Asymmetric Catalysis

DOI: 10.1002/anie.201203092

Catalytic Asymmetric Claisen Rearrangement of Enolphosphonates: Construction of Vicinal Tertiary and All-Carbon Quaternary Centers**

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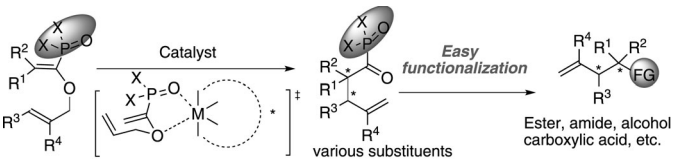
The development of a one-step catalytic method for the enantioselective construction of contiguous tertiary and all-carbon quaternary centers is a challenging task but of great significance.[1,2] Among the limited number of available approaches for the assembly of such sterically congested structures by a single transformation, the Claisen rearrangement, well-known as one of the most effective carbon–carbon bond-formation strategies, has shown promise. Since its discovery one century ago,[3] the Claisen rearrangement has become a powerful method 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 the early stages. Until now, only Hiersemann's copper[5] and Jacobsen's hydrogen-bonding catalysts[6] have been applied to catalytic versions of asymmetric Claisen rearrangement. Both of these methods are excellent but rely heavily on ketocarboxylic acid derivatives as substrates, thus affording products with limited generality that are in most cases difficult to further functionalize. Moreover, there are only a few examples of the use of these catalytic systems for the direct formation of a quaternary carbon center in the presence of a vicinal tertiary center, with moderate to good stereoselectivities. In this regard, the development of a novel catalytic enantioselective Claisen rearrangement as an alternative efficient method for the 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, remains an important goal.[7]

Recently, many groups including our own have reported that a phosphonate group on the substrate is able to tightly coordinate to metal ions and provide excellent enantiocontrol through chelation with an additional binding site, which is adjacent to the phosphonate group, to chiral metal catalysts.[8] We thus envisioned that enolphosphonates would be favorable bidentate substrates for metal-catalyzed Claisen rearrangement reactions (Scheme 1). 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 the first catalytic enantioselective Claisen rearrangement of enolphosphonates



Scheme 1. Claisen rearrangement of enolphosphonates.

for the synthesis of a wide range of α-ketophosphonate derivatives with contiguous tertiary and quaternary carbon centers in excellent yields and selectivities.

Initially, a convenient protocol was developed for substrate preparation. These compounds could be simply obtained by treating allylic bromides with α-ketophosphonates in the presence of DBU.[10] Next, based on our previous success in the use of metal/TBOx complexes in catalytic asymmetric reactions of ketophosphonates,[11] we investigated the use of Al/TBOx complexes in the Claisen rearrangement of enolphosphonate **S1** (Table 1, entry 1).[12] However, no rearrangement product was detected. When the Cu/TBOx complex was used, the reaction proceeded slowly to give the product with 70% yield but in racemic form (Table 1, entry 2). Bidentate bisoxazoline ligands instead of tetradentate TBOx ligands were then examined. To our delight, when the (*R*,*R*)-PhBOX ligand (**L1**) was used the product was obtained with 88% yield and 93% *ee* in 2 hours (Table 1, entry 3).[13,14] When the aminoindanol-derived bisoxazoline ligand **L2** was used the rearrangement product was obtained in 93% *ee* but with lower yield (Table 1, entry 4). Other metal triflates and copper sources were also tested but none of them gave more-satisfying results.[10] A screen of solvents indicated that several solvents were suitable for this reaction and that the enantioselectivity could be improved when the reaction was performed in a dichloromethane/*n*-hexane (1:5) solvent mixture (Table 1, entry 5).[10] The best results were achieved when the catalyst loading was lowered to 5 mol% (Table 1, entry 6). Unfortunately, the use of this dichloromethane/*n*-hexane (1:5) solvent mixture failed to increase the enantioselectivity when ligand **L2** was used (Table 1, entry 7). Interestingly, in the presence of **L1** the catalyst loading could even be lowered to 0.1 mol% without significant detrimental effect on the selectivity and yield, although

