L-Threonine-Derived Novel Bifunctional Phosphine-Sulfonamide Catalyst-Promoted Enantioselective Aza-Morita-Baylis—Hillman Reaction	Phản ứng Aza-Morita-Baylis—Hillman chọn lọc đối quang tăng cường bằng chất xúc tác Phosphine-Sulfonamide nhị chức mới lạ có nguồn gốc từ L-Threonine
ABSTRACT	TÓM TẮT
A series of novel bifunctional	Một loạt chất xúc tác hữu cơ

phosphine—sulfonamide organic catalysts were designed and readily prepared from natural amino acids, and they were utilized to promote enantioselective aza-Morita—Baylis—Hillman (MBH) reactions. L-Threonine-derived phosphine—sulfonamide 9b was found to be the most efficient catalyst, affording the desired aza-MBH adducts in high yields and with excellent enantioselectivities.

Nucleophilic organic catalysts employing trivalent phos- phines as Lewis bases are widely used in synthetic organic chemistry.1 Compared with similarly substituted amines, phosphines are generally less basic and more nucleophilic; thus chiral phosphines often show unique catalytic activities in asymmetric synthesis. Despite tremendous applications of phosphine-catalyzed reactions in organic synthesis, development of chiral phosphine catalysts is still at its early stage, and design of highly efficient and readily available chiral phosphines remains a huge challenge. Our group has been investigating primary amino acid based asymmetric organocatalytic synthetic methods in the past few years,2p,3 and asymmetric amino catalysis via chiral primary amines has been established as a powerful and versatile tool in asymmetric synthesis.

To further expand amino acid based asymmetric catalysis, we were interested in establishing novel chiral phosphines based on simple amino acid scaffolds. Bifunctional catalytic systems have been widely used in organic chemistry, and the synergistic interactions of two functionalities have been proven to be extremely powerful

phosphine—sulfonamide nhị chức mới lạ đươc thiết kế và điều chế từ các axit amin tự nhiên, và chúng được dùng để tăng cường các phản ứng aza-Morita—Baylis—Hillman (MBH). Chúng tôi nhận thấy Phosphine—sulfonamide 9b có nguồn gốc từ L-Threonine là chất xúc tác hiