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Construction of Vicinal Tertiary and All Carbon Quaternary Centers by Catalytic Asymmetric Claisen Rearrangement of Enolphosphonates

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Abstract

A Cu-catalyzed enantioselective Claisen rearrangement of easily-accessible enolphosphonates using commercially available (*R, R*)-PhBOX as the chiral ligand was developed. A wide range of rearrangement products with contiguous tertiary and all carbon quaternary centers were obtained in excellent yields and stereoselectivities. The α -ketophosphonate products could be easily transformed into other functional groups in high efficiency.

Keywords

asymmetric catalysis; catalytic Claisen rearrangement; BOX ligands; copper; quaternary carbon centers

A one-step catalytic method for the enantioselective construction of contiguous tertiary and all-carbon quaternary centers is a challenging task but of great significance.^[1,2] Among the limited number of available approaches for the assembly of such sterically congested structures *via* a single transformation, the Claisen rearrangement, well-known as one of the most effective carbon-carbon bond formation strategies, has shown to be promising. Since its discovery one century ago,^[3] the Claisen rearrangement has become a powerful tool widely used by synthetic organic chemists.^[4] Despite many efforts made in this field, the development of the catalytic asymmetric Claisen rearrangement is still in an immature stage. Until now, Hiersemann's copper^[5] and Jacobsen's hydrogen bonding catalysts^[6] have realized catalytic versions of asymmetric Claisen rearrangement. Both of their methods are excellent but relied heavily on ketocarboxylic acid derivatives, affording products with limited generality that are in most cases difficult for further functionalization. Moreover, with these reported catalytic systems, there are only few examples of the direct formation of

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author. CCDC 877511 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

a quaternary carbon center in the presence of a vicinal tertiary center with moderate to good stereoselectivities. In this regard, it remains an extremely significant yet elusive goal for discovering novel catalytic enantioselective Claisen rearrangement as an alternative competent method for rapid creation of vicinal tertiary and quaternary carbon center motifs, which are widely present in complex natural products as well as medicinal and biologically active molecules.^[7]

Recently, many groups including our own have reported that the phosphonate group is able to tightly coordinate to metal ions and provide excellent enantiocontrol with additional binding site adjacent to the phosphonate group through chelation with chiral metal catalysts.^[8] We thus envisioned that enolphosphonates would be more favored bidentate substrates for metal-catalyzed Claisen rearrangement reactions (Figure 1). More importantly, the corresponding products, α -ketophosphonates, are well-known as one of the most synthetically useful phosphorous motifs and could undergo various transformations with ease and efficiency.^[9] *Herein, we are glad to report our recent success with the first catalytic enantioselective Claisen rearrangement of enolphosphonate approach which provides a large scope of α -ketophosphonate derivatives with contiguous tertiary and quaternary carbon centers in excellent yields and selectivities.*

Studies were initiated by the development of a convenient protocol for substrates preparation. These compounds could indeed be simply obtained by treating allylic bromides with α -ketophosphonates in the presence of DBU.^[10] Next, based on our previous success in catalytic asymmetric reactions of ketophosphonates using metal/TBOx complexes,^[11] we investigated the Claisen rearrangement of enolphosphonate **S1** using Al/TBOx complexes (Table 1, entry 1).^[12] However, no rearrangement product was detected. By switching to the Cu/TBOx complex, the reaction proceeded slowly to give the product with 70% yield but in *racemic* form (entry 2). Bidentate bisoxazoline ligands instead of tetradentate TBOx ligands were then examined. To our delight, ligand **1** (*R, R*)-PhBOX gave the product with 88% yield and 93% ee in 2 hours (entry 3).^[13,14] Aminoindanol-derived bisoxazoline ligand **2** provided the rearrangement product in 93% ee but lower yield (entry 4). Other metal triflates and copper sources were also tested but none of them gave more satisfying results.^[10] A further solvent screening indicated that several solvents were suitable for this reaction and the enantioselectivity could be improved when the reaction was performed in a DCM/hexane (1:5) solvent mixture (entry 5).^[10] Lowering catalyst loading to 5 mol% eventually gave the best results (entry 6). Unfortunately, this solvent mixture did not increase the enantioselectivity when ligand **2** was used (entry 7). Interestingly, the catalyst loading could even be lowered to 0.1 mol% without significant detrimental effect on the selectivity and yield, although longer reaction time was required (entry 8). Decreasing the reaction temperature to 0°C failed to give rise to further improved enantioselectivity (entry 9). It's noteworthy that the size of **R** group in the phosphonate motif does not have a profound effect on the reaction. Substrates **S2** and **S3** with either a smaller or a larger **R** group all gave the desired product with slightly lower selectivities (entries 10 and 11).

