Asymmetric tandem Michael addition-vlide olefination reaction for the synthesis of optically active cyclohexa-1,3-diene derivatives[†]

Long-Wu Ye,^a Shou-Bing Wang,^b Qing-Gang Wang,^a Xiu-Li Sun,^a Yong Tang^{*a} and Yong-Gui Zhou*^b

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The reaction of a crotonate-derived chiral phosphonium salt with α , β -unsaturated carbonyl compounds in the presence of Cs₂CO₃ affords optically active cyclohexa-1,3-diene derivatives with up to 90% ee in good yields.

Cyclohexa-1,3-dienes and their derivatives are frequently used as versatile intermediates in the synthesis of natural products¹ and biologically active compounds.² The ylide-initiated Michael addition-olefination reaction has been established as a promising method for the preparation of such highly functionalized compounds due to its unambiguous positioning and good stereoselectivity.^{2e,3} To date, however, its asymmetric version using a chiral phosphonium ylide has not yet been developed. The reason, most likely, is that the chiral inductive center is far from the reaction site (Scheme 1), which usually leads to low enantioselectivity.⁴ As part of our on-going research project on ylide reactions and their applications in organic synthesis,⁵ we reported a tandem reaction of allylic sulfur ylides with α,β -unsaturated ketones for the preparation of functionalized multisubstituted cyclohexadiene epoxides.⁶ On the basis of this reaction, we developed a tandem Michael addition-ylide olefination for the creation of highly functionalized cyclohexadiene.⁷ It is envisioned that the aforementioned reaction will afford optically active cyclohexa-1,3-dienes by employing a chiral phosphorus ylide. Very





Scheme 1 Tandem Michael addition-ylide olefination reaction.



Scheme 2 Chiral phosphines screened.

recently, we found that a 2,2'-bis(diphenylphosphino)-1,1'biphenyl (BIPHEP)-derived phosphorus ylide reacted with α,β -unsaturated ketones to give the desired cyclohexa-1,3dienes with good to high ees in good yields. To the best of our knowledge, this represents the first example of the asymmetric tandem ylide Michael addition-olefination reaction. In this communication, we wish to report the preliminary results.

Initially, we tested (S)-BINAP 1a-derived phosphonium salt 2a in the presence of Cs₂CO₃ using chalcone 3a as a model substrate.^{8a-8e} As shown in Table 1, salt 2a could afford optically active annulation product 4a with 36% ee at room temperature (entry 1, Table 1). This result encouraged us to explore other chiral phosphine-derived salts (Scheme 2). It was found that phosphonium salts derived from chiral MeO-BIPHEP^{8f,8g} could give better ees than 2a (entries 2–8. Table 1). For example, (R)-2-MeO-MeOBIPHEP-derived phosphonium salt 1d could furnish 83% ee in 62% yield (entry 4, Table 1). The enantiomeric excess was slightly decreased when using KOBu^t instead of Cs₂CO₃ as a base (entries 4-5, Table 1). The reaction temperature proved also to influence the enantioselection. Elevating the temperature from room temperature to 50 °C resulted in an obvious decrease of the ee when (R)-2-MeO-MeOBIPHEP 1d was used (entry 4 vs. 8, Table 1). Solvent effects were also examined. In CH₃CN and toluene, both the yield and enantiomeric excess decreased (entries 6-7, Table 1).

Under the optimal conditions, the generality of this tandem ylide annulation reaction was investigated by studying a variety of α,β -unsaturated carbonyl compounds. As shown

^a State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China.

E-mail: tangy@mail.sioc.ac.cn

^b Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China. E-mail: ygzhou@dicp.ac.cn

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Table 1 Effects of reaction conditions on the tandem Michael addition-ylide olefination reaction^a



1	1a	THF	Cs ₂ CO ₃	52	36
2	1b	THF	Cs_2CO_3	45	56
3	1c	THF	Cs_2CO_3	58	63
4	(R)-1d	THF	Cs_2CO_3	62	83
5	(<i>R</i>)-1d	THF	Bu ^t OK	61	81
6	(<i>R</i>)-1d	CH ₃ CN	Cs_2CO_3	58	46
7	(<i>R</i>)-1d	Toluene	Cs_2CO_3	38	44
8^d	(<i>R</i>)-1d	THF	Cs_2CO_3	56	71

^a Reagents and conditions: base (0.23 mmol), 2 (0.17 mmol) in solvent (1.5 mL), room temperature, 45 min, then 3a (32 mg, 0.15 mmol) in solvent (1.5 mL) was added and stirred for another 48 h at room temperature. ^b Isolated yield. ^c Determined by chiral HPLC. ^d At 50 °C.

