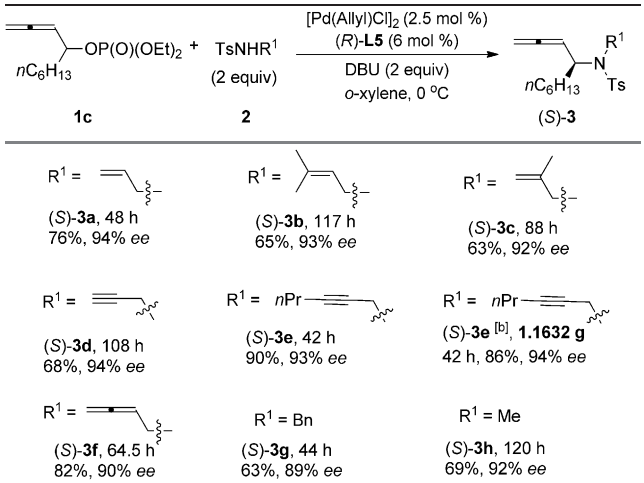


(3)

With the optimized conditions in hand, we explored the scope of both allenyl phosphates and amines. First, we tested the scope of 4-methylbenzenesulfonamides **2**, which bear different unsaturated C–C bonds, with substrate **1c** (Table 2). When R^1 was a substituted allylic group, such as 3-methylbut-2-en-1-yl and 2-methylallyl, the reaction occurred smoothly, resulting in a good yield and excellent enantioselectivity ((*S*)-**3b** and (*S*)-**3c**). Amines with synthetically interesting propargyl groups or even an additional allenyl group may also be used in the reaction and gave the products in excellent yields and *ee* values ((*S*)-**3d** to (*S*)-**3f**). Besides allyl, propargyl, and 2,3-allenyl groups, Bn and Me groups were also tolerated and led to the corresponding products with moderate to good yields (63–69 %) and excellent enantioselectivities (89–92 % *ee*), indicating that the C–C double or triple bond(s) in tosylamides **2** does not compete with the allene unit in phosphates **1** by coordination with the metal center (see also Scheme 2). We also investigated the reaction of **2e** with **1c** on a 1 g scale under the optimized conditions, and obtained (*S*)-**3e** in 86 % yield and 94 % *ee*.

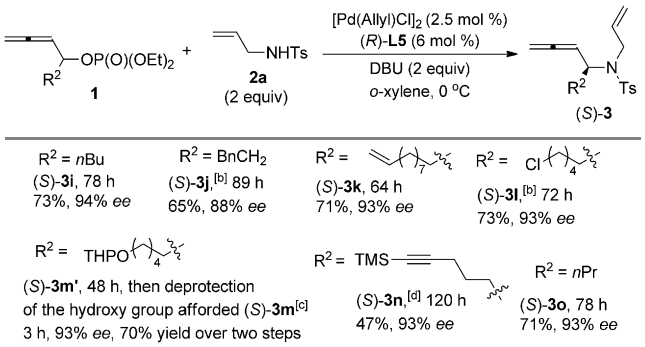
Furthermore, various differently substituted 2,3-allenyl phosphates **1** were tested in this reaction (Table 3). Many synthetically useful functional groups, such as halides, OTHP, alkenyl, and alkynyl groups, were tolerated to afford the corresponding products with 88–94 % *ee*. It was interesting to observe that the differentiation between butyl or propyl groups and the three-carbon propadienyl group was also possible.

Table 2: Asymmetric amination of 2,3-allenyl phosphate **1c** with different R^1-substituted 4-methylbenzenesulfonamides **2**.[a]



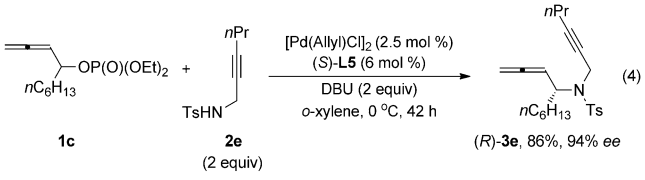
[a] The reaction was conducted with 1.0 mmol of **1c**, 2.0 equiv of **2**, 2.5 mol % of $Pd(Allyl)Cl]_2$, 6.0 mol % of (*R*)-**L5**, and 2 equiv of DBU in 10 mL of *o*-xylene; [b] 1 g-scale reaction was conducted.

