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Kinetic Resolution of Propargylic Ethers via [2,3]-Wittig Rearrangement to Synthesize Chiral α-Hydroxyallenes

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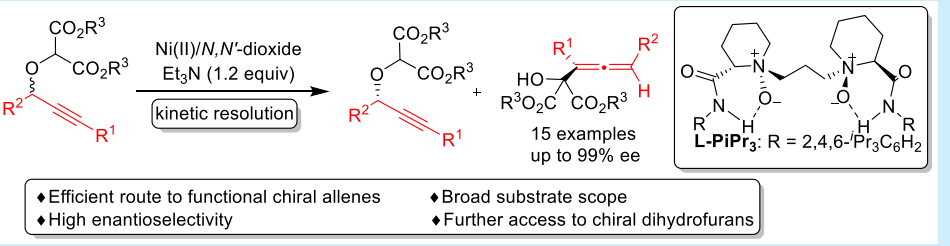

ABSTRACT: An efficient kinetic resolution of propargyloxy dicarbonyl compounds via asymmetric [2,3]-Wittig rearrangement was achieved by using a chiral *N,N′*-dioxide/Ni^{II} complex catalyst. Various chiral α-allenyl alcohols were obtained in high enantioselectivities under mild conditions. The utility of this method was readily demonstrated in the asymmetric synthesis of the chiral 2,5-dihydrofuran derivative.

α-Hydroxyallenes widely exist in a series of natural biological products and also serve as versatile synthetic intermediates in organic transformations.[1] The construction of α-hydroxyallenes has attracted considerable attention for decades, and several catalytic enantioselective synthetic methods have been developed, such as desymmetrization reaction,[2] Aldol-like reaction,[3] arylboration reaction,[4] Petasis reaction,[5] and rearrangement reaction.[6] Among them, [2,3]-Wittig rearrangement[7,8] of propargylic ethers[9] provides an efficient and facile route to elaborated functionalized α-hydroxyallenes. Recently, our group described an asymmetric propargyl [2,3]-Wittig rearrangement of oxindole derivatives using a chiral *N,N′*-dioxide/Ni^{II} complex, and the corresponding 3-hydroxy 3-substituted oxindoles bearing an allenyl group were obtained in good results (Scheme 1a).[6c] Moreover, chiral dihydrofuran derivatives represent important structural motifs existing in natural products,[10] such as diplobifuranylone B,[11] (+)-furanomycin,[12] and cryptoresinol (Scheme 1c),[13] and intramolecular hydroalkoxylation of chiral α-hydroxyallenes[14] is usually one of the most powerful strategies to construct these scaffolds. In consequence, development of new and efficient catalytic asymmetric approaches for their rapid access is in high demand.

With this aim, we envisioned that chiral Lewis acid catalysts were potentially capable to realize kinetic resolution of racemic propargyloxymalonate derivatives via asymmetric [2,3]-Wittig rearrangement. As shown in Scheme 1b, chiral Lewis acid complexes could recognize one enantiomer and promote it to rearrange into an axial chiral α-hydroxyallene product via chirality transfer, leaving behind the enrichment of the other enantiomer. However, on the one hand, control of the regio-

Scheme 1. Asymmetric Propargylic [2,3]-Wittig Rearrangement and Representative Related Compounds

