Synthetic Methods

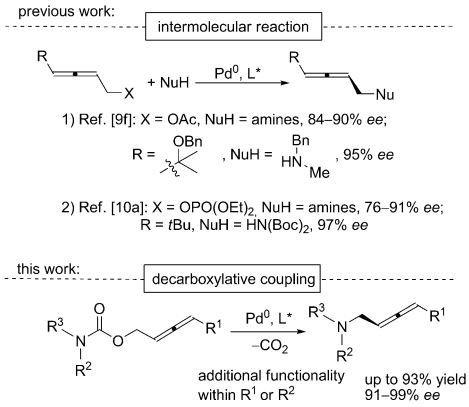
DOI: 10.1002/anie.201204796

Enantioselective Decarboxylative Amination: Synthesis of Axially Chiral Allenyl Amines**

*Baoqiang Wan and Shengming Ma**

Naturally occurring biomolecules that display chirality are enantiomerically enriched and different enantiomers show different biological activities. Thus, the development of new enantioselective approaches for chiral compounds are still of great interest. Allenes are now an important class of compounds and versatile intermediates in organic synthesis.[1] Thus, efficient methodologies for synthesizing allenes is of current interest for organic chemists.[2] The synthesis of axially chiral allenes are particularly important because of their efficient chirality transfer[3] and their existence as core structures in natural products and pharmaceuticals.[4] Typically, the synthesis of axially chiral allenes relies on the resolution of racemic allenic precursors[5] and the chirality transfer of chiral propargyl alcohols[6] or propargyl amine derivatives.[7] However, most of these procedures require stoichiometric amounts of enantiomerically enriched chiral compounds, and are thus inefficient. Recently, asymmetric catalysis for the synthesis of chiral allenes has attracted much attention.[8–10] Trost et al.[9f] and Imada et al.[10a] have independently reported the asymmetric synthesis of allenyl amines with 76–91% *ee* by using intermolecular reactions. Interestingly, in two reported examples, 95 or 97% of *ee* has been realized (Scheme 1, top). Herein, we disclose a different protocol for the construction of axially chiral allenyl amines, bearing an extra hydroxy group or C=C bond, by the decarboxylative amination[11] of allenyl N-tosylcarbamates; the products are obtained in 91–99% *ee* (Scheme 1, bottom).

Initially, we successfully established the palladium-catalyzed decarboxylative amination of N-tosylcarbamates for the synthesis of racemic allenyl amines. After screening the reaction conditions, it was observed that the reaction of **1** could proceed smoothly to afford the allenyl amines **2** by utilizing 5 mol% of $[Pd(PPh_3)_4]$ in CH_2Cl_2 at 40 °C. The scope of decarboxylative reaction of the N-tosylcarbamates **1** was



Scheme 1. Enantioselective synthesis of axially chiral allenes via an α-methylene π-allylpalladium intermediate. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

investigated and the results are listed in Table 1. Some issues should be noted: 1) the yields of these reactions are good to excellent; 2) functional groups such as alkynyl, allenyl, and alkenyl, were tolerated in the reaction; 3) when $R^2 = H$, the reaction afforded the monoallenylation product **2n** and the diallenylation product **2n′** in 73% and 8% yields, respectively, upon isolation.

With this approach in hand, we envisioned that such a decarboxylative amination reaction could afford the axially chiral allenes if a chiral catalyst was used. The N-tosylcarbamate **1a** was chosen as a model substrate to optimize the reaction conditions for the enantioselective decarboxylation. Firstly a variety of chiral phosphine ligands were examined in THF (Scheme 2). The results with the most commonly used ligands for enantioselective allylation are disappointing: The use of (*S*)-binap [(*S*)-**L1**] gave only 22% *ee*,[12] and the reaction failed to afford the desired product **2a** when using either the Trost ligand (*R*,*R*)-**L2** or (*R*,*R*)-**L3**.[13] It is exciting to observe that the results with biphenyl ligands are much better. A much higher enantioselectivity was observed in the reactions using (*R*)-**L4** and (*S*)-Segphos. Additional screening based on the results of (*S*)-Segphos led to the observation that the reaction with (*S*)-DTBM-Segphos gave the best enantioselectivity (86% *ee*) albeit with a low yield. Thus, (*S*)-DTBM-Segphos was chosen as the ligand for optimization studies for improving the yield and enantioselectivity.

