Asymmetric Catalysis

DOI: 10.1002/ange.201404643

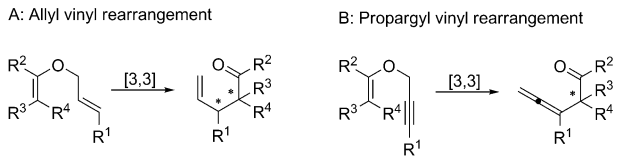
Nickel(II)-Catalyzed Asymmetric Propargyl and Allyl Claisen Rearrangements to Allenyl- and Allyl-Substituted β-Ketoesters**

*Yangbin Liu, Haipeng Hu, Haifeng Zheng, Yong Xia, Xiaohua Liu, Lili Lin, and Xiaoming Feng**

Dedicated to Professor Li-Xin Dai on the occasion of his 90th birthday

Abstract: *Highly efficient catalytic asymmetric Claisen rearrangements of O-propargyl β-ketoesters and O-allyl β-ketoesters have been accomplished under mild reaction conditions. In the presence of the chiral N,N′-dioxide/Ni^{II} complex, a wide range of allenyl/allyl-substituted all-carbon quaternary β-ketoesters was obtained in generally good yield (up to 99%) and high diastereoselectivity (up to 99:1 d.r.) with excellent enantioselectivity (up to 99% ee).*

Claisen rearrangement and its variants have enjoyed unparalleled value because of the utility of the products in the synthesis of complex organic structures.[1] The development of a general array of catalytic asymmetric rearrangements represents a highly desirable goal. The classic Claisen rearrangement of allyl vinyl ethers can give access to γ,δ-unsaturated carbonyl compounds with contiguous stereogenic centers (Scheme 1 A). By relying on either chiral Lewis acids,[2] Jacobsen's guanidinium salts,[3] N-heterocyclic carbenes,[4] or chiral transition metal systems,[5] the catalytic asymmetric rearrangements of allyl vinyl ethers were achieved with an excellent level of enantioselectivity. Comparatively, the enantioselective catalytic version of the propargyl vinyl rearrangement[6] continues to be relatively rare although it provides an useful route to synthetically valuable functionalized allenes (Scheme 1 B).[7] Modern strategies for the stereoselective construction of the propargyl rearrangements are primarily based on either auxiliary controlled versions at high temperature[8] or using optically active propargyl alcohols in the presence of gold(I).[9] To date, only one group made a breakthrough in the asymmetric catalytic propargyl Claisen rearrangements, that is the group of Kozlowski recently reported on the first asymmetric Saucy–Marbet rearrangement for the synthesis of allenyl oxindoles and spirolactones catalyzed by palladium(II)/binap.[10] The exploration of cheap and efficient chiral Lewis acids instead of precious metals is obviously expected to expand the availability and generality of the reaction. Herein, we disclosed a general asymmetric propargyl vinyl rearrangement to a series of allenyl-substituted cyclic β-ketoesters by an easily available chiral *N,N′*-dioxide/nickel(II) complex. The method also enables the asymmetric allyl vinyl rearrangement to give a wide range of allyl-substituted β-ketoesters with vicinal tertiary-quaternary stereocenters. Excellent diastereo- and enantioselectivities were obtained at a good catalytic turnover under mild reaction conditions.



Scheme 1. Allyl vinyl rearrangment versus propargyl vinyl rearrangement.

Initially, we synthesized the propargyl vinyl ethers **1** (PVEs) utilizing the Mitsunobu reaction[11] according to the report from the group of Jacobsen.[3b] Low to moderate yields of the isolated *O*-propargyl ketoesters were obtained in a single step from the propargyl alcohol and β-ketoester. The ester group was introduced into the substrate with the anticipation that it could provide an additional binding site for the Lewis acid catalysts and thus improve the enantiocontrol.[12] Based on our previously established metal/*N,N′*-dioxide complex,[13] we investigated the asymmetric Claisen rearrangement of the *O*-propargyl β-ketoester **1a** (Table 1, entries 1–4). We were delighted to find that **1a** engaged in the rearrangement to afford the desired allenic derivative **2a** in 84% yield and 91% *ee* when promoted by 5 mol% of the **L1**/$Ni(OTf)_2$ complex (Table 1, entry 4). Encouragingly, the reactions proceeded with unanimously excellent enantioselectivities (98% *ee*) when the *N,N′*-dioxides **L2**, **L4**, and **L5**, containing 2,6-dimethylaniline subunits, served as the chiral ligands (Table 1, entries 5, 7, and 8). However, performing the reaction at 0 °C resulted in dramatic loss of reactivity (Table 1, entry 9).