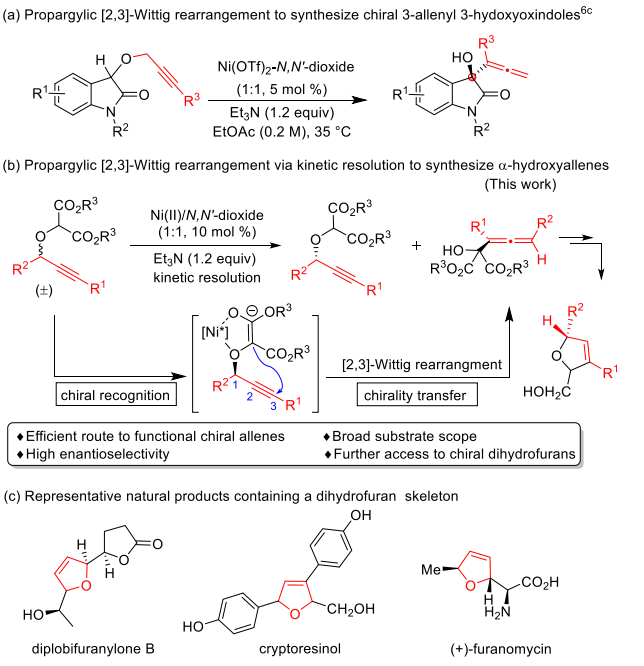

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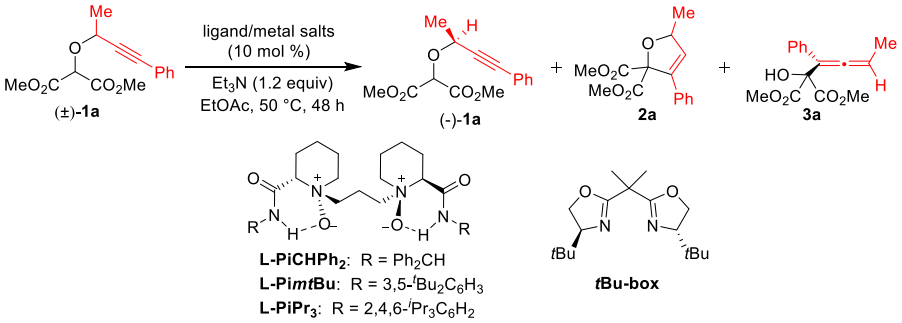
Table 1. Optimization of the Reaction Conditions[a]



			1a/2a			3a	
entry	ligand	metal salts	yield (%)[b]	1a:2a	ee (%)[c]	yield (%)[b]	ee (%)[c]
1	**L-PiCHPh$_2$**	Ni(OTf)$_2$	52	26/74	29/56	29	92
2	**L-Pi*m*tBu**	Ni(OTf)$_2$	69	5/95	−/11	32	38
3	**L-PiPr$_3$**	Ni(OTf)$_2$	89	99/1	8/−	14	98
4	**L-PiPr$_3$**	Ni(ClO$_4$)$_2$·6H$_2$O	75	98/2	26/−	24	99
5[d]	**L-PiPr$_3$**	Ni(ClO$_4$)$_2$·6H$_2$O	50	93/7	93/−	46	97
6	***t*Bu-box**	Ni(OTf)$_2$	84	99/1	0/−	−	−

[a]Unless otherwise noted, the reactions were performed with ligand/metal salts (1:1, 10 mol %), **1a** (0.1 mmol), and Et$_3$N (1.2 equiv) in EtOAc (1.0 mL) at 50 °C for 48 h. [b]Isolated yield, and the ratio of **1a** to **2a** in the bracket represents was determined via HPLC analysis. [c]Determined by HPLC analysis on a chiral stationary phase. [d]The reaction was performed in 0.3 mL of EtOAc.

and stereoselectivity was the foreseeable challenge in developing such a synergistic kinetic resolution/[2,3]-Wittig rearrangement reaction having several competitive side reactions. On the other hand, the propargylic ethers show low reactivity in that the alkyne sp centers distort the transition-state geometries. Herein, we wish to disclose the results in this endeavor. A chiral *N*,*N*′-dioxide-Ni^{II} complex[15,16] was found to be efficient in promoting asymmetric propargyl [2,3]-Wittig rearrangement via kinetic resolution of α-propargyloxy dicarbonyl compounds with high to excellent enantioselectivities. This methodology was further applied in the asymmetric synthesis of a chiral 2,5-dihydrofuran derivative.

Initially, we commenced our investigation with the kinetic resolution of racemic α-propargyloxy dicarbonyl compound **1a** by [2,3]-Wittig rearrangement (Table 1). **L-PiCHPh$_2$**/Ni(OTf)$_2$, which is efficient in our previous work,[6c] was tested in EtOAc (1.0 mL) at 50 °C in the presence of Et$_3$N. [2,3]-Wittig rearrangement of the racemic compound **1a** took place smoothly, giving the corresponding chiral α-hydroxyallene **3a** in 29% yield with 92% ee (entry 1). Meanwhile, the unreacted α-propargyloxy ether **1a** along with dihydrofuran byproduct **2a** was isolated together (the ratio of **1a** to **2a**, ca. 26:74, 29% ee for **1a**, 56% ee for **2a**).[17] Due to a similar R_f value, column separation of **1a** and **2a** was unsuccessful. Next, other metal salts were investigated by coordinating with **L-PiCHPh$_2$**, but no better results were given (see SI, p S4 for further details). Then, chiral *N*,*N*′-dioxide ligands were examined (entries 2 and 3), and it was found that both the amino acid skeleton and steric hindrance of amide moiety of the ligands had a significant influence on the regio- and enantioselectivity. When **L-Pi*m*tBu** was used, the separated major compound was **2a** (**1a**:**2a** = 5:95, 69% yield in total, 11% ee for **2a**), and allene **3a** was isolated in 32% yield with 38% ee (entry 2). In sharp contrast, the use of **L-PiPr$_3$** prevented the formation of dihydrofuran **2a**, albeit the allene **3a** was afforded in 14% yield with 98% ee (entry 3). Switching Ni(OTf)$_2$ to Ni(ClO$_4$)$_2$·6H$_2$O resulted in the improved ee value for recovered **1a** and a slightly better isolated yield for allene (entry 4). To our delight, when the reaction was performed with a higher concentration, the α-propargyloxy ether **1a** was recovered in 50% yield (**1a**/**2a**, 93/7) with 93% ee, and allene **3a** was separated in 46% yield with 97% ee (entry 5; see SI for further details). In comparison, the Ni^{II}/bisoxazoline catalyst was not able to promote the titled rearrangement reaction (entry 6).