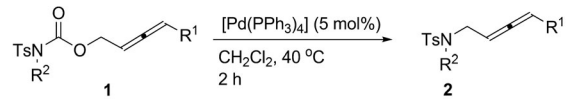
Next, the effect of solvent (1,4-dioxane, DME, CH_2Cl_2, toluene, and DMF) was studied, and DMF resulted in the complete consumption of **1a** and highest enantioselectivity (Table 2, entries 1–6). By conducting the reaction at 25 °C, the enantioselectivity was improved to 91% *ee* (entry 7). Finally,

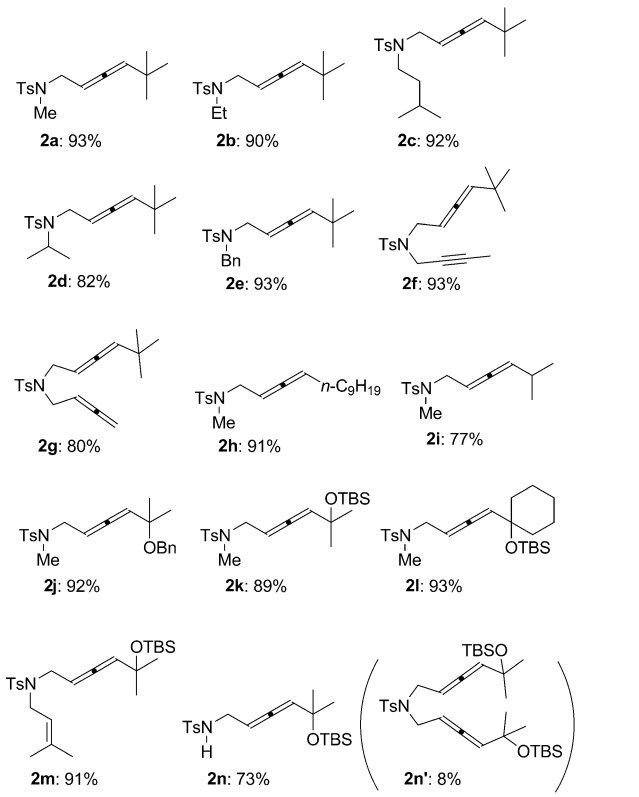
[*] B. Wan, Prof. Dr. S. Ma
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (P.R. China)
E-mail: masm@sioc.ac.cn
Prof. Dr. S. Ma
Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University
3663 North Zhongshan Lu, Shanghai 200062 (P.R. China)

[**] Financial support from the National Natural Science Foundation of China (21232006) and the Major State Basic Research and Development Program (2011CB808700) is greatly appreciated. We thank Minyan Wang from our research group for reproducing the results for compounds **2i**, (*S*)-**2d**, and (*S*)-**2v**.

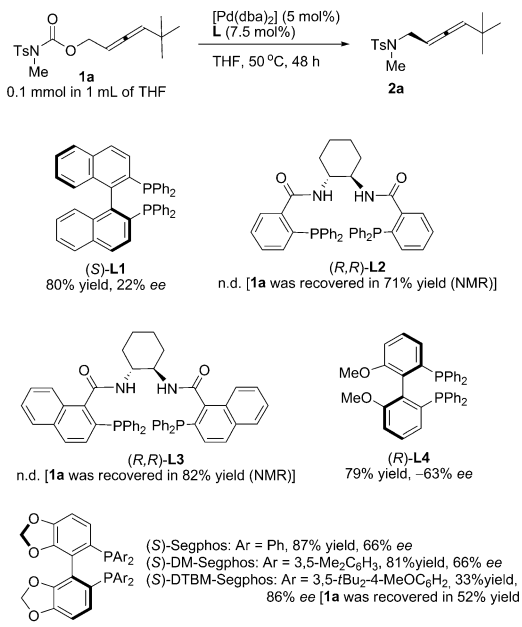
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204796.