With the fully optimized reaction conditions in hand, a wide range of substrates were examined and the rearrangement products were obtained with good to excellent yields and stereoselectivities (Table 2). Other than dimethyl substitutions as **R**¹ and **R**² groups on the enolphosphonates, substrates bearing various cyclic ring substituents provided **2–4** with similar levels of enantioselectivities. In addition to aryl group, aliphatic **R**³ groups were also tolerated and products **5, 6** and **7-(S)** were obtained with similar results but longer reaction time. The steric bulk of **R**³ group has no significant effect on the enantioselectivity. Instead of the phenyl group, substrates bearing large naphthyl rings were also examined, generating **8** and **9** with high enantioselectivities respectively. For conjugated substrates, the reaction had to be carried out at 0°C to attenuate the background reaction, providing **10** with 90% ee.

It is interesting to note that the existence of substituents **R**⁴ did not prevent the rearrangement which has seldom been studied in previous reports. Enolphosphonates bearing either alkyl group or halogen atom as the **R**⁴ group all underwent the rearrangement reaction to give α -ketophosphonates **11–13** in high efficiency. Unfortunately, under optimized reaction conditions, substrates bearing either *cis*-cinnamyl or 3, 3-disubstituted allylic segment failed to proceed rearrangement reactions which indicates that our method still has its own limitations at current stage.^[15] However, the utilization of commercially available (*S,S*)-PhBOX ligand as an alternative strategy enabled to generate the products **1-(R)** and **7-(S)** with opposite sense of chirality from the same starting materials.

More importantly, the construction of vicinal chiral tertiary and all-carbon quaternary centers was successfully achieved by this rearrangement protocol. With two different **R**¹ and **R**² group on the double bond of the enolphosphonates,^[16] the substrate bearing tetrahydronaphthyl ring underwent the Claisen rearrangement to give the desired product **14** in 95% yield, >97:3 dr, and 87% *ee*.^[17] Encouraged by this result, we also found that substrates bearing heteroatoms such as oxygen and sulfur were well tolerated under the reaction conditions, furnishing the product **15** and **16** in good yields and stereoselectivities respectively.^[17] The absolute stereochemistry of the Claisen rearrangement products was unambiguously assigned on the basis of the X-ray structure of the carboxylic acid obtained from the hydrolysis of rearrangement product **17**.^[10]

A plausible transition-state model was then proposed as a well-defined tetrahedral substrate-catalyst complex in which bidentate chelation control result in excellent enantioface differentiation (Figure 2).^[4k,13b,18] As depicted, the substrate tightly bound to the catalyst was assumed to arrange in a chair-like configuration that the enolphosphonate unit approaches the *Si* face of allylic ether moiety, which is opposite to the bulky phenyl ring on the BOX ligand.^[19] This proposed transition-state model is fully consistent with the observed stereochemical outcome as well as reaction reactivity^[20] and was further used for predicting the relative stereochemistry.

To highlight the synthetic utility of this methodology, the Claisen rearrangement product, α -ketophosphonate **1**, was examined for further functionalization. Gratifyingly, we found that the phosphonate group could be easily transformed into various functional groups under mild reaction conditions (Scheme 1). First, the α -ketophosphonates **1** acted as a masked acyl chloride and could readily react with alcohols/amines to give the corresponding ester/amide products. Furthermore, these transformations could be carried out in a simple one-pot procedure. Additionally, under basic conditions, α -ketophosphonate **1** hydrolyzed to give the carboxylic acid product without any loss of enantioselectivity. The amino acid derivative can be accessed straightforwardly by treating **1** with L-valine methyl ester in refluxing 1,2-dichloroethane(DCE). Moreover, the carbonyl group of **1** could be functionalized by simple reduction. While DIBAL-H was utilized, the α -ketophosphonate **1** was converted to α -hydroxy phosphonates but with poor diastereoselectivity. When being treated with LiAlH₄, **1** underwent complete reduction to give the alcohol product.