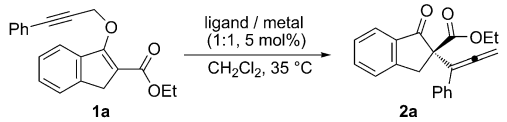
Then, the substrate scope of the asymmetric propargyl vinyl rearrangement was surveyed with various substituents at

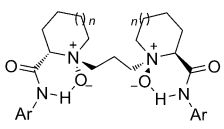
[*] Y. B. Liu, H. P. Hu, H. F. Zheng, Y. Xia, Prof. Dr. X. H. Liu, Dr. L. L. Lin, Prof. Dr. X. M. Feng
Key Laboratory of Green Chemistry & Technology
Ministry of Education, College of Chemistry
Sichuan University, Chengdu 610064 (China)
E-mail: xmfeng@scu.edu.cn
Prof. Dr. X. M. Feng
State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000 (China)

[**] We thank the National Basic Research Program of China (973 Program: 2011CB808600), the National Natural Science Foundation of China (21290182, 21321061 and 21172151), and the Ministry of Education (20110181130014) for financial support.

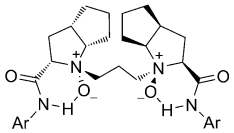
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201404643.

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





L1: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$, *n* = 1
L2: Ar = 2,6-Me$_2$C$_6$H$_3$, *n* = 1
L3: Ar = C$_6$H$_5$, *n* = 1
L4: Ar = 2,6-Me$_2$C$_6$H$_3$, *n* = 0