Table 1: $[Pd(PPh_3)_4]$-catalyzed decarboxylation of the N-tosylcarbamates **1**.



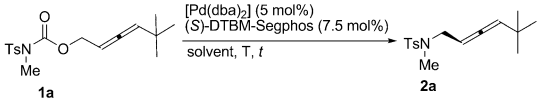


TBS = *tert*-butyldimethylsilyl, Ts = 4-toluenesulfonyl.



Scheme 2. Ligand effect on the enantioselective decarboxylative amination of **1a**. dba = dibenzylideneacetone, n.d. = not detected.

Table 2: Solvent effect on the enantioselective decarboxylative amination of **1a**.[a]

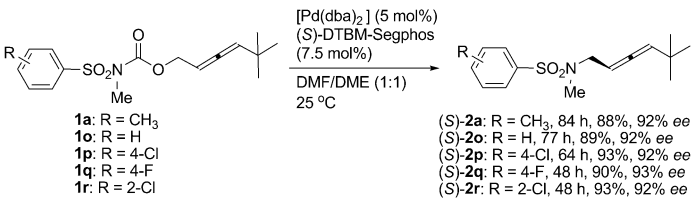


Entry	Solvent	T [°C]	t [h]	**1a** (rec.) [%][b]	**2a** Yield [%][c]	*ee* [%][d]
1	THF	50	48	52	33	86
2	1,4-dioxane	50	48	12	75	82
3	DME	50	48	29	40	87
4	CH_2Cl_2	50	48	67	20	74
5	toluene	50	48	17	70	84
6	DMF	50	48	0	85	88
7[e]	DMF	25	96	0	79	91
8[e]	DMF/DME	25	84	0	88	92

[a] Under argon, a mixture of **1a** (0.1 mmol), $[Pd(dba)_2]$ (5 μmol), and (*S*)-DTBM-Segphos (7.5 μmol) was stirred in 1 mL of the indicated solvent. [b] recovered starting compound **1a**, determined by ^{1}H NMR analysis using 1,3,5-trimethylbenzene as the internal standard. [c] Yield of isolated product. [d] Determined by HPLC analysis using a chiral stationary phase. [e] The reaction was carried out on a 0.5 mmol scale in 2 mL of DMF/DME (1:1). DME = dimethoxyethane, DMF = *N*,*N*′-dimethylformamide, THF = tetrahydrofuran.

it was observed that a combination of DMF and DME led to a higher yield and enantioselectivity (entry 8).

Substituents on the phenyl ring have a limited influence on the yields and enantioselectivities (Scheme 3). The 4-Cl and 2-Cl substituents on the phenyl ring were also suitable in this reaction, thus providing an opportunity for elaboration of the product.



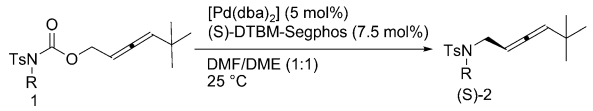
Scheme 3. The effect of the substituent of the phenyl ring on the reaction.

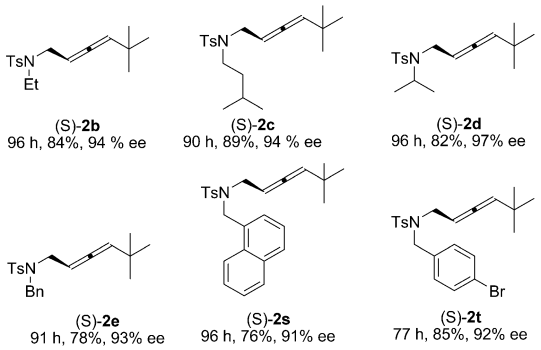
Notably, the R group on the nitrogen atom greatly influences the enantioselectivity, and an isopropyl group gave the best result with a 97% *ee* (Table 3). The absolute configuration was assigned by analogy to that of (*S*)-**2t**, the configuration of which was determined by a single-crystal X-ray diffraction study (Figure 1).[14]