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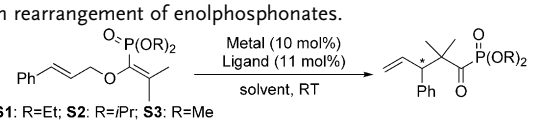
[**] Support of this research was provided by the NSF (CHE-1049551) and NIH (P50 GM086 145-01). We thank Dr. Antoni Jurkiewicz for NMR, Dr. Ian M. Steele for X-ray analysis and Dr. Furong Sun (UIUC) for MS data. Dr. David Dickson is acknowledged for his original work for this project.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201203092.

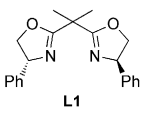
Table 1: Screening of reaction conditions for the copper-catalyzed Claisen rearrangement of enolphosphonates.

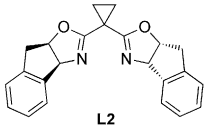


S1: R=Et; **S2**: R=*i*Pr; **S3**: R=Me

Entry[a]	Metal	S	Ligand	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Me_2AlCl	**S1**	TBOx	CH_2Cl_2	24	N.R.	N.D.
2	$Cu(OTf)_2$	**S1**	TBOx	CH_2Cl_2	16	70	0
3	$Cu(OTf)_2$	**S1**	**L1**	CH_2Cl_2	2	88	93
4	$Cu(OTf)_2$	**S1**	**L2**	CH_2Cl_2	4	80	93
5	$Cu(OTf)_2$	**S1**	**L1**	CH_2Cl_2/*n*-hexane[d]	4	90	96
6[e]	$Cu(OTf)_2$	**S1**	**L1**	CH_2Cl_2/*n*-hexane[d]	4	90	97
7[e]	$Cu(OTf)_2$	**S1**	**L2**	CH_2Cl_2/*n*-hexane[d]	24	69	83
8[f]	$Cu(OTf)_2$	**S1**	**L1**	CH_2Cl_2/*n*-hexane[d]	72	76	93
9[e,g]	$Cu(OTf)_2$	**S1**	**L1**	CH_2Cl_2/*n*-hexane[d]	72	80	97
10[e]	$Cu(OTf)_2$	**S2**	**L1**	CH_2Cl_2/*n*-hexane[d]	2	84	95
11[e]	$Cu(OTf)_2$	**S3**	**L1**	CH_2Cl_2/*n*-hexane[d]	2	86	95

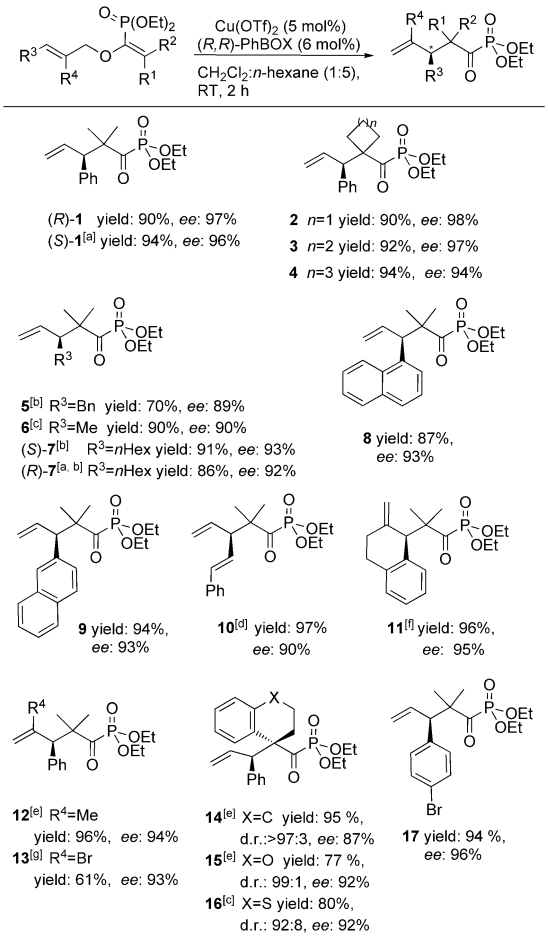
[a] All reactions performed at 0.1 mmol scale. [b] Yield of the isolated product. [c] Determined by HPLC on a chiral staionary phase. [d] Dichloromethane/*n*-hexane = 1:5. [e] 5 mol% of catalyst. [f] 0.1 mol% of catalyst. [g] Reaction performed at 0°C. N.R. = no reaction, N.D. = not determined, Tf = trifluoromethanesulfonyl.





