Chirality Transfer

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Synergistic Kinetic Resolution and Asymmetric Propargyl Claisen Rearrangement for the Synthesis of Chiral Allenes

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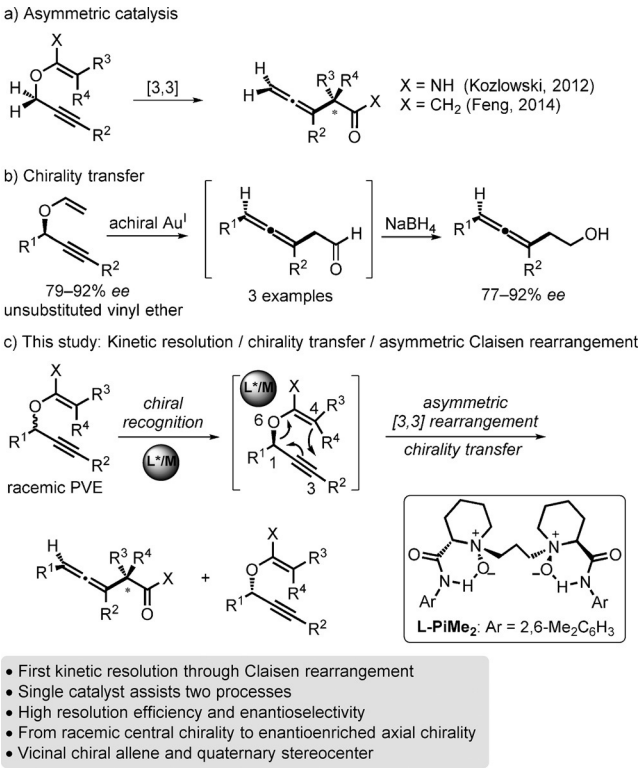
Abstract: *The asymmetric propargyl Claisen rearrangement provides a convenient entry to chiral allene motifs. Herein, we describe the development of a kinetic resolution and asymmetric rearrangement of racemic propargyl vinyl ethers. This transformation afforded chiral allene products along with the enantiomerically enriched substrate in good yields with excellent diastereo- and enantioselectivity. The complete chirality transfer and facially selective rearrangement enabled the simultaneous construction of an axially chiral allenic unit and a quaternary carbon stereocenter.*

Allenes are commonly encountered in natural products with biological activity, and also serve as versatile intermediates in organic synthesis.[1] Among various synthetic approaches, the Claisen rearrangement[2] of propargyl vinyl ethers[3] (PVEs) is a simple and effective protocol for the preparation of elaborated functionalized allenes. The direct catalytic asymmetric rearrangement of achiral PVEs to generate achiral allenyl-substituted quaternary carbon stereocenters has been reported previously (Scheme 1 a).[4] Moreover, when chiral PVEs are used for the rearrangement, the central chirality can be transferred into axial chirality through a concerted sigmatropic process, as successfully illustrated by Sherry and Toste,[5] who used an achiral Au^I complex to transform enantiomerically enriched PVEs into axially chiral allenic alcohols (Scheme 1 b). Although this discovery enabled access to chiral allenes, it depended on high stereochemical fidelity of the transformation of optically active alcohols into chiral PVEs.[6] Thus, we sought to explore a more valuable enantioselective variant that would enable the use of racemic substrates instead of enantiomerically enriched starting materials.

We envisioned the possibility of an enantioselective Claisen rearrangement that took advantage of chirality transfer by kinetic resolution.[7] The chiral catalyst used should achieve two objectives: kinetic resolution of racemic PVEs and ligand-controlled enantioselective Claisen rearrangement (Scheme 1 c). It should recognize one enantiomer of a racemic PVE, which would then undergo a catalytic asymmetric Claisen rearrangement. Thus, the axially chiral allene unit and the neighboring quaternary carbon stereocenter could be constructed simultaneously by chiral recognition and chirality transfer. Herein, we demonstrate the application of a chiral *N*,*N*′-dioxide–nickel(II) catalyst[8] in the development of a synergistic kinetic resolution and catalytic asymmetric propargyl Claisen rearrangement. A series of chiral allene derivatives and enantiomerically enriched PVEs were obtained in good yields with excellent diastereo- and enantioselectivity.