Interestingly, with the synthetically attractive tertiary alcohol group as R^1, the decarboxylative reaction proceeded smoothly to afford the axially chiral allenyl amines in 93–97% *ee* (Table 4). To our delight, the en-allene (*S*)-**2m** was obtained, and can be used for additional cyclization.[15]

To emphasize the practicability of the methodology, the reactions of **1u** and **1m** were conducted on a one-gram scale, thus affording the desired products (*S*)-**2u** and (*S*)-**2m**, respectively, in 97% *ee* (Scheme 4). The reaction of **1w**

Table 3: Enantioselective decarboxylative amination of the N-tosylcarbamates **1**. The effect of the R group.





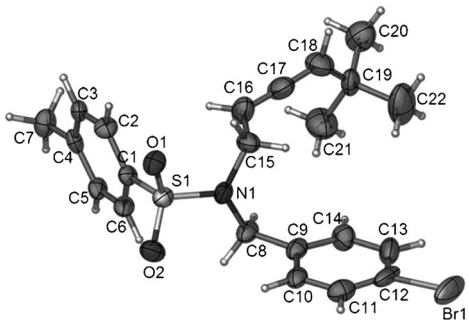
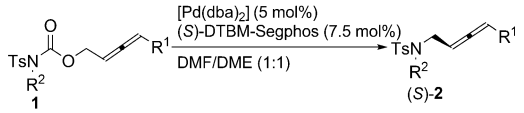
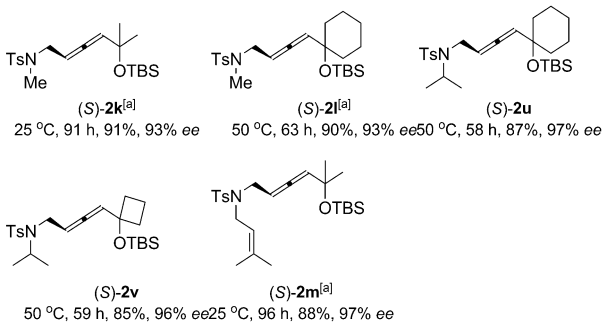


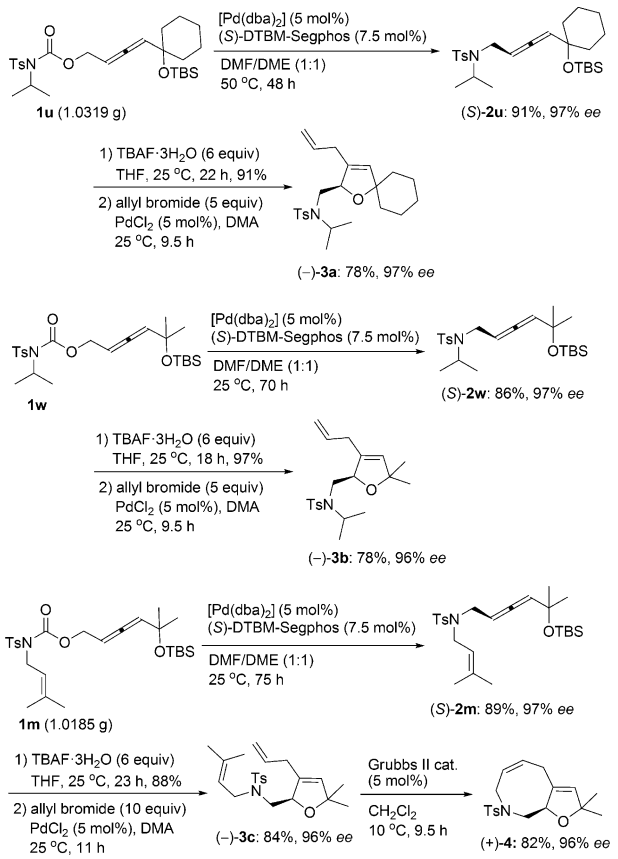
Figure 1. ORTEP representation of (*S*)-**2t**. Thermal ellipsoids are shown at 30% probability.