Table 3: Asymmetric amination of different 2,3-allenyl phosphates **1** with *N*-allyl-4-methylbenzenesulfonamide (**2a**).[a]



[a] Reaction conducted with 1.0 mmol of **1**, 2.0 equiv of **2a**, 2.5 mol % of $[Pd(Allyl)Cl]_2$], 6.0 mol % of (*R*)-**L5**, and 2 equiv of DBU in 10 mL of *o*-xylene; [b] with $[Pd(\pi\text{-cinnamyl})Cl]_2$ as metal catalyst instead of $[Pd(Allyl)Cl]_2$; [c] deprotection of the hydroxy group with $TsOH\cdot H_2O$ (0.2 equiv) in MeOH at RT for 3 h; [d] with 16 % recovered allenol phosphate determined by ^1H NMR analysis.

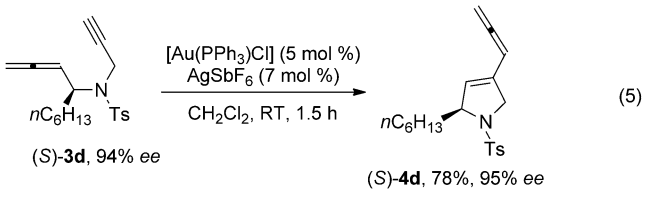
As expected, the reaction of **1c** with **2e** in the presence of (*S*)-**L5** as the ligand under the optimized conditions afforded the enantiomer (*R*)-**3e** in excellent yield and high enantioselectivity [Eq. (4)].



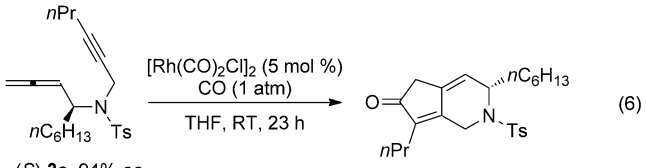
(4)

These chiral products with more than one π-bond are synthetically very useful.[4,5] (*S*)-**3d** may be easily converted to 2,5-dihydropyrrole derivative (*S*)-**4d**, which bears an addi-

tional allene unit, under the catalysis by [Au(PPh$_3$)Cl] and AgSbF$_6$. (*S*)-**4d** was obtained in 78% yield and 95% *ee* with the *ee* value retained [Eq. (5)].[4f] The Pauson–Khand reaction of allenyne (*S*)-**3e** with CO catalyzed by [Rh(CO)$_2$Cl]$_2$ afforded the bicyclic ketone (*S*)-**4e** in 62% yield and 94% *ee* [Eq. (6)].[8]



(*S*)-**3d**, 94% *ee* (*S*)-**4d**, 78%, 95% *ee* (5)



(*S*)-**3e**, 94% *ee* (*S*)-**4e**, 62%, 94% *ee* (6)

The absolute configurations of the products were assigned on the basis of an X-ray single-crystal diffraction study of (*S*,*E*)-**5e**[9] (Figure 1), which was formed from (*S*)-**4e** and 2,4-dinitrophenyl hydrazine [Eq. (7)].