Scheme 1. Access to axially chiral allenes through Claisen rearrangement.

We began our investigation with the kinetic resolution of a racemic phosphonate-substituted propargyl vinyl ether[9] by Claisen rearrangement (Table 1). Racemic propargyl alcohols can be readily prepared by a Sonogashira cross-coupling reaction or the 1,2-addition of an alkyne and an aldehyde.[10] In view of the excellent performance of chiral *N*,*N*′-dioxide–metal complexes in the asymmetric Claisen rearrangement,[4b] we treated *rac*-**1a** with **L-PiMe$_2$**/Ni(OTf)$_2$ in CH_2Cl_2 at 35 °C.

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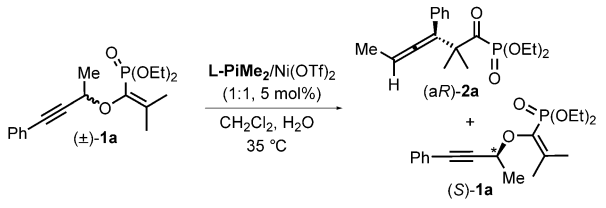
Table 1: Influence of reaction time on kinetic resolution.



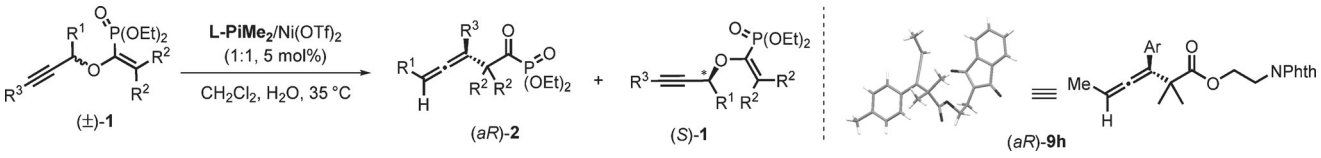
Entry[a]	*t* [h]	**2a**		**1a**	
		Yield [%][b]	*ee* [%][c]	Yield [%][b]	*ee* [%][c]
1	1.5	31	95.5	60	51
2	3	43	97.5	48	99
3	5	44	96.5	46.5	99
4	8	42	95.3	46	99
5	10	39.5	93.4	45.5	99
6	12	37.5	90.5	45	99

[a] All reactions were carried out with *rac*-**1a** (0.10 mmol), L-**PiMe$_2$**/Ni(OTf)$_2$ (1:1, 5 mol%), and H_2O (5.0 μL) in CH_2Cl_2 (1.0 mL) at 35 °C. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis on a chiral stationary phase. Tf = trifluoromethanesulfonyl.

To our delight, the desired kinetic resolution through [3,3] rearrangement occurred smoothly (Table 1, entry 1).[11] The efficiency of the kinetic resolution was highly sensitive to the conversion. The best outcome was observed after 3 h, when the allene **2a** had formed in 43% yield with 97% *ee* and PVE **1a** was recovered in 48% yield with 99% *ee* (Table 1, entry 2). As the reaction time increased, both the yield and the *ee* value of product **2a** decreased slightly (Table 1, entries 3–6). This deterioration of the yield mainly resulted from the generation of unidentified by-products from the allene (as monitored by TLC).[12] The continued consumption of the unreacted enantiomer **1a** was sluggish, thus indicating excellent discrimination of the enantiomers of **1a** by the L-**PiMe$_2$**/Ni^{II} complex.

Having optimized the reaction protocol, we investigated the kinetic resolution of different phosphonate-substituted propargyl vinyl ethers by Claisen rearrangement (Table 2). As expected, the inverse-configuration allene *ent*-**2a** and ether *ent*-**1a** were provided enantioselectively by the ligand enantiomer (Table 2, entry 2).[13] Gratifyingly, the kinetic resolution of PVEs with diethyl, cyclopentyl, or cyclohexyl substituents at the terminal vinyl unit proceeded with very high selectivity (Table 2, entries 3–5). When a chloro, bromo, ester, or methyl substituent was present at the *para* (or *meta*) position of the aryl group on the alkyne unit (Table 2, entries 6–10), high enantioselectivity was observed for the formation of the rearrangement product **2** (**2e**–**i**, 90–95% *ee*), and **1e**–**i** were recovered with 98–99% *ee*. The resolution time was shorter for reactant **1h** with an electron-donating substituent than for those bearing electron-withdrawing substituents (Table 2, entry 9 versus entries 6–8 and 10). The 1-naphthyl-substituted PVE *rac*-**1j** underwent excellent kinetic resolution to give enantiomerically enriched **2j** with 97% *ee*, while PVE **1j** was recovered with 98% *ee* (Table 2, entry 11). Encouraged by these results, we further investigated the tolerance of the catalytic system toward various alkyl substituents at the stereogenic center of the PVE. Variation of the length of the alkyl chain (substrates *rac*-**1k**,**l**,**n**,**o**) or the degree of steric hindrance (substrate *rac*-**1m**)