Table 4: Enantioselective decarboxylative amination of **1** bearing a TBS-protected alcohol unit.[a]





[a] The *ee* value was determined for the corresponding alcohol after removal of the TBS group; see the Supporting Information.

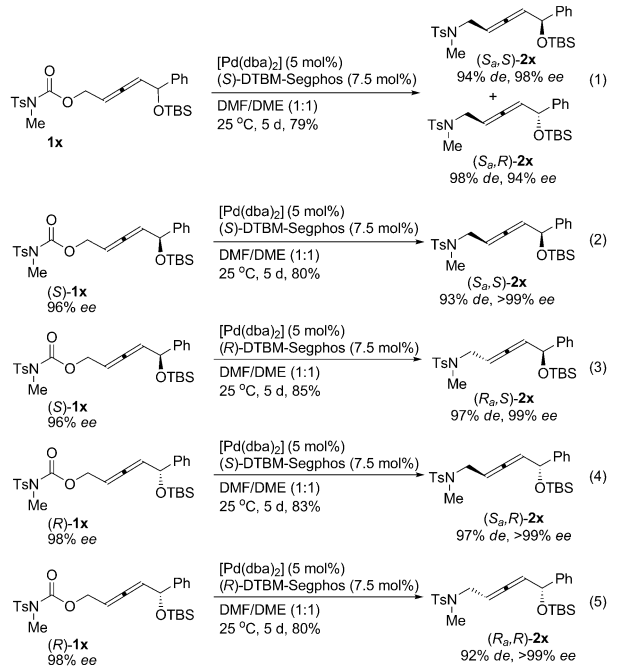


Scheme 4. Synthesis of the 2,5-dihydrofuran derivatives **3** and **4**. DMA = diemthylacetamide, TBAF = tetra-*n*-butylammonium fluoride.

afforded **2w** in 97% *ee*. After removal of the TBS group from (*S*)-**2u**, (*S*)-**2w**, and (*S*)-**2m** to afford the corresponding allenols, the palladium(II)-catalyzed cyclization was performed in the presence of allyl bromide, thus providing the 2,5-dihydrofuran derivatives (−)-**3a**, (−)-**3b**, and (−)-**3c** with complete chirality transfer.[16] The triene (−)-**3c** with an N-allylic unit could be transformed into the hetero-bicyclic diene product **4** in 82% yield and 96% *ee* using a ring-closing metathesis reaction at 10 °C.

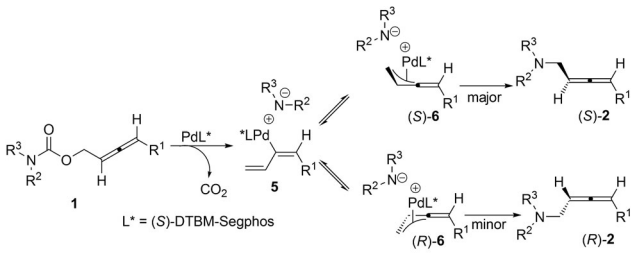
Furthermore, the reaction of **1x**, bearing a secondary alcoholic group, afforded a pair of diastereoisomers (d.r. = 1:1) with high *ee* values [Scheme 5, Eq. (1)]. When the optically active substrates having a central chirality such as (*S*)-**1x** and (*R*)-**1x** were used, all four isomers (S_a,*S*)-**2x**, (R_a,*S*)-**2x**, (S_a,*R*)-**2x**, and (R_a,*R*)-**2x** were obtained successfully with this protocol using either (*S*)-DTBM-Segphos or (*R*)-DTBM-Segphos as the ligand. It is interesting to observe that there is a case for matched or mismatched pairs between the chiral substrates and the ligand affording different diastereoisomeric excess [Scheme 5, Eqs. (2)–(5)].

