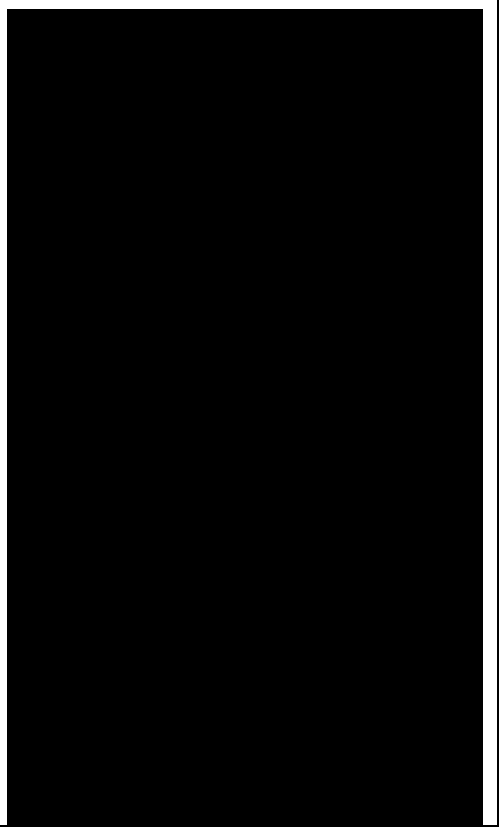
Chiral phosphinothiourea organocatalyst in the enantioselective Morita-Baylis-Hillman reactions of aromatic aldehydes with	Chất xúc tác hữu cơ phosphinothiourea chiral trong các phản ứng Morita- Baylis-Hillman chọn lọc đối quang của các andehit thơm với

methyl vinyl ketone The Morita-Baylis-Hillman (MBH) reaction is a powerful tool for the atom-economic construction of densely functionlized a- methylene-p-hydroxycarbonyl derivatives which serve as valuable building blocks in organic synthesis.1 The development of a suitable asymmetric version of this reaction has attracted considerable interest in recent years.2 Various chiral organocatalysts including quinidine-derived p-isocupreidine,3 BINOL-derived Brensted acid,4 and bifunctional aminothiourea5 have been notably developed for the asymmetric MBH reaction to achieve high enantiomeric excesses. Enantiomer còn có nghĩa là isome quang Bis(thio)ureas derived from chiral trans-1,2-diaminocyclo-hexane, isophorone-diamine (IPDA), and H8-BINAM were also proven to be efficient organocatalysts for the asymmetric MBH reactions of various aldehydes with 2-cyclohexen-1-one as described by Nagasawa, Berkessel and Shi, respectively.6 However, Morita-Baylis-Hillman reactions involving methyl vinyl ketone (MVK) as reaction partner usually afforded the corresponding products in moderate enantioselectivities.2,7 To the best of our knowledge, the	methyl vinyl ketone Phản ứng Morita-Baylis-Hillman (MBH) là một công cụ mạnh để xây dựng hiệu quả nguyên tử của các dẫn xuất a-methylene-p-hydroxycarbonyl chức hóa đậm đặc, những chất này đóng vai trò là các thành phần cơ bản có giá trị trong quá trình tổng hợp hữu cơ. Sự phát triển của phiên bản bất đối xứng phù hợp của phản ứng này đã thu hút rất nhiều sự quan tâm của các nhà nghiên cứu trong những năm gần đây. Các chất hữu cơ chiral khác bao gồm p-isocupreidine có nguồn gốc từ quinidine,3 axit Brensted có nguồn gốc từ BINOL,4 và aminothiourea nhị chức cũng đã được thiết kế riêng cho phản ứng MBH bất đối xứng để cho ra lượng dư đối quang cao. 

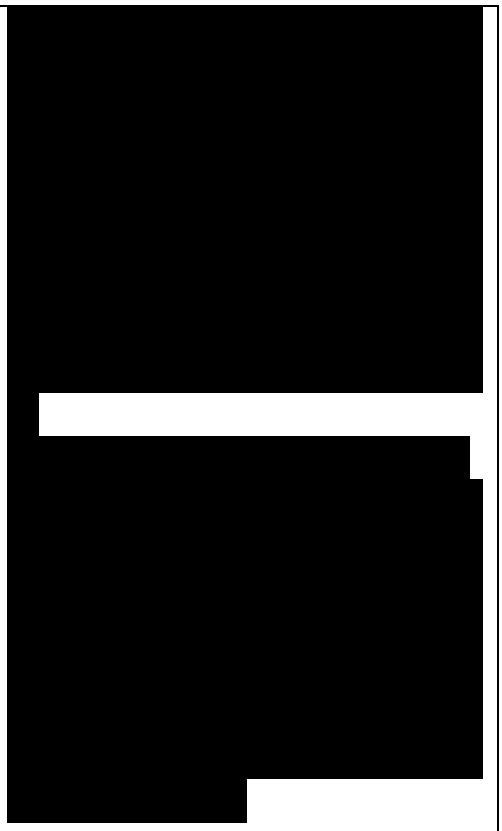
highest enantioselectivity of this kind of MBH reaction was 83% ee using chiral tertiary amine/proline cocatalysts.7d

Cyclohexane-based aminothiourea has been extensively studied in recent years as a bifunctional organocatalyst for asymmetric catalysis.8 In 2004, Yudin and co-workers reported cyclohexane- based iminophosphines derived from the ring-opening of aziridine for transition metal catalysis.9 Due to the structural analogy between aminothiourea and iminophosphine, we envisioned that the overlapped structure, that is, phosphinothiourea (Fig. 1), could serve as a new class of bifunctional organocatalysts for enantiose- lective catalysis. As tertiary phosphines are effective catalysts for the MBH reaction, it is conceivable that the phosphinothiourea could catalyze this reaction in an enantioselective fashion.