Table 2: Kinetic resolution of racemic propargyl enol phosphonates.

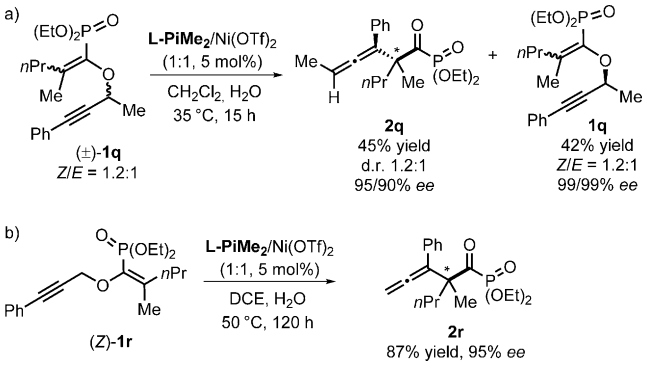


Entry		*rac*-**1**			*t* [h]	**2**		**1**	
		R^1	R^2	R^3		Yield [%][a]	*ee* [%][b]	Yield [%][a]	*ee* [%][b]
1	*rac*-**1a**	Me	Me	Ph	3	42 (**2a**)	97	45 (**1a**)	99
2[c]	*rac*-**1a**	Me	Me	Ph	3	44 (*ent*-**2a**)[d]	−97	48 (*ent*-**1a**)[d]	−99
3	*rac*-**1b**	Me	Et	Ph	16	46 (**2b**)	98	47 (**1b**)	99
4	*rac*-**1c**	Me	-$(CH_2)_4$-	Ph	24	45 (**2c**)	95	48 (**1c**)	99
5	*rac*-**1d**	Me	-$(CH_2)_5$-	Ph	10	40 (**2d**)	92	42 (**1d**)	98
6	*rac*-**1e**	Me	Me	4-ClC_6H_4	20	43 (**2e**)	90	46 (**1e**)	99
7	*rac*-**1f**	Me	Me	4-BrC_6H_4	20	48 (**2f**)	90	46 (**1f**)	98
8	*rac*-**1g**	Me	Me	4-$MeO_2CC_6H_4$	16	45 (**2g**)	93	40 (**1g**)	99
9	*rac*-**1h**	Me	Me	4-MeC_6H_4	2	41 (**2h**)	95	47 (**1h**)	98
10	*rac*-**1i**	Me	Me	3-BrC_6H_4	16	44 (**2i**)	90	47 (**1i**)	99
11	*rac*-**1j**	Me	Me	1-naphthyl	11	36 (**2j**)	97	47 (**1j**)	98
12	*rac*-**1k**	Et	Me	Ph	9	46 (**2k**)	97	48 (**1k**)	98
13	*rac*-**1l**	*n*Pr	Me	Ph	10	44 (**2l**)	95	46 (**1l**)	99
14	*rac*-**1m**	*i*Pr	Me	Ph	18	38 (**2m**)	92	40 (**1m**)	98
15	*rac*-**1n**	*n*Bu	Me	Ph	10	47 (**2n**)	95	45 (**1n**)	99
16	*rac*-**1o**	CH_2CH_2Ph	Me	Ph	14	46 (**2o**)	93	47 (**1o**)	99
17	*rac*-**1p**	$CH_2CH_2SCH_3$	Me	Ph	12	36 (**2p**)	92	33 (**1p**)	99

[a] Yield of the isolated product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] The opposite enantiomer of the *N*,*N*′-dioxide ligand was used. [d] Determined by ^{1}H NMR analysis. Phth = phthaloyl.