At this moment we do not have a working model to predict the absolute configuration of the allene moiety for this reaction. On the basis of the results presented in Scheme 2, we reason that the binaphthyl backbone in the **L1** and the biphenyl backbone in **L4** and Segphos are responsible for the high catalytic reactivities since the Trost ligands **L2** and **L3**



Scheme 5. Decarboxylation of *rac*-**1x**, (*S*)-**1x**, and (*R*)-**1x**, thus affording allenes having axial chirality and central chirality.

demonstrated a very slow reaction. The biphenyl backbone in the **L4** and SEGPHOS ligands are responsible for the high enantioselectivity, and has been additionally fine-tuned by the steric effect of the 3,5-*t*Bu-4-MeOC_6H_2 together with the solvent effect shown in Table 2. A rationale for this reaction is shown in Scheme 6.



Scheme 6. Proposed mechanism.

In conclusion, a novel intramolecular decarboxylative amination protocol for the synthesis of axially chiral allenes containing synthetically attractive functionalities has been developed with excellent enantioselectivities and good yields. The synthetic utility of optically active allenyl amines involving axial-to-central chirality transfer and the extra functionalities, such as an alcohol and C=C bond, should make this protocol of particular value in organic and medicinal chemistry. Further studies to expand the scope of this reaction and application of the chiral products are ongoing in our laboratory.

Experimental Section

(*S*)-**2u** (Scheme 4): [Pd(dba)$_2$] (57.8 mg, 0.1 mmol), (*S*)-DTBM-Segphos (178.0 mg, 0.15 mmol), and a mixed solvent system (6.0 mL, DMF/DME = 1:1) were added sequentially to a flame-dried Schlenk tube under argon. The mixture was stirred at 25 °C with a preheated oil bath for 30 min. Then **1u** (1.0319 g, 2.0 mmol) and the mixed solvent system (2.0 mL; DMF/DME = 1:1) were added sequentially to the above solution. The resulting mixture was stirred at 25 °C. After completion, as monitored by TLC, the reaction was quenched with Et_2O (30 mL), H_2O (30 mL), extracted with Et_2O (3 × 20 mL), and dried over anhydrous Na_2SO_4. Filtration, evaporation, and chromatography on silica gel (eluent: petroleum ether/ethyl ether 20:1) afforded (*S*)-**2u** (860.8 mg, 91 % yield, 97 % *ee*) as a liquid. HPLC conditions: IA column, rate = 0.7 mL min^{-1}, eluent: hexane/*i*PrOH 100:1, λ = 214 nm, t_R(major) = 12.3 min, t_R(minor) = 13.9 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.4 Hz, 2H, Ar-H), 7.28 (d, J = 9.0 Hz, 2H, Ar-H), 5.37–5.24 (m, 2H, HC=C=CH), 4.13 (heptet, J = 6.6 Hz, 1H, NCH), 3.90 (ddd, J_1 = 15.9 Hz, J_2 = 5.7 Hz, J_3 = 3.0 Hz, 1H, one proton of NCH_2), 3.76 (ddd, J_1 = 15.9 Hz, J_2 = 6.9 Hz, J_3 = 2.7 Hz, 1H, one proton of NCH_2), 2.42 (s, 3H, CH_3), 1.72–1.17 (m, 10H, 5 × CH_2), 1.12 (d, J = 6.6 Hz, 3H, CH_3), 1.08 (d, J = 6.9 Hz, 3H, CH_3), 0.87 (s, 9H, 3 × CH_3), 0.07 ppm (s, 6H, 2 × CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 201.6, 142.8, 138.3, 129.5, 126.9, 101.7, 92.7, 73.2, 49.5, 41.8, 39.0, 38.8, 25.8, 25.6, 22.30, 22.27, 21.5, 21.4, 20.8, 18.2, −2.1, −2.2 ppm; IR (neat): $\tilde{\nu}$ = 2934, 2886, 2857, 1963, 1599, 1463, 1444, 1391, 1342, 1252, 1187, 1154, 1091, 1050, 1023, 1004 cm^{-1}; MS (70 ev, EI) *m*/*z* (%): 477 (M^+, 0.07), 420 (M^+−C_4H_9, 45.92), 91 (100); HRMS calcd for $C_{26}H_{43}NO_3SSi$ (M^+): 477.2733, found: 477.2720.