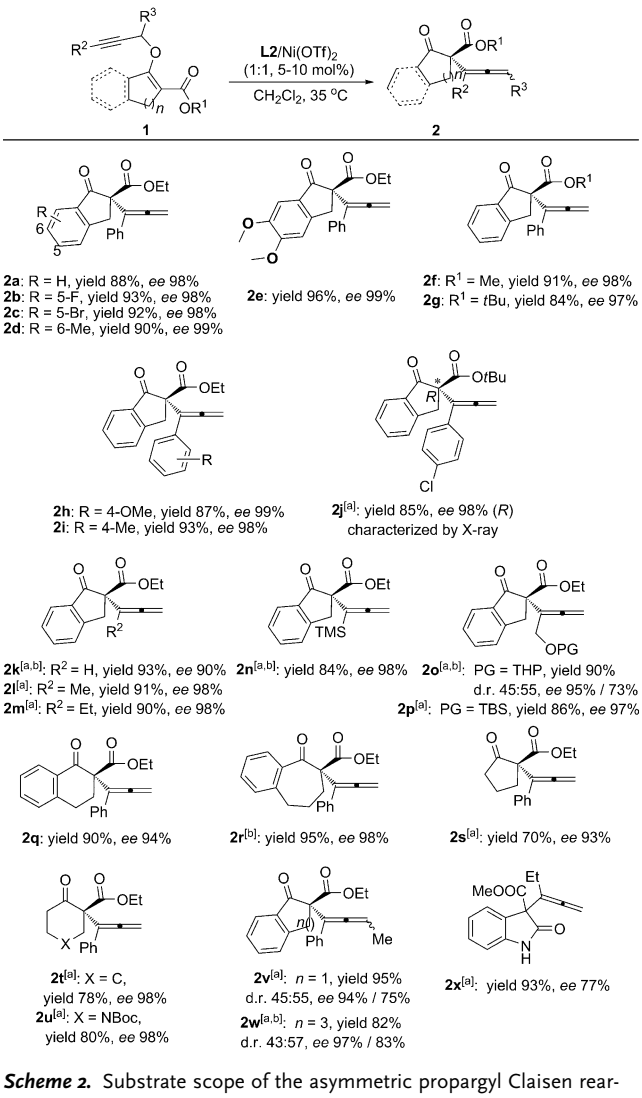


L5: Ar = 2,6-Me$_2$C$_6$H$_3$

Entry	Ligand	Metal source	Yield [%][b]	*ee* [%][c]
1	**L1**	Sc(OTf)$_3$	14	51
2	**L1**	Yb(OTf)$_3$	91	65
3	**L1**	Cu(OTf)$_2$	57	10
4	**L1**	Ni(OTf)$_2$	84	91
5	**L2**	Ni(OTf)$_2$	88	98
6	**L3**	Ni(OTf)$_2$	85	80
7	**L4**	Ni(OTf)$_2$	70	98
8	**L5**	Ni(OTf)$_2$	73	98
9[d]	**L2**	Ni(OTf)$_2$	trace	–

[a] Unless otherwise noted, all reactions were performed with **1a** (0.10 mmol), ligand/metal (1:1, 5 mol%) in CH_2Cl_2 (1.0 mL) at 35 °C for 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] At 0 °C for 48 h. Tf = trifluoromethanesulfonyl.

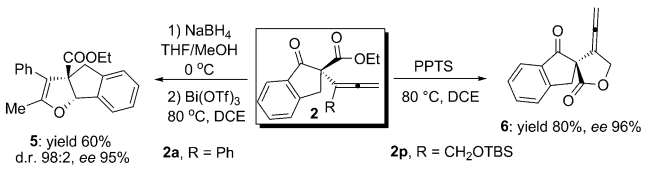
the propargyl group and β-ketoester unit (Scheme 2). Both electron-donating and electron-withdrawing substituents on the 1*H*-indone backbone of the substrate (**1a**–**e**) were tolerated in the asymmetric rearrangement. Varying the ester groups of the β-ketoesters (**1f**,**g**) delivered the similar levels of enantioselectivity to that of **1a**. Aryl substituents (R^2) at the terminal position of the alkynyl group (**1h**–**j**) had no obvious influence on the yields and enantioselectivities. Meanwhile, the absolute configuration of the propargyl Claisen rearrangement product **2j** was unambiguously determined to be *R* on the basis of X-ray single-crystal diffraction.[14] Moreover, neither the simplest unsubstituted congener **1k**, nor aliphatic substituents in **1l**,**m**, nor the TMS group in **1n** prevented the enantioselective rearrangement. Notably, the THP-protected substrate **1o**, generated from 1,4-butanediol, gave the rearrangement product **2o** in 90% yield, and 95% and 73% *ee* for the two diastereomers, respectively. Comparatively, the TBS-protected substrate **1p** delivered the allenic product **2p** in higher enantioselectivity (97% *ee*). Cyclic β-ketoesters of fused aromatic rings (**1q**,**r**) were as effective as the simple saturated aliphatic ring (**1s**,**t**) and a heterocycle (**1u**) with regard to the enantioselectivities (93–98% *ee*). It is noteworthy that a substituent (R^3) on the *O*-propargyl units was also favorable for products (**2v**,**w**) with vicinal a chiral allene and an all-carbon quaternary center in satisfactory yields. High enantioselectivity was obtained for one diastereomer, albeit moderate for the other. It indicates that the catalyst has excellent facial discrimination of the β-ketoesters, and the minor *ee* value for the other diastereomer results from the competition of the instinctive diastereoselection of the racemic substrates. And no obvious resolution



Scheme 2. Substrate scope of the asymmetric propargyl Claisen rearrangement. The reactions were performed with **1** (0.10 mmol), **L2**/Ni(OTf)$_2$ (1:1, 5 mol%) in CH_2Cl_2 (1.0 mL) at 35 °C for 24–96 h (for details, see the Supporting Information). Yields of the isolated products were reported. The *ee* values were determined by HPLC analysis using a chiral stationary phase. [a] Catalyst loading: 10 mol%. [b] Reaction performed in CH_2ClCH_2Cl (1.0 mL) at 50 °C. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl, THP = 2-tetrahydropyranyl, TMS = trimethylsilyl.