had no adverse effect on the efficiency of kinetic resolution (Table 2, entries 12–16). Furthermore, the kinetic resolution through Claisen rearrangement took place efficiently when a sulfur-containing group was present (substrate *rac*-**1p**), although the allene product **2p** and resolved PVE **1p** were isolated in only moderate yield (Table 2, entry 17). These results show that central chirality can be efficiently transferred to axial chirality in this Claisen rearrangement in the presence of the chiral **L-PiMe$_2$**/Ni(OTf)$_2$ catalyst.[14] Furthermore, these resolved chiral allenes bearing ketophosphonate functional groups were confirmed to be useful in a variety of transformations (see the Supporting Information).[15]

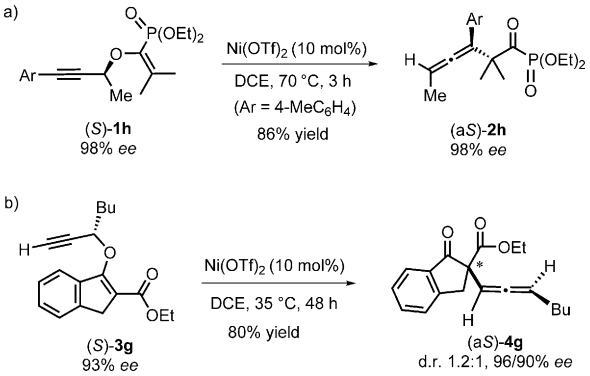
Further investigations were carried out with substrates bearing two different alkyl substituents at the vinyl terminal unit. The resolution efficiency was less affected by the *Z*/*E* configuration of double-bond isomers, as shown by the recovery of **1q** with excellent *ee* values of the two isomers (Scheme 2a). The allenic ketophosphonate **2q** was also formed in satisfying yield with good *ee* values. Notably, the same chiral catalyst also promoted the enantioselective transformation of the achiral single isomer[16] (*Z*)-**1r** into **2r** with a quaternary carbon stereocenter in 87% yield with 95% *ee* (Scheme 2b). This example indicated that the catalyst was also suitable for the enantiocontrol of the vinyl unit. On the basis of the above results, we thus envisioned that synergistic cooperation of the kinetic resolution and asymmetric propargyl Claisen rearrangement of racemic PVEs would enable the rapid construction of allene derivatives with vicinal axial chirality and quaternary centers.



Scheme 2. Claisen rearrangement of unsymmetrical vinyl propargyl ethers.

Next, we expanded the present resolution system to the reaction of a variety of cyclic propargyl vinyl ether derivatives, which would afford chiral allene-substituted cyclic β-ketoesters (Table 3). It was found that carbocyclic substrates with diverse ring sizes were tolerated (Table 3, entries 1–3). The corresponding rearrangement products **4a–c** were obtained with high enantioselectivity (92–96% *ee*) and diastereoselectivity (9:1–24:1), and PVEs **3a–c** were recovered with 96–99% *ee*. The efficiency of the kinetic resolution generally improved as the size of the ring increased; meanwhile, a slight increase in temperature was required to ensure a high reaction rate. When cyclohexyl-based substrate *rac*-**3d** was used, the allenic cyclohexanone derivative **4d** was isolated in 37% yield with 99% *ee* and d.r. 50:1, and PVE **3d** was recovered in 45% yield with 92% *ee* (Table 3, entry 4). When a hydrogen or an alkyl substituent was present at the alkyne terminus, the reaction proceeded with good chiral recognition and facial selectivity for the rearrangement (Table 3, entries 5 and 6). Further exploration of the impact of substitution on the alkyne unit showed that increased steric congestion at the stereogenic carbon center of *n*-butyl-substituted **3g** resulted in lower diastereo- and enantioselectivity (Table 3, entry 7).