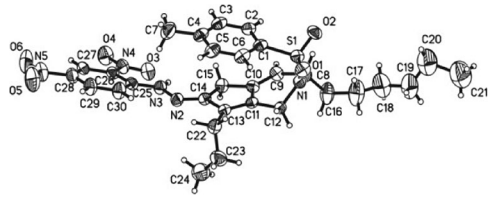
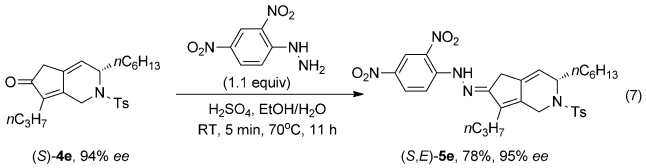


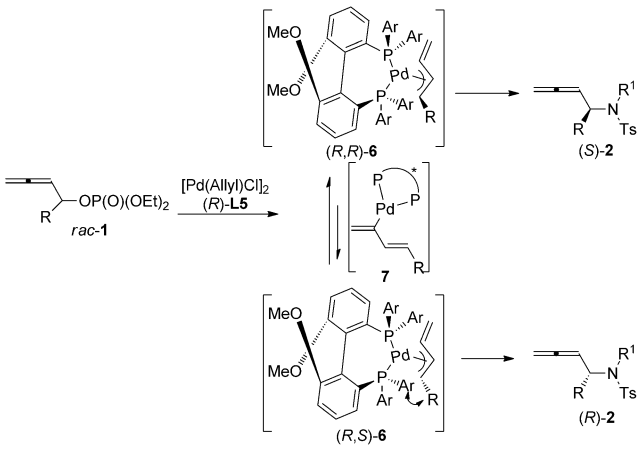
Figure 1. ORTEP representation of (*S*,*E*)-**5e**.



(*S*)-**4e**, 94% *ee* (*S*,*E*)-**5e**, 78%, 95% *ee* (7)

A working model to predict the absolute configuration of the products is shown in Scheme 2. With (*R*)-**L5** as the chiral ligand, the oxidative addition of a chiral palladium species with **1** would afford both (*R*,*R*)- and (*R*,*S*)-α-methylene-π-allylpalladium intermediate **6**, which may be in equilibrium with each other via intermediate **7**. (*R*,*S*)-**6** may be disfavored since there is a steric interaction of the R group with the Ar group of the chiral ligand. Thus, (*S*)-2,3-allenyl amines (*S*)-**2** are formed as the products in high enantioselectivity via (*R*,*R*)-**6** (Scheme 2).

In summary, we have developed a highly enantioselective protocol for the asymmetric allenylation of N-substituted *p*-toluenesulfonamides with the readily available racemic 2,3-allenyl phosphates.[10] Salient features of this process are mild



Scheme 2. Model to predict the absolute configuration of the products using (*R*)-**L5**.

reaction conditions, readily available starting materials/catalyst, and excellent enantioselectivity. The products may be easily transformed to different chiral, cyclic compounds. Further investigations on the scope and applications of this transformation are still being pursued in our laboratory.