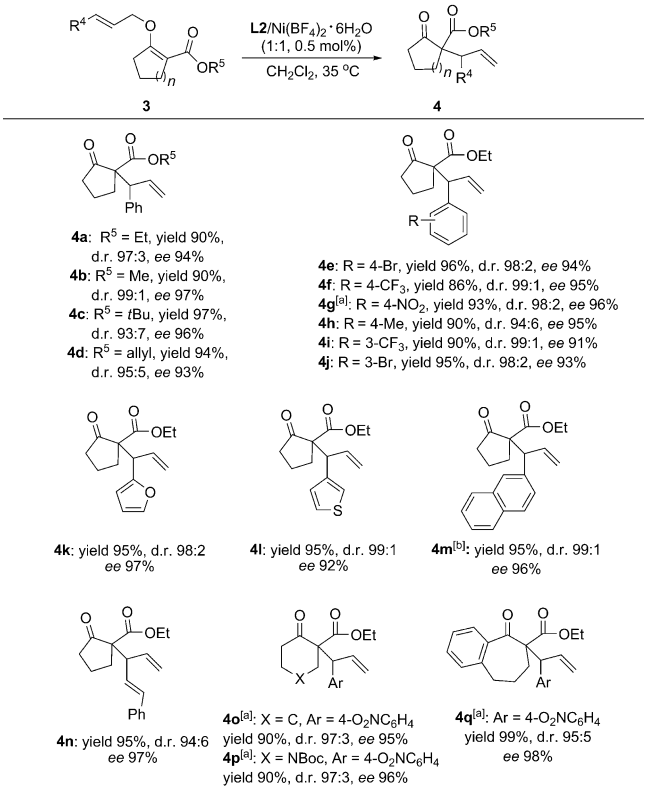
process occurred in the asymmetric rearrangement. Moreover, the Saucy–Marbet–Claisen rearrangement of the propargyl-substituted indole **1x** also proceeded smoothly with high yield and moderate enantioselectivity.

To evaluate the potential of the allenic products of the rearrangement for constructing interesting and useful chiral building blocks, additional transformations were carried out (Scheme 3). The carbonyl group of the allenyl-substituted β-ketoester **2a** was reduced by $NaBH_4$, then the nucleophilic hydroxy group attacked to allenyl motif in the presence of Bi(OTf)$_3$ to form the polycyclic product **5** in moderate yield, and high diastereo- and enantioselectivity. Interestingly, a cascade reaction occurred when **2p** was treated with PPTS, thus affording the sterically congested spirolactone **6**.

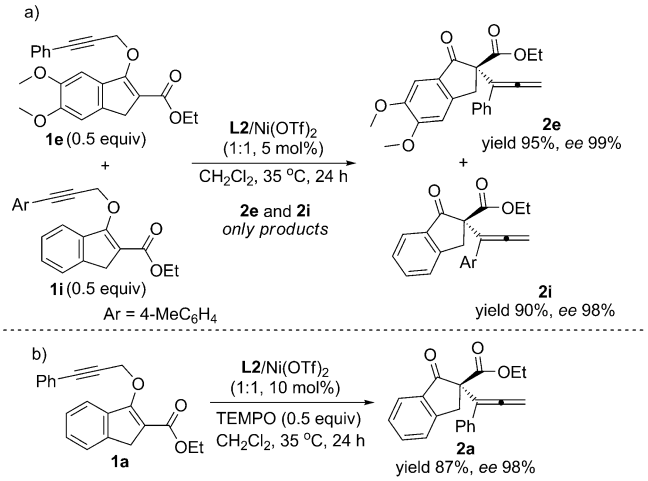


Scheme 3. Application of the catalytic asymmetric rearrangement reaction. DCE = CH_2ClCH_2Cl, PPTS = pyridinium *p*-toluenesulfonate, THF = tetrahydrofuran.