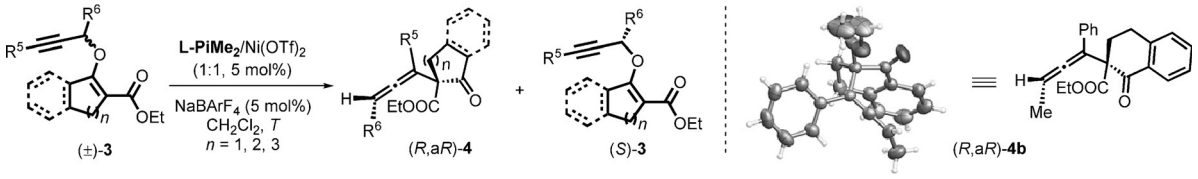
Enantiomerically enriched chiral PVEs were also employed as precursors in the Ni(OTf)$_2$-catalyzed Claisen rearrangement (Scheme 3). Treatment of the recovered substrate (*S*)-**1h** afforded (a*S*)-**2h** in 86% yield with complete chirality transfer; this product is the opposite enantiomer of the product obtained with the kinetic-resolution system (Scheme 3a). A high reaction temperature was required in this case, thus indicating that the **L-PiMe$_2$** ligand could lower the activation energy. Moreover, in the absence of the chiral ligand, the reaction of (*S*)-**3g** proceeded with low diastereoselectivity in favor of the enantiomer of the product formed with the kinetic-resolution system[17] (Scheme 3b). These results indicate that complete central-to-axial chirality transfer occurs in this propargyl Claisen rearrangement and that the effect of ligand control is predominant over the substrate-induction effect for the formation of the new stereogenic carbon center.



Scheme 3. Claisen rearrangement of enantiomerically enriched substrates. DCE = 1,2-dichloroethane.

In conclusion, we have developed an enantioselective Claisen rearrangement of racemic propargyl vinyl ethers. The synergistic kinetic resolution and asymmetric rearrangement were efficiently promoted by the nickel(II)–*N*,*N*′-dioxide catalytic system. Various racemic linear and cyclic propargyl vinyl ether derivatives successfully underwent the rearrangement to furnish diverse allene derivatives with high diastereo- and enantioselectivity, and the other enantiomer of the substrate was recovered with good optical purity. Vicinal axially chiral allenic and quaternary stereocenters could be constructed simultaneously. Both enantiomers of the allenes could be obtained through either the kinetic-resolution protocol or the central-to-axial chirality transfer method.

Table 3: Kinetic resolution and asymmetric Claisen rearrangement of racemic propargyl enol esters.



Entry	T [°C]	t [h]	**4**	Yield [%][a]	*ee* [%][b]	d.r.[c]	**3**	Yield [%][a]	*ee* [%][b]
1	−20	1	$n=1$ (**4a**)	51	92	9:1	$n=1$ (**3a**)	43	96
2	0	5	$n=2$ (**4b**)	45	95	24:1	$n=2$ (**3b**)	40	99
3	35	23	$n=3$ (**4c**)	48	96	15:1	$n=3$ (**3c**)	48	96
4	0	25	**4d**	37	99	50:1	**3d**	45	92
5	0	20	R = H (**4e**)	47	98	49:1	R = H (**3e**)	50	95
6	0	11	R = Et (**4f**)	43	98	24:1	R = Et (**3f**)	47	92
7	0	20	**4g**	45	92	9:1	**3g**	48	93

[a] Yield of the isolated product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] The diastereomeric ratio was determined by ^{1}H NMR or HPLC analysis. $NaBArF_4 = NaB[3,5\text{-}(CF_3)_2C_6H_3]_4$.

Further studies on the asymmetric Claisen rearrangement are ongoing.

Acknowledgements

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Keywords: allenes · asymmetric catalysis · chirality transfer · Claisen rearrangement · kinetic resolution

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[12] We tried to isolate and characterization the by-product(s) formed by the deterioration of allene **2a**; however, the ^1H NMR spectrum was quite complex.

[13] Ligand *ent*-**L-PiMe$_2$** was initially synthesized from (*R*)-2-piperidinecarboxylic acid.

[14] The absolute configuration of derivative **9h** (Ar = 4-MeC_6H_4) was characterized to be a*R* by X-ray crystal-structure analysis, thus indicating that the corresponding allene **2h** had the a*R* configuration. Please see the Supporting Information.

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[16] The single isomer (*Z*)-**1r** was separated smoothly from the *E* isomer by subjecting the *E*/*Z* mixture of **1r** to column chromatography twice.

[17] This outcome showed that the chirality transfer was not efficient at inducing the enantioselective construction of the quaternary carbon center in this case.

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