a longer reaction time was required (Table 1, entry 8). Decreasing the reaction temperature to 0°C failed to give rise to further improvement to the enantioselectivity (Table 1, entry 9). Notably the size of the R group on the phosphonate motif does not have a significant effect on the reaction. Substrates **S2** and **S3**, with either a smaller or a larger R group than that of **S1**, both gave the desired product with only slightly lower selectivity (Table 1, entries 10 and 11).

With the fully optimized reaction conditions established, a wide range of substrates were examined and the rearrangement products were obtained with good to excellent yields and stereoselectivities (Scheme 2). With regard to the R^1 and R^2 groups on the enolphosphonates, substrates bearing a range of cyclic substituents provided the desired products **2**–**4** with similar levels of enantioselectivity as product **1**, which has a dimethyl substituent. For the R^3 group, in addition to an aryl group, aliphatic R^3 groups were also tolerated and products **5**, **6**, and (*S*)-**7** were obtained with similar results but with longer reaction times than for product **1**. The steric bulk of the R^3 group has no significant effect on the enantioselectivity. Substrates bearing large naphthyl rings, in place of the phenyl group, were also examined, and **8** and **9** were generated with high enantioselectivities. For conjugated substrates, the reaction had to be carried out at 0°C to attenuate the background reactions, thus providing **10** with 90% *ee*. Notably the existence of R^4 substituents, which have seldom been studied in previous reports, did not prevent the rearrangement. Enolphosphonates bearing either an alkyl group or halogen atom as the R^4 group all underwent the rearrangement reaction to give α-ketophosphonates **11**–**13** in



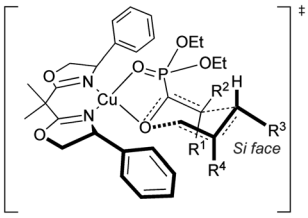
Scheme 2. Substrate scope for Cu^{II}/PhBOX catalyzed asymmetric Claisen rearrangement reaction. All reactions were performed on a 0.1 mmol scale. The yields are of the isolated products. The diastereomeric ratio (d.r.) was determined by ^1H NMR analysis of the crude mixture. Enantioselectivity was determined by HPLC on a chiral stationary phase. The absolute configuration was assigned by X-ray crystallographic analysis of the hydrolyzed product of **17** and the rest were assigned by analogy. [a] (*S*, *S*)-PhBOX ligand used instead. [b] Reaction time: 72 h. [c] Reaction time: 10 h. [d] Reaction performed at 0°C. [e] Reaction time: 4 h. [f] Reaction time: 24 h. [g] Reaction time: 1 week. Bn = benzyl.

high efficiency. Unfortunately, under the optimized reaction conditions, substrates bearing either *cis*-cinnamyl or a 3, 3-disubstituted allylic moiety failed to undergo rearrangement reactions, thus indicating that our method still has its own limitations at the current stage.[15] The utilization of the commercially available (*S*,*S*)-PhBOX ligand enabled us to generate the products (*R*)-**1** and (*S*)-**7**, which have the opposite sense of chirality than the products obtained from the same starting materials but with the (*R*,*R*)-PhBOX ligand (**L1**).