The bifunctional phosphinothiourea was not documented before for asymmetric catalysis until recently Shi and Shi10 reported the BINOL-derived phosphinothioureas as organocatalysts in the

Figure 1. Overlap approach to design new catalyst.

presence of carboxylic acid as co-catalyst for the asymmetric aza-Morita-Baylis-Hillman reaction. However, the reaction usually takes a long time. Herein, we report a new class of phosphinothiourea organocatalysts, derived from trans-2-amino- 1-(diphenylphosphino)cyclohexane (1),11 which are fairly effective bifunctional organocatalysts for the enantioselective MBH reaction of arylaldehydes with MVK to give the corresponding adducts in up to 94% ee and good to excellent yields.



The organocatalysts 2a-f12 are easily prepared by condensation of (R,R)-2-amino-1-(diphenylphosphino)cyclohexane (1) with 1.1 equiv of the corresponding iso(thio)cyanate or isocyanate under mild conditions (Fig. 2, see Supplementary data).

We initially chose the reaction of MVK with p-nitrobenzalde-hyde to screen the phosphinothioureas as bifunctional organocat- alysts for the MBH reaction. To our delight, when using CH_2Cl_2 as solvent, the reaction completed in 45 min with catalyst 2a to provide the desired MBH product in 71% yield and 85% ee (Table 1, entry 3). Longer reaction time afforded lower chemical yield

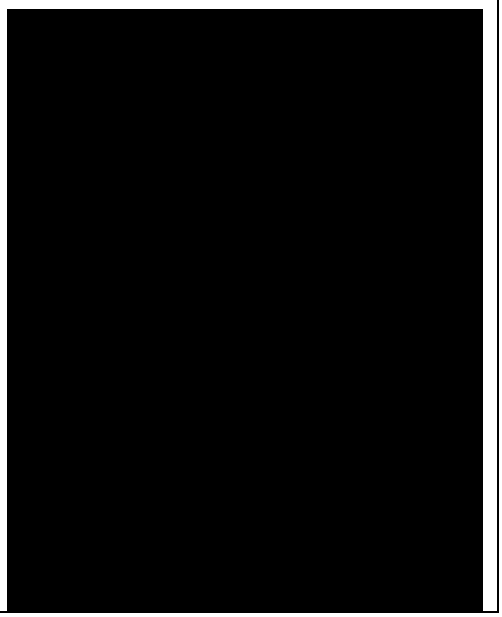


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Table 1
Screening of the catalysts for the reaction of MVK and 4-nitrobenzaldehydea
a Unless stated otherwise, the reactions were conducted with 10 mol % of organocatalyst, 5 equiv of MVK in CH2Cl2 (0.2 M) at 13 °C.

b Isolated yields. c Determined by chiral HPLC. d 5 mol % 2a was used. e Not determined.

to the over reaction with MVK (entries 4 and 5 vs 3). The thiourea moiety proved to be critical for the MBH reaction in terms of both yield and enantioselectivity. Urea derivative 2b was ineffective under identical conditions (entry 7). Surprisingly, catalyst 2c gave poor enantioselectivity, albeit with high yield (entry 8). Substitution at the 4-position of phenyl has no obvious effect on the enanti-oselectivity (entries 3, 9, and 10). Bearing an alkyl group, the phosphinothiourea 2f afforded good level of enantioselectivity, but low yield (entry 11).

Further optimization including various solvents, temperature, and substrate concentration in the presence of catalyst 2a led to the optimal reaction conditions (see Supplementary data): using 2a as catalyst, the

reaction of 5 equiv of MVK with 0.3 M of p-nitro-benzaldehyde in CHCl3 completed in 15 min at 13 °C to provide the desired product in 75% yield and 94% ee.

Under the optimized conditions, the substrate scope in terms of aromatic aldehydes was first investigated. As indicated in Table 2, reaction of MVK with strong electron-deficient aldehydes usually proceeded very quickly (within 1 h) to provide the desired

organocatalyst, 5 equiv of MVK in CHG3 (0.3 M) at 13 °C. b Isolated yields.

c The ee was determined by chiral HPLC, and the absolute configuration was determined by comparison of optical rotation with that of literature report.7c,13

Figure 3. Proposed transition state.

products in very good yields and excellent enantioselectivities (90-94% ee, entries 1-5). Both mono- and di-halogen substituted arylaldehydes are tolerated to generate the products in high enantioselectivities (87-92% ee) albeit with moderate yields (entries 6-9). The reactions with non-substituted benzaldehyde and 2-naphthylaldehyde proceeded slowly to afford the product in high enantioselecitvity (90%

ee), but low yields (entries 10 and 11). As a general trend, the reaction with electron-rich arylaldehyde proved to be difficult and complex mixture was observed.

The observed absolute configuration could be explained by the plausible transition state illustrated in Figure 3. The thiourea moiety forms hydrogen-bond with the aldehyde carbonyl. The cyclo-hexyl scaffold forces the phosphinoyl associated enolate to attack the activated carbonyl from the si-face to generate the R configuration.

In summary, we have developed a highly enantioselective Mori- ta-Baylis-Hillman reaction involving the addition of MVK to aromatic aldehydes catalyzed by a phosphinothiourea organocata- lyst derived from trans-2-amino-1-(diphenylphosphino)cyclohex-ane. The reaction proceeds under very mild conditions to afford the desired product in a short time period in good to excellent yields with generally excellent enantiomeric excesses (87-94% ee). Further efforts are underway with a focus on improving the catalyst activity and the scope of substrate as well as the mechanism of the asymmetric MBH reaction.

Enantiomer còn có nghĩa là isome quang