Upon investigation of the propargyl vinyl rearrangement, we were glad to find that the catalyst system of *N*,*N*′-dioxide **L2**/$Ni(BF_4)_2$ was capable of the asymmetric Claisen rearrangement of *O*-allyl β-ketoesters (Scheme 4). Remarkably, a variety of allyl rearrangement products bearing continuous tertiary-quaternary stereocenters was obtained in good to excellent yields (90–99%), high diastereoselectivities (94:6–99:1 d.r.), and enantioselectivities (91–98% *ee*). The catalyst loading was lowered to 0.5 mol% without deterioration of the yields and stereoselectivities. Neither the ester group of the β-ketoesters nor the substituents at the allyl group had an adverse effect on the yield and the stereoselectivity (**4a–j**). Also of note, the reaction could be extended to heteroaromatic and condensed-ring substrates, thus affording the corresponding products (**4k–m**) in excellent results. The conjugated substituent was also well tolerated and gave the desired [3,3]-rearrangement product **4n**. The six-membered and fused aromatic ring substrates **3o–q** also coupled with satisfied yields and stereoselectivities.[15]



Scheme 4. Substrate scope of the asymmetric allyl Claisen rearrangement. The reactions were performed with **3** (0.10 mmol), **L2**/$Ni(BF_4)_2{\cdot}6H_2O$ (1:1, 0.5 mol%) in CH_2Cl_2 (1.0 mL) at 35 °C for 1–48 h (for details, see the Supporting Information). Yields of isolated products reported. The *ee* values and d.r. were determined by HPLC analysis using a chiral stationary phase. [a] Catalyst loading: 2.0 mol%. [b] Catalyst loading: 1.0 mol%.



Scheme 5. Investigating mechanism experiment. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical.

To obtain information about the reaction mechanism, some control experiments were carried out. The crossover reaction of **1e** and **1i** indicates the propargyl rearrangement proceeds in an intramolecular concerted manner (Scheme 5a). The radical pair intermediate is ruled out according to the results that TEMPO had no effect on the reaction outcome[16] (Scheme 5b). HRMS analysis of the mixture of $Ni(OTf)_2$, *N*,*N*′-dioxide **L2**, and **1a** (1:1:1) confirmed the coordination of the substrate to the catalyst. A peak at *m*/*z* 1061.3521 was detected and corresponded to the complex $[Ni^{2+} + \mathbf{L2} + \mathbf{1a} + TfO^-]^+$(cal. *m*/*z* 1061.3492). In line with the X-ray structure of the chiral *N*,*N*′-dioxide/metal complexes[17] and the product **2j**,[14] the possible stereochemical model was considered in Figure 1. The substrate **1j** coordinates tightly to the Lewis acid catalyst through the ether oxygen atom and the carbonyl group of the auxiliary ester group. The propargyl unit preferentially approaches the enolate ether from the

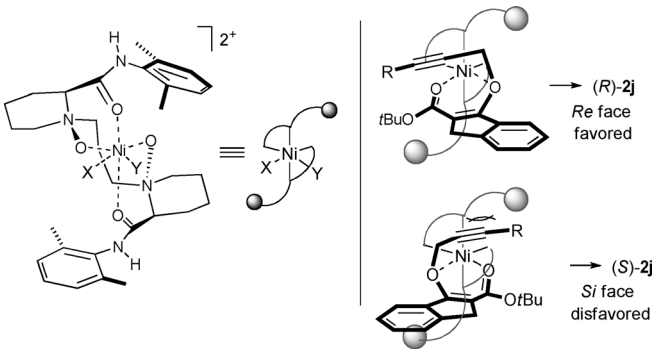


Figure 1. Proposed stereochemical model of the propargyl rearrangement.

Re face.[18] Therefore, the *R*-configurated product **2j** was generated in high enantioversion.

In summary, we have successfully developed highly enantioselective Claisen rearrangement of both propargyl and allyl vinyl ethers. The readily available chiral *N*,*N*′-dioxide/nickel(II) complex accelerated the reaction in high efficiency and stereoselectivity under mild reaction conditions. High catalyst turnover was smoothly realized for the asymmetric allyl vinyl rearrangement. Meanwhile, a wide range of substrates was well tolerated with high yield and enantioselectivity. The rearrangement products demonstrated great potential for the rapid access to functionalized chiral building blocks. Further studies on expanding the scope of this reaction to the construction of useful chiral compounds and on further elucidation of catalytic mechanism is in progress.