Received: June 19, 2012
Published online: September 7, 2012

Keywords: allene · amination · chirality · enantioselectivity · synthetic methods

[1] For recent reviews on the chemistry of allenes, see: a) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; b) S. Ma, *Aldrichimica Acta* **2007**, *40*, 91; c) M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45; d) S. Ma, *Acc. Chem. Res.* **2009**, *42*, 1679; e) B. Alcaide, P. Almendros, T. M. d. Campo, *Chem. Eur. J.* **2010**, *16*, 5836; f) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954; g) F. Inagaki, S. Kitagaki, C. Mukai, *Synlett* **2011**, 594; h) F. López, J. L. Mascarñas, *Chem. Eur. J.* **2011**, *17*, 418; i) S. Yu, S. Ma, *Angew. Chem.* **2012**, *124*, 3128; *Angew. Chem. Int. Ed.* **2012**, *51*, 3074.

[2] For reviews on the synthesis of allenes, see: a) L. K. Sydnes, *Chem. Rev.* **2003**, *103*, 1133; b) *Modern Allene Chemistry*, *Vol. 1 and 2* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**; c) N. Krause, A. Hoffmann-Röder, *Tetrahedron* **2004**, *60*, 11671; d) K. M. Brummond, J. E. Deforrest, *Synthesis* **2007**, 795; e) M. Ogasawara, *Tetrahedron: Asymmetry* **2009**, *20*, 259; f) S. Yu, S. Ma, *Chem. Commun.* **2011**, *47*, 5384; g) *Cumulenes and Allenes, Science of Synthesis*, *Vol. 44* (Ed.: N. Krause), Thieme, Stuttgart, **2007**.

[3] For recent reviews on the chemistry of allenes involving chirality transfer, see: a) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701; b) N. Krause, V. Belting, C. Deutsch, J. Erdsack, H. Fan, B. Gockel, A. Hoffmann-Röder, N. Morita, F. Volz, *Pure Appl. Chem.* **2008**, *80*, 1063; c) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994.

[4] For reviews, see: A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196.

[5] a) R. Rossi, P. Diversi, *Synthesis* **1973**, 25; b) C. Manzuna Sapu, J. E. Bäckwall, J. Deska, *Angew. Chem.* **2011**, *123*, 9905; *Angew. Chem. Int. Ed.* **2011**, *50*, 9731.

[6] a) J. A. Marshall, M. A. Wolf, E. M. Wallace, *J. Org. Chem.* **1997**, *62*, 367; b) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978; c) X. Pu, J. M. Ready, *J. Am. Chem. Soc.* **2008**, *130*, 10874; d) M. Y. Wang, N. Yokokawa, H. Ohmiya, M. Sawamura, *Org. Lett.* **2012**, *14*, 816.

[7] a) V. K.-Y. Lo, C.-M. Che, *Org Lett.* **2008**, *10*, 517; b) V. K.-Y. Lo, C.-Y. Zhou, M.-K. Wong, C.-M. Che, *Chem. Commun.* **2010**, *46*, 213.

[8] a) K. Mikami, A. Yoshida, *Angew. Chem.* **1997**, *109*, 892; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 858; b) J. W. Han, N. Tokunaga, T. Hayashi, *J. Am. Chem. Soc.* **2001**, *123*, 12915; c) T. Hayashi, N. Tokunaga, K. Inoue, *Org Lett.* **2004**, *6*, 305; d) C.-Y. Li, X.-L. Wang, X.-L. Sun, Y. Tang, J.-C. Zheng, Z.-H. Xu, Y.-G. Zhou, L.-X. Dai, *J. Am. Chem. Soc.* **2007**, *129*, 1494; e) H. Liu, D. Leow, K.-W. Huang, C.-H. Tan, *J. Am. Chem. Soc.* **2009**, *131*, 7212; f) J. Ye, S. Li, B. Chen, W. Fan, J. Kuang, J. Liu, Y. Liu, B. Miao, B. Wan, Y. Wang, X. Xie, Q. Yu, W. Yuan, S. Ma, *Org. Lett.* **2012**, *14*, 1346.