Experimental Section

Typical procedure: [Pd(Allyl)Cl]$_2$ (9.1 mg, 0.025 mmol), (*R*)-3,4,5-(MeO)$_3$-MeOBIPHEP (56.4 mg, 0.06 mmol), **2a** (424.7 mg, 2.0 mmol), DBU (302.0 mg, 2.0 mmol) in *o*-xylene (5 mL), and **1c** (292.6 mg, 1.0 mmol) in *o*-xylene (5 mL) were added sequentially to a Schlenk tube under nitrogen atmosphere at room temperature. The reaction was monitored by TLC (eluent: petroleum ether/ethyl acetate = 5/1) and complete after stirring at 0 °C for 48 hours. After filtration through a short column of silica gel with EtOAc (50 mL) and evaporation of the volatiles, the residue was purified by column chromatography on silica gel to afford (*S*)-**3a** (264.9 mg, 76%, 94% *ee*, eluent: petroleum ether/ethyl acetate = 40/1, HPLC condition: Chiralpak IC column; eluent, *n*-hexane/*i*PrOH = 92/8; rate, 0.7 mL min^{-1}; λ = 254 nm; t_R = 17.7 min (minor), 18.5 min (major)) as a liquid. $[\alpha]^{20}_D = -89.5$ (c = 1.12, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ = 7.71 (d, J = 8.4 Hz, 2H, ArH), 7.27 (d, J = 8.1 Hz, 2H, ArH), 5.97–5.74 (m, 1H, =CH), 5.17 (d, J = 17.1 Hz, 1H, one proton of =CH$_2$), 5.08 (d, J = 9.9 Hz, 1H, one proton of =CH$_2$), 4.85 (q, J = 6.4 Hz, 1H, =CH), 4.75–4.57 (m, 2H, =CH$_2$), 4.45–4.29 (m, 1H, CH), 3.85 (dd, J_1 = 16.4 Hz, J_2 = 5.6 Hz, 1H, one proton of CH$_2$), 3.65 (dd, J_1 = 16.2 Hz, J_2 = 6.6 Hz, 1H, one proton of CH$_2$), 2.41 (s, 3H, CH$_3$), 1.63–1.44 (m, 2H, CH$_2$), 1.39–1.11 (m, 8H, 4 × CH$_2$), 0.87 ppm (t, J = 6.6 Hz, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 208.5, 142.9, 138.0, 136.1, 129.4, 127.2, 116.7, 90.1, 76.9, 56.7, 46.5, 32.7, 31.6, 28.7, 26.1, 22.4, 21.4, 13.9 ppm; IR (neat) $\tilde{\nu}$ = 2952, 2928, 2858, 1954, 1638, 1598, 1495, 1456, 1375, 1345, 1305, 1162, 1091, 1016 cm^{-1}; MS (EI) *m*/*z* (%) 347 (M^+, 0.26), 308 (100); elemental analysis calcd for $C_{20}H_{29}NO_2S$: C 69.12, H 8.41, N 4.03; found: C 68.91, H 8.33, N 3.92.

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[1] A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216–1236; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196–1216.

[2] a) X. Pu, X. Qi, J. M. Ready, *J. Am. Chem. Soc.* **2009**, *131*, 10364 – 10365; b) F. Cai, X. Pu, X. Qi, V. Lynch, A. Radha, J. M. Ready, *J. Am. Chem. Soc.* **2011**, *133*, 18066 – 18069.

[3] S. Yu, S. Ma, *Chem. Commun.* **2011**, *47*, 5384 – 5418.

[4] For examples, see: a) S.-K. Kang, B.-S. Ko, D.-M. Lee, *Tetrahedron Lett.* **2002**, *43*, 6693 – 6696; b) H. Ohno, K. Miyamura, Y. Takeoka, T. Tanaka, *Angew. Chem.* **2003**, *115*, 2751 – 2754; *Angew. Chem. Int. Ed.* **2003**, *42*, 2647 – 2650; c) H. Ohno, Y. Takeoka, Y. Kadoh, K. Miyamura, T. Tanaka, *J. Org. Chem.* **2004**, *69*, 4541 – 4544; d) H. Ohno, T. Mizutani, Y. Kadoh, K. Miyamura, T. Tanaka, *Angew. Chem.* **2005**, *117*, 5243 – 5245; *Angew. Chem. Int. Ed.* **2005**, *44*, 5113 – 5115; e) X. Jiang, X. Cheng, S. Ma, *Angew. Chem.* **2006**, *118*, 8177 – 8181; *Angew. Chem. Int. Ed.* **2006**, *45*, 8009 – 8013; f) S. I. Lee, S. H. Sim, S. M. Kim, K. Kim, Y. K. Chung, *J. Org. Chem.* **2006**, *71*, 7120 – 7123; g) F. Inagaki, C. Mukai, *Org. Lett.* **2006**, *8*, 1217 – 1220; h) H. Ohno, T. Mizutani, Y. Kadoh, A. Aso, K. Miyamura, N. Fujii, T. Tanaka, *J. Org. Chem.* **2007**, *72*, 4378 – 4389; i) S. H. Sim, S. I. Lee, J. Seo, Y. K. Chung, *J. Org. Chem.* **2007**, *72*, 9818 – 9821; j) J. H. Park, S. Y. Kim, S. M. Kim, S. I. Lee, Y. K. Chung, *Synlett* **2007**, 453 – 459; k) J. H. Park, E. Kim, H.-M. Kim, S. Y. Choi, Y. K. Chung, *Chem. Commun.* **2008**, 2388 – 2390.