Having identified the optimized reaction conditions in hand, we investigated the substrate scope of the reaction. Due to the separation problem, only the allene products **3** were isolated and fully characterized. As depicted in Scheme 2, varying the diester groups affected the reactivity. Substrate **1a** with methyl ester and substrate **1b** bearing ethyl ester had higher activity than substrate **1c** with sterically congested *tert*-butyl ester, but their products **3a**−**3c** were isolated in high enantioselectivities (97−99% ee). Aryl substituents at the terminal position α-propargyloxy ethers were investigated, and the position of the substituents had a limited impact on the yield and selectivity (**3e**−**3g**, 43−45% yields, and 97−99% ee). Substrates either with an electron-donating substituent (methyl or methoxyl) or with an electron-withdrawing substituent (chloro, ester, and trifluoromethyl) underwent kinetic resolution/asymmetric [2,3]-Wittig rearrangement smoothly and afforded the corresponding α-allenyl alcohols (**3d**, **3h**−**j**) in good yields (42−47%) with high enantioselectivities (91−98% ee). Moreover, 1-naphthyl-substituted product **3k** and 2-thiophenyl-containing product **3l** were formed with good ee values (90% ee and 95% ee). Regardless of the steric hindrance of R^2 groups at the stereogenic center (isopropyl, *n*-butyl, and benzyl), all these propargylic ethers could give excellent enantioselectivities (**3m**−**3o**, 96%−98% ee). The absolute configuration of **3o** was determined to be (a*R*) by X-ray crystallographic analysis (CCDC 1951577).

To further demonstrate the potential of this protocol, we first carried out the gram-scale successive kinetic resolution/[2,3]-Wittig rearrangement of racemic 4-phenylbut-3-yn-2-ol derived **1a** for the synthesis of both enantiomers of chiral α-allenyl alcohol **3a** (Scheme 3a). By treatment of 8.0 mmol of

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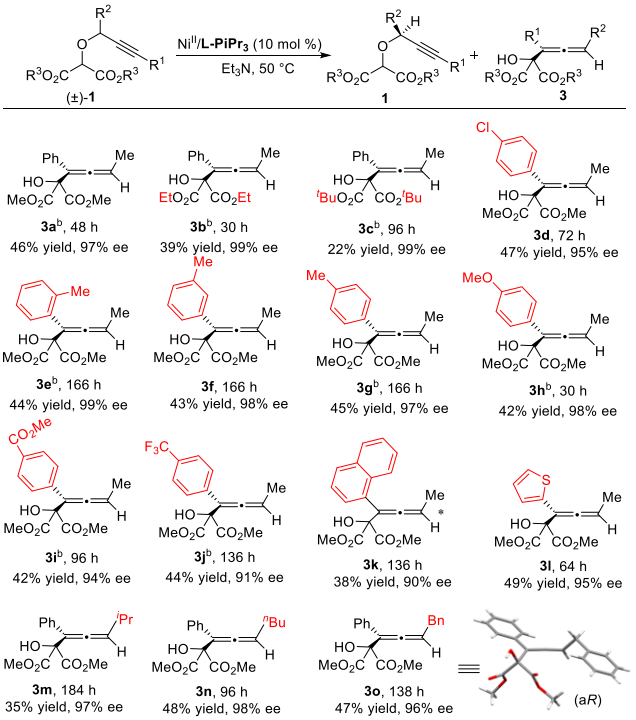
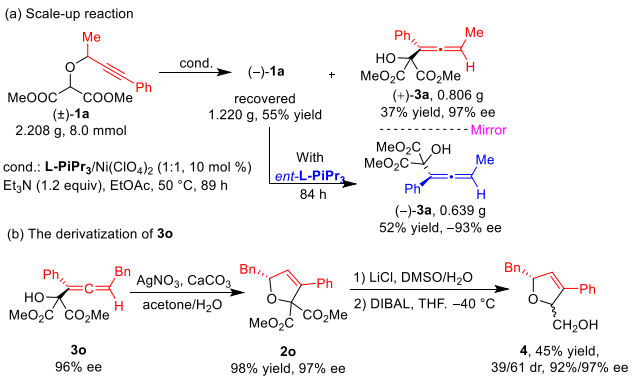
Scheme 2. Kinetic Resolution and Asymmetric [2,3]-Wittig Rearrangement of Racemic Propargyl Ethers[a]