[9] For the synthesis of chiral allenes via an α-methylene π-allylpalladium intermediate using malonates as the nucleophiles, see: a) M. Ogasawara, H. Ikeda, T. Nagano, T. Hayashi, *J. Am. Chem. Soc.* **2001**, *123*, 2089; b) M. Ogasawara, K. Ueyama, T. Nagano, Y. Mizuhata, T. Hayashi, *Org Lett.* **2003**, *5*, 217; c) M. Ogasawara, T. Nagano, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 5764; d) M. Ogasawara, Y. Ge, A. Okada, T. Takahashi, *Eur. J. Org. Chem.* **2012**, 1656; e) Y. Imada, K. Ueno, K. Kutsuwa, S.-I. Murahashi, *Chem. Lett.* **2002**, 140; f) B. M. Trost, D. R. Fandrick, D. C. Dinh, *J. Am. Chem. Soc.* **2005**, *127*, 14186; g) T. Nemoto, M. Kanematsu, S. Tamura, Y. Hamada, *Adv. Synth. Catal.* **2009**, *351*, 1773.

[10] a) Y. Imada, M. Nishida, K. Kutsuwa, S.-I. Murahashi, T. Naota, *Org Lett.* **2005**, *7*, 5837; b) Y. Imada, M. Nishida, T. Naota, *Tetrahedron Lett.* **2008**, *49*, 4915; c) A. Boutier, C. Kammerer-Pentier, N. Krause, G. Prestat, G. Poli, *Chem. Eur. J.* **2012**, *18*, 3840.

[11] For review on decarboxylative allylation reactions, see: J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846, and references therein.

[12] For some reports on the enantioselective allylation using chiral binap, see: a) N. Kinoshita, T. Kawabata, K. Tsubaki, M. Bando, K. Fuji, *Tetrahedron* **2006**, *62*, 1756; b) M. Braun, F. Laicher, T. Meier, *Angew. Chem.* **2000**, *112*, 3637; *Angew. Chem. Int. Ed.* **2000**, *39*, 3494; c) Y. Wang, K. Ding, *J. Org. Chem.* **2001**, *66*, 3238; d) K. Fuji, N. Kinoshita, K. Tanaka, *Chem. Commun.* **1999**, 1895.

[13] For some reviews on enantioselective allylation using the Trost ligand, see: a) B. M. Trost, D. L. van Vranken, *Chem. Rev.* **1996**, *96*, 395; b) B. M. Trost, *Acc. Chem. Res.* **1996**, *29*, 355; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.

[14] Crystal data for compound *S*-**2t**: $C_{22}H_{26}BrNO_2S$; $MW = 448.41$, monoclinic, space group $P2(1)$, final R indices $[I > 2\sigma(I)]$, $R1 = 0.0371$, $wR2 = 0.0769$, R indices (all data) $R1 = 0.0619$, $wR2 = 0.0876$, $a = 16.1961(8)$, $b = 9.1134(5)$, $c = 16.9321(2)$ Å, $\alpha = 90$, $\beta = 118$, $\gamma = 90°$, $V = 2211.1(2)$ Å^3, $T = 173(2)$ K, $Z = 4$, reflections collected/unique 25939/7746 ($R_{int} = 0.0452$), number of observations $[> 2\sigma(I)]$ 5779, parameters: 487. CCDC 885180 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] For selected examples of cyclization of en-allenes, see: a) A. Z. González, D. Benitez, E. Tkatchouk, W. A. Goddard, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 5500; b) H. Teller, S. Flügge, R. Goddard, A. Fürstner, *Angew. Chem.* **2010**, *122*, 1993; *Angew. Chem. Int. Ed.* **2010**, *49*, 1949; c) M. Alcarazo, T. Stork, A. Anoop, W. Thiel, A. Fürstner, *Angew. Chem.* **2010**, *122*, 2596; *Angew. Chem. Int. Ed.* **2010**, *49*, 2542; d) J.-F. Zhao, T.-K. Loh, *Angew. Chem.* **2009**, *121*, 7368; *Angew. Chem. Int. Ed.* **2009**, *48*, 7232.

[16] S. Ma, W. Gao, *J. Org. Chem.* **2002**, *67*, 6104.