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 groups on the double bond of the enolphosphonates,[16] the substrate bearing a tetrahydronaphthyl ring underwent the Claisen rearrangement to give the desired

product **14** in 95% yield, > 97:3 d.r., 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 products **15** and **16**, respectively, in good yield and stereoselectivity.[17] The absolute stereochemistry of the Claisen rearrangement products was unambiguously assigned on the basis of the X-ray structure of the carboxylic acid that was obtained from the hydrolysis of rearrangement product **17**.[10,17]

A plausible transition-state model is proposed as the well-defined tetrahedral substrate/catalyst complex, in which bidentate chelation control results in excellent enantioface differentiation (Scheme 3).[4k,13b,18] As depicted, the substrate, tightly bound to the catalyst, is assumed to arrange in a chair-

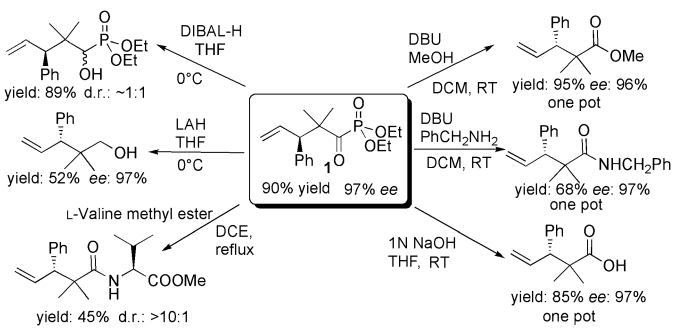


Scheme 3. Proposed transition state.

like configuration so that the enolphosphonate unit approaches the *Si* face of the allylic ether moiety, which is positioned 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 used for predicting the relative stereochemistry.

To highlight the synthetic utility of this method, 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 4). First, the α-ketophosphonates **1** acted as a masked acyl chloride and could readily react with alcohols and amines to give the corresponding ester and 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 1,2-dichloroethane (DCE), which is heated to reflux. Moreover, the carbonyl group of **1** could be transformed by a simple reduction. When DIBAL-H was utilized, the α-ketophosphonate **1** was converted into an α-hydroxy phosphonate but with poor diastereoselectivity. When **1** was treated with $LiAlH_4$, the ketophosphonate group was completely reduced to give the alcohol product.

In summary, we have successfully developed the first copper-catalyzed enantioselective Claisen rearrangement of enolphosphonates. A number of desired α-ketophosphonate products with diverse substitents were obtained in excellent yields and stereoselectivities and these products can easily undergo further functionalization to provide various chiral building blocks, effectively. Significantly, this method provides a single-step rapid construction of chiral motifs, with contiguous tertiary and all-carbon quaternary centers bearing unfunctionalized substituents, that 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.



Scheme 4. Synthetic applications of rearrangement product **1**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminium hydride, LAH = lithium aluminium hydride.

Received: April 23, 2012
Published online: ■■ ■■, ■■■■

Keywords: asymmetric catalysis · BOX ligands · Claisen rearrangement · copper · quaternary carbon centers

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[15] A detailed explanation of the substrate scope as well as the limitations of this reaction can be found in the Supporting Information.

[16] As a result of 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 Scheme 3. 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.

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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, thus possibly leading to no reaction activity for Claisen rearrangement.

Communications

Asymmetric Catalysis

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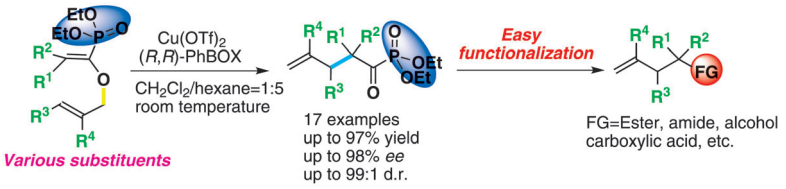
Catalytic Asymmetric Claisen Rearrangement of Enolphosphonates: Construction of Vicinal Tertiary and All-Carbon Quaternary Centers



A copper-catalyzed enantioselective Claisen rearrangement of easily accessible enolphosphonates using the commercially available 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 substituent in the products could be easily transformed into other functional groups.