[a]Unless otherwise noted, the reactions were performed with **L-PiPr$_3$**/Ni(ClO$_4$)$_2$·6H$_2$O (10 mol %, 1:1), **1** (0.2 mmol), and Et$_3$N (1.2 equiv) in EtOAc (0.6 mL) at 50 °C. [b]**1** (0.1 mmol) in EtOAc (0.3 mL).

Scheme 3. Gram-Scale Reaction and Derivatization



(±)-**1a** in the presence of 10 mol % **L-PiPr$_3$**/Ni(ClO$_4$)$_2$·6H$_2$O complex for 89 h, the isolated (a*R*)-**3a** was obtained in 37% yield with 97% ee. The recovered crude materials were subsequently subjected to the catalyst system of *ent*-**L-PiPr$_3$**/Ni(ClO$_4$)$_2$·6H$_2$O complex for 84 h to give (a*S*)-**3a** with 93% ee. Moreover, the asymmetric synthesis of the basic skeleton of natural product cryptoresinol was accomplished from the isolated allenyl alcohol product. As shown in Scheme 3b, the product **3o** could be easily transformed into dihydrofuran **2o** in 98% yield and 97% ee by treating with AgNO$_3$ and CaCO$_3$. Then, the de-esterification of dihydrofuran **2o** followed by reduction with DIBAL provided the desired product **4** in 45% total yield and high enantioselectivity (92%/97% ee). Although moderate diastereoselectivity (39/61 dr) was afforded, it should be noted that the diastereomers could be isolated by flash chromatography.

The absolute configuration of the recovered **1a** was assigned to be (*S*) by comparison of the optical rotations with (*R*)-3-butyn-2-ol (98% ee) derived **1a**.[18] It implied that the (*R*)-**1a** preferred to undergo [2,3]-Wittig rearrangement in the presence of **L-PiPr$_3$**/Ni(ClO$_4$)$_2$·6H$_2$O catalyst, which delivered (a*R*)-**3a** as the product. Based on this information and our previous studies,[6c,19] a possible catalytic model was proposed. As depicted in Figure 1, the substrate **1o** undergoes

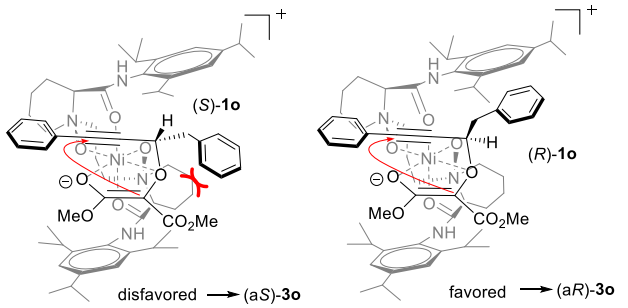


Figure 1. Proposed asymmetric induction models for **3o**.

deprotonation assisted by Et$_3$N to form the enolization intermediate, which coordinates tightly to the Lewis acid catalyst through the ether oxygen atom and the enolate ion from the auxiliary ester group. Due to the steric hindrance between the Bn group and amino acid skeleton unit, (*S*)-**1o** was unlikely to coordinate with the **L-PiPr$_3$**/Ni(ClO$_4$)$_2$·6H$_2$O catalyst (Figure 1, left); in contrast, the bonded (*R*)-**1o** was ready to undergo rearrangement (right), delivering (a*R*)-**3o** via center-chirality transfer to axial chirality.

In conclusion, we have successfully developed an asymmetric [2,3]-Wittig rearrangement via kinetic resolution of racemic propargyloxy dicarbonyl compounds. The current protocol provides an efficient and facile access to chiral α-hydroxyallenes with various substituents in high enantioselectivities. These functionalized α-hydroxyallenes could be easily converted to related 2,5-dihydrofuran derivatives. Further studies on other type of asymmetric [2,3]-Wittig rearrangement and its application are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00649.

Experimental detals; analytical data (NMR, HPLC, ESI-HRMS, IR, CD) (PDF)

Accession Codes

CCDC 1951577 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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