in Table 2, various α,β -unsaturated arylketones are good substrates for this reaction to give the desired products with high enantioselectivities in good yields. Both methoxy and bromo groups on the aryl ring of chalcones proved to be well-tolerated and influenced the enantioselectivities slightly (entries 1–6, Table 2). The ester group of phosphonium salt 2d had little effect on the enantioselectivity. For instance, the tert-butyl ester gave a slightly lower ee than the methyl ester (entry 1 vs. 3, Table 2). 1-Phenyl-but-2-en-1-one 3e gave the desired cyclohexadienes with 78% ee in 53% yield (entry 7, Table 2). As expected, the same tandem cyclization was

 Table 2
 Assembly of optically active cyclohexa-1,3-diene derivatives
 via chiral phosphonium ylide"



Entry	R	$R^1/R^2/R^3$	Yield $(\%)^b$	ee (%) ^c
1	CO ₂ Me	Ph/H/Ph (3a)	62	83
2^d	$\overline{CO_2Me}$	Ph/H/Ph (3a)	64	84
3	$CO_2^{t}Bu$	Ph/H/Ph (3a)	55	79
4	$\overline{CO_2Me}$	$p-BrC_6H_4/H/Ph$ (3b)	73 $(85)^e$	80
5	$\overline{CO_2Me}$	p-OMeC ₆ H ₄ /H/Ph (3c)	65	90
6	$\overline{CO_2Me}$	o-BrC ₆ H ₄ /H/Ph (3d)	$60(73)^e$	80
7	$\overline{CO_2Me}$	Me/H/Ph (3e)	53	78
8^{f}	CO_2Me	Me/H/H (3f)	67	25
9	CO_2Me	$p-MeC_6H_4/CH_3CO/CH_3$ (3g)	Trace	
10	Ph	Ph/H/Ph (3a)	79	30
11	$\mathrm{CO}_2\mathrm{Me}$	$C_6H_{13}/H/CH_3$ (3h)	Trace	_

^a Reagents and conditions: Cs₂CO₃ (74 mg, 0.23 mmol), 2 (0.17 mmol) in THF (1.5 mL), room temperature, 45 min, then 3 (0.15 mmol) in THF (1.5 mL) was added and stirred for further 48-72 h at room temperature. ^b Isolated yield. ^c Determined by chiral HPLC. ^d Using (S)-1d-derived phosphonium salts. e 1.5 equiv. of 2, 1.8 equiv. of Cs₂CO₃. ^f At 0 °C.



Stereochemical model. Fig. 1

carried out using an (S)-2-MeO-MeOBIPHEP 1d-derived phosphonium salt instead of an (R)-2-MeO-MeOBIPHEP-1d-derived phosphonium salt to give the opposite enantioselectivity with 84% ee (entries 1 and 2, Table 2). Thus, both enantiomers could be obtained easily just by the choice of the phosphonium salt. In addition, increasing the amount of phosphonium salt from 1.1 equivalents to 1.5 equivalents improved the yield obviously with well-maintained enantioselectivities (entries 4 and 6, Table 2). (E)-But-2-enal worked well to give the desired product in 67% yield with 25% ee (entry 8). Only a trace amount of the products was observed when both the enone with β -substituent and (E)-dec-3-en-2-one were employed (entries 9 and 11). Using chalcone as a substrate, cinnamyl phosphonium salt afforded good yield and 30% ee (entry 10).

In order to determine the absolute configuration, we developed a single crystal of enantiopure product⁹ 4f. By X-ray analysis, however, the unit cell is symmetric and the absolute configuration cannot be assigned by this way. Fortunately, optically active product 4f is a known compound¹⁰ and by comparing the rotation, it is assigned as 'S' configuration. On the basis of this result, a stereochemical model shown in Fig. 1 was developed to explain the stereoselection. The ylide attacked the enone from the re-face due to the steric hindrance.

The current reaction is very useful in organic synthesis.^{2a,10,11} For example, reduction of 4a with DIBAL-H, followed by Dess-Martin oxidation, provided biologically active compound 5 in a total 83% yield with 82% ee (Scheme 3).^{1a} In these transformations, the ee was well maintained.

In conclusion, we have developed an efficient method for the preparation of optically active cyclohexa-1,3-dienes using a BIPHEP-derived phosphonium salt. This provides the first example of the asymmetric tandem ylide Michael additionolefination reaction. The easily available phosphonium salts, in particular the recovery^{5d} and the reuse of chiral phosphines, make the present method potentially useful. Further investigations into the synthetic applications of the current tandem asymmetric reaction are in progress in our laboratory.

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Scheme 3 Synthesis of biologically active compound 5.

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