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

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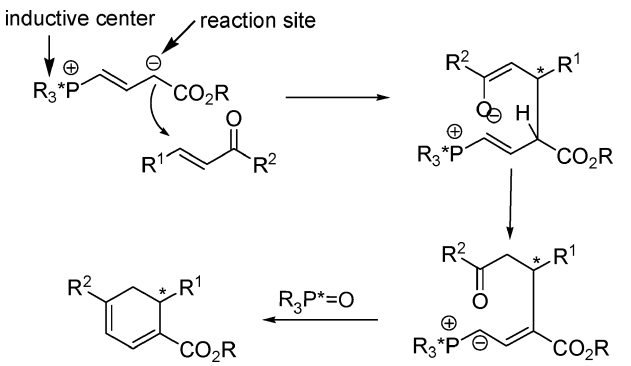
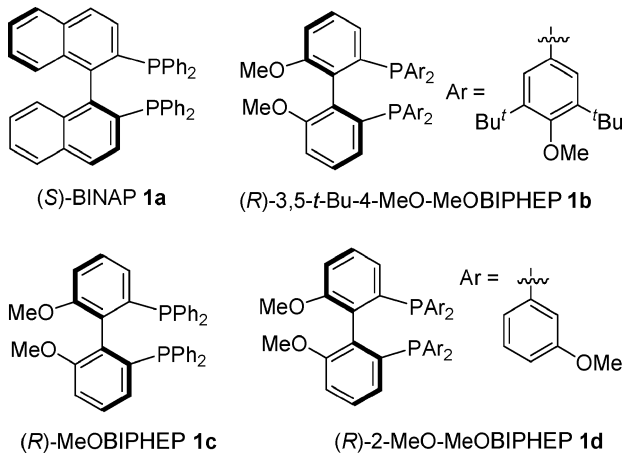
The reaction of a crotonate-derived chiral phosphonium salt with α,β-unsaturated carbonyl compounds in the presence of Cs_2CO_3 affords optically active cyclohexa-1,3-diene derivatives with up to 90% ee in good yields.

Cyclohexa-1,3-dienes and their derivatives are frequently used as versatile intermediates in the synthesis of natural products[1] 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 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-1,3-dienes 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.



Scheme 1 Tandem Michael addition–ylide olefination reaction.



Scheme 2 Chiral phosphines screened.

Initially, we tested (*S*)-BINAP **1a**-derived phosphonium salt **2a** in the presence of Cs_2CO_3 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 Cs_2CO_3 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 CH_3CN 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

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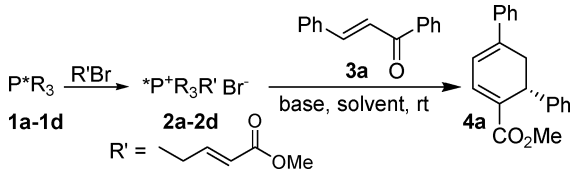
Table 1 Effects of reaction conditions on the tandem Michael addition–ylide olefination reaction[a]

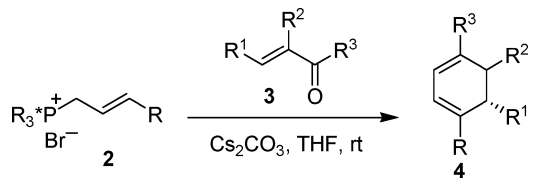


Entry	P^*R_3	Solvent	Base	Yield (%)[b]	ee (%)[c]
1	**1a**	THF	Cs_2CO_3	52	36
2	**1b**	THF	Cs_2CO_3	45	56
3	**1c**	THF	Cs_2CO_3	58	63
4	(*R*)-**1d**	THF	Cs_2CO_3	62	83
5	(*R*)-**1d**	THF	Bu^tOK	61	81
6	(*R*)-**1d**	CH_3CN	Cs_2CO_3	58	46
7	(*R*)-**1d**	Toluene	Cs_2CO_3	38	44
8[d]	(*R*)-**1d**	THF	Cs_2CO_3	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[a]



Entry	R	$R^1/R^2/R^3$	Yield (%)[b]	ee (%)[c]
1	CO_2Me	Ph/H/Ph (**3a**)	62	83
2[d]	CO_2Me	Ph/H/Ph (**3a**)	64	84
3	$CO_2{}^tBu$	Ph/H/Ph (**3a**)	55	79
4	CO_2Me	*p*-BrC_6H_4/H/Ph (**3b**)	73 (85)[e]	80
5	CO_2Me	*p*-$OMeC_6H_4$/H/Ph (**3c**)	65	90
6	CO_2Me	*o*-BrC_6H_4/H/Ph (**3d**)	60 (73)[e]	80
7	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	CO_2Me	C_6H_{13}/H/CH_3 (**3h**)	Trace	—

[a] Reagents and conditions: Cs_2CO_3 (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 Cs_2CO_3. [f] At 0 °C.

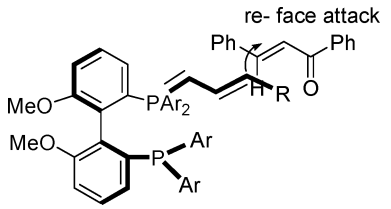


Fig. 1 Stereochemical model.

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 product[9] **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 compound[10] 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 addition–olefination 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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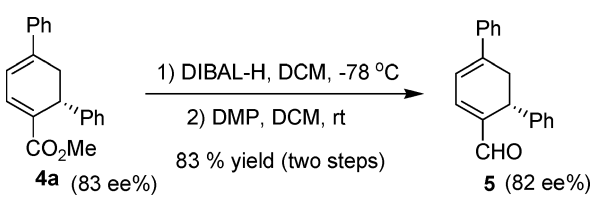

Scheme 3 Synthesis of biologically active compound **5**.

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