Experimental Section

General experimental procedure for the propargyl Claisen rearrangement (for details, see the Supporting Information): $Ni(OTf)_2$ (1.7 mg, 5 mol%) and the *N*,*N*′-dioxide ligand **L2** (2.7 mg, 5 mol%) were stirred in CH_2Cl_2 (1.0 mL) for 0.5 h at 35 °C. Subsequently, the substrate **1** was added, and the resulting mixture was stirred at 35 °C for the indicated time. The residue was purified by flash chromatography on silica gel (1:10, Et_2O/petroleum ether) to afford the desired product **2**.

Received: April 24, 2014
Published online: September 11, 2014

Keywords: allenic compounds · asymmetric catalysis · heterocycles · nickel · rearrangement

[1] For recent reviews, see: a) H. Ito, T. Taguchi, *Chem. Soc. Rev.* **1999**, *28*, 43; b) M. Hiersemann, L. Abraham, *Eur. J. Org. Chem.* **2002**, 1461; c) U. Nubbemeyer, *Synthesis* **2003**, 961; d) A. M. Martín Castro, *Chem. Rev.* **2004**, *104*, 2939; e) *The Claisen Rearrangment* (Eds.: M. Hiersemann, U. Nubbemeyer), Wiley-VCH, Weinheim, **2007**; f) E. A. Ilardi, C. E. Stivala, A. Zakarian, *Chem. Soc. Rev.* **2009**, *38*, 3133; g) J. Rehbein, M. Hiersemann, *Synthesis* **2013**, 1121.

[2] a) L. Abraham, R. Czerwonka, M. Hiersemann, *Angew. Chem.* **2001**, *113*, 4835; *Angew. Chem. Int. Ed.* **2001**, *40*, 4700; b) L. Abraham, M. Körner, P. Schwab, M. Hiersemann, *Adv. Synth. Catal.* **2004**, *346*, 1281; c) L. Abraham, M. Körner, M. Hiersemann, *Tetrahedron Lett.* **2004**, *45*, 3647; d) J. Troendlin, J. Rehbein, M. Hiersemann, O. Trapp, *J. Am. Chem. Soc.* **2011**, *133*, 16444; e) J. Tan, C. H. Cheon, H. Yamamoto, *Angew. Chem.* **2012**, *124*, 8389; *Angew. Chem. Int. Ed.* **2012**, *51*, 8264.

[3] a) C. Uyeda, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 9228; b) C. Uyeda, A. R. Rötheli, E. N. Jacobsen, *Angew. Chem.* **2010**, *122*, 9947; *Angew. Chem. Int. Ed.* **2010**, *49*, 9753.

[4] a) J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810; b) L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2013**, *135*, 58.

[5] a) M. E. Geherty, R. D. Dura, S. G. Nelson, *J. Am. Chem. Soc.* **2010**, *132*, 11875; b) E. C. Linton, M. C. Kozlowski, *J. Am. Chem. Soc.* **2008**, *130*, 16162.

[6] For reviews on propargyl Claisen rearrangement, see: a) D. Tejedor, G. Méndez-Abt, L. Cotos, F. García-Tellado, *Chem. Soc. Rev.* **2013**, *42*, 458. For selected examples of propargyl rearrangement in organic synthesis, see: b) A. Saito, A. Kanno, Y. Hanzawa, *Angew. Chem.* **2007**, *119*, 4005; *Angew. Chem. Int. Ed.* **2007**, *46*, 3931; c) P. Mauleón, J. L. Krinsky, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 4513; d) K. Tanaka, E. Okazaki, Y. Shibata, *J. Am. Chem. Soc.* **2009**, *131*, 10822; e) H. Cao, H. Jiang, W. Yao, X. Liu, *Org. Lett.* **2009**, *11*, 1931; f) H. Jiang, W. Yao, H. Cao, H. Huang, D. Cao, *J. Org. Chem.* **2010**, *75*, 5347; g) A. Gille, J. Rehbein, M. Hiersemann, *Org. Lett.* **2011**, *13*, 2122; h) E. Okazaki, R. Okamoto, Y. Shibata, K. Noguchi, K. Tanaka, *Angew. Chem.* **2012**, *124*, 6826; *Angew. Chem. Int. Ed.* **2012**, *51*, 6722; i) Y. Xiong, S. E. Schaus, J. A. Porco, Jr., *Org. Lett.* **2013**, *15*, 1962.