[5] For some books and reviews about the cyclization of allenes with an additional unsaturated C–C bond, see: a) H. F. Schuster, G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, **1984**; b) N. Krause, A. S. K. Hashmi, *Modern Allene Chemistry*, Wiley-VCH, Weinheim, **2004**; c) S. Ma, *Chem. Rev.* **2005**, *105*, 2829 – 2871; d) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954 – 1993.

[6] a) B. M. Trost, D. R. Fandrick, D. C. Dinh, *J. Am. Chem. Soc.* **2005**, *127*, 14186 – 14187; b) M. Ogasawara, H. L. Ngo, T. Sakamoto, T. Takahashi, W. Lin, *Org. Lett.* **2005**, *7*, 2881 – 2884; c) M. Ogasawara, Y. Ge, K. Uetake, T. Takahashi, *Org. Lett.* **2005**, *7*, 5697 – 5700; d) Y. Imada, M. Nishida, K. Kutsuwa, S.-I. Murahashi, T. Naota, *Org. Lett.* **2005**, *7*, 5837 – 5839; e) Y. Imada, M. Nishida, T. Naota, *Tetrahedron Lett.* **2008**, *49*, 4915 – 4917; f) A. Boutier, C. Kammerer-Pentier, N. Krause, G. Prestat, G. Poli, *Chem. Eur. J.* **2012**, *18*, 3840 – 3844; g) B. Wan, S. Ma, *Angew. Chem.* **2013**, *125*, 459 – 463; *Angew. Chem. Int. Ed.* **2013**, *52*, 441 – 445. For non-enantioselective reactions with carbon or nitrogen nucleophiles, see: h) D. Djahanbini, B. Cazes, J. Gore, *Tetrahedron Lett.* **1984**, *25*, 203; i) D. Djahanbini, B. Cazes, J. Gore, *Tetrahedron* **1987**, *43*, 3441; j) M. Ogasawara, H. Ikeda, T. Hayashi, *Angew. Chem.* **2000**, *112*, 1084; *Angew. Chem. Int. Ed.* **2000**, *39*, 1042; k) S. Ma, S. Zhao, *Org. Lett.* **2000**, *2*, 2495; l) B. Wan, G. Jia, S. Ma, *Org. Lett.* **2012**, *14*, 46.

[7] Q. Li, C. Fu, S. Ma, *Angew. Chem.* **2012**, *124*, 11953 – 11956; *Angew. Chem. Int. Ed.* **2012**, *51*, 11783 – 11786.

[8] T. Kobayashi, Y. Koga, K. Narasaka, *J. Organomet. Chem.* **2001**, *624*, 73 – 87.

[9] Crystal data for compound (*S*,*E*)-**5e**: $C_{30}H_{37}N_5O_6S$, $MW = 595.71$, monoclinic space group, *P*21, final *R* indices [$I > 2\sigma(I)$], $R1 = 0.0692$, $wR2 = 0.1882$; *R* indices (all data), $R1 = 0.0950$, $wR2 = 0.2221$; $a = 9.9096(7)$ Å, $b = 10.1964(7)$ Å, $c = 15.3893(12)$ Å, $\alpha = 90.00°$, $\beta = 90.267(6)°$, $\gamma = 90.00°$, $V = 1554.95(19)$ Å^3, $T = 293(2)$ K, $Z = 2$, reflections collected/unique 10203/5658 ($R_{int} = 0.0299$), number of observations [$> 2\sigma(I)$] 4107, parameters: 382. CCDC 980203 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.

[10] The allenols were prepared from terminal propargylic alcohols according to the published procedure: J. Kuang, S. Ma, *J. Org. Chem.* **2009**, *74*, 1763 – 1765.