In summary, we have successfully developed the first Cu-catalyzed enantioselective Claisen rearrangement of enolphosphonates. A number of desired α -ketophosphonate products with diverse substitution patterns were obtained in excellent yields and stereoselectivities which easily undergo further functionalization to provide various chiral building blocks effectively. Significantly, this methodology provides a single-step rapid construction of chiral motifs with contiguous tertiary and all-carbon quaternary centers bearing unfunctionalized substituents, which are otherwise difficult to access. Since the starting materials as well as the catalysts are readily available and the highly enantioenriched products can be easily functionalized, this reaction is expected to be widely applicable for asymmetric synthesis.

Future efforts will be directed at expanding the substrate scope and synthesis of complex natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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15. A detailed explanation of substrate scope as well as its limitation can be found in Supporting Information.
16. Due to the relative steric bulk of the phosphonate group, we were able to synthesize and isolate *E*-isomers of enolphosphonates.
17. The relative stereochemistry was determined by the proposed transition state as shown in Figure 2.
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19. A possible boat-like transition state cannot be excluded.

20. Substrates bearing either *cis*-Cinnamyl or 3,3'-disubstituted allylic ether segment might have a severe 1,3-diaxial repulsion in the chair-like transition state, which possibly leads no reaction activity for Claisen rearrangement.

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Figure 1.
Claisen rearrangement of enolphosphonates

Figure 2.
Proposed transition state

Scheme 1.

Synthetic applications of rearrangement product **1** DBU=1,8-Diazabicyclo[5.4.0]undec-7-ene, DIBAL-H= Diisobutylaluminium hydride, LAH=Lithium aluminium hydride

Table 1

Screening of reaction conditions for Cu-catalyzed Claisen rearrangement of enolphosphonates

Entry ^[a]	Metal	Substrate	Ligand	Solvent	Time	Yield(%) ^[b]	ee(%) ^[c]
1	Me ₂ AlCl	S1	TBOx	DCM	24 h	N. R.	N. D.
2	Cu(OTf) ₂	S1	TBOx	DCM	16 h	70	0
3	Cu(OTf) ₂	S1	1	DCM	2 h	88	93
4	Cu(OTf) ₂	S1	2	DCM	4 h	80	93
5	Cu(OTf) ₂	S1	1	[d]	4 h	90	96
6 ^[e]	Cu(OTf) ₂	S1	1	[d]	4 h	90	97
7 ^[e]	Cu(OTf) ₂	S1	2	[d]	24 h	69	83
8 ^[f]	Cu(OTf) ₂	S1	1	[d]	72 h	76	93
9 ^{[e]/[g]}	Cu(OTf) ₂	S1	1	[d]	72 h	80	97
10 ^[e]	Cu(OTf) ₂	S2	1	[d]	2 h	84	95
11 ^[e]	Cu(OTf) ₂	S3	1	[d]	2 h	86	95

^[a]All reactions performed at 0.1 mmol scale.^[b]Isolated yields.^[c]Determined by chiral HPLC.^[d]Dichloromethane(DCM)/hexane=1:5.^[e]5 mol% catalyst loading.^[f]0.1 mol% catalyst loading.

lg/Reaction performed at 0°C.

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Table 2

Substrate scope for Cu(II)/PhBOX catalyzed asymmetric Claisen rearrangement reaction^{[a]–[c]}

[a] All reactions performed at 0.1 mmol scale.

[b] Isolated yields.

[c] Diastereomeric ratio (dr) determined by ^1H NMR of the crude mixture. Enantioselectivity determined by chiral HPLC. Absolute configuration was assigned by X-ray crystallographic analysis of the hydrolyzed product of **17** and the rest were assigned by analogy.

$[d]$ (*S, S*)-PhBOX ligand used instead

$[e]$ Reaction time: 72 h.

[f] Reaction time: 10 h

$[g]$ Reaction performed at 0°C.

$[h]$ Reaction time: 4 h

[i] Reaction time: 24 h

[j] Reaction time: 1 week.