[7] For reviews on allenes in organic synthesis, see: a) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701; b) A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196; c) N. Krause, A. S. K. Hashimi, *Modern Allene Chemistry*, Wiley-VCH, Weinheim, **2004**; d) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; e) B. J. Cowen, S. J. Miller, *Chem. Soc. Rev.* **2009**, *38*, 3102; f) C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, *Chem. Rev.* **2011**, *111*, 1954; g) S. Yu, S. Ma, *Angew. Chem.* **2012**, *124*, 3128; *Angew. Chem. Int. Ed.* **2012**, *51*, 3074; h) J. Ye, S. Ma, *Acc. Chem. Res.* **2014**, *47*, 989.

[8] For selected examples of auxiliary controlled diastereoselective versions, see: a) M. O. Frederick, R. P. Hsung, R. H. Lambeth, J. A. Mulder, M. R. Tracey, *Org. Lett.* **2003**, *5*, 2663; b) K. C. M. Kurtz, M. O. Frederick, R. H. Lambeth, J. A. Mulder, M. R. Tracey, R. P. Hsung, *Tetrahedron* **2006**, *62*, 3928.

[9] For selected examples of optical propargyl alcohols, see: a) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978; b) B. D. Sherry, L. Maus, B. N. Laforteza, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 8132; c) R. A. Brawn, J. S. Panek, *Org. Lett.* **2007**, *9*, 2689; d) Y. Tang, L. Shen, B. J. Dellaria, R. P. Hsung, *Tetrahedron Lett.* **2008**, *49*, 6404; e) B. Lü, X. Jiang, C. Fu, S. Ma, *J. Org. Chem.* **2009**, *74*, 438.

[10] a) T. Cao, J. Deitch, E. C. Linton, M. C. Kozlowski, *Angew. Chem.* **2012**, *124*, 2498; *Angew. Chem. Int. Ed.* **2012**, *51*, 2448; b) T. Cao, E. C. Linton, J. Deitch, S. Berritt, M. C. Kozlowski, *J. Org. Chem.* **2012**, *77*, 11034.

[11] K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551.

[12] When the ester group was replaced with CH_2OTBS, the rearrangement product was obtained only in less 20% yield and 3% *ee* under the optimized reaction conditions.

[13] For reviews, see: a) X. H. Liu, L. L. Lin, X. M. Feng, *Acc. Chem. Res.* **2011**, *44*, 574; b) X. H. Liu, L. L. Lin, X. M. Feng, *Org. Chem. Front.* **2014**, *1*, 298; For recent examples, see: c) W. D. Cao, X. H. Liu, R. X. Peng, P. He, L. L. Lin, X. M. Feng, *Chem. Commun.* **2013**, *49*, 3470; d) M. S. Xie, X. H. Liu, X. X. Wu, Y. F. Cai, L. L. Lin, X. M. Feng, *Angew. Chem.* **2013**, *125*, 5714; *Angew. Chem. Int. Ed.* **2013**, *52*, 5604; e) W. Li, X. H. Liu, F. Tan, X. Y. Hao, J. F. Zheng, L. L. Lin, X. M. Feng, *Angew. Chem.* **2013**, *125*, 11083; *Angew. Chem. Int. Ed.* **2013**, *52*, 10883; f) K. Zheng, L. L. Lin, X. M. Feng, *Acta Chim. Sinica* **2012**, *70*, 1785; g) M. S. Xie, X. X. Wu, G. Wang, L. L. Lin, X. M. Feng, *Acta Chim. Sinica* **2014**, *72*, 856.

[14] CCDC 995994 (**2j**) 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] The NO_2 group was introduced for the other substrates that could not be synthesized according to the general method.

[16] J. J. Gajewski, *Acc. Chem. Res.* **1997**, *30*, 219.

[17] K. Zheng, X. H. Liu, J. N. Zhao, Y. Yang, L. L. Lin, X. M. Feng, *Chem. Commun.* **2010**, *46*, 3771.

[18] The steric hindrance between the propargyl unit and the bulky aniline moiety of ligand might be disfavor for the enantioselective reaction, as shown in the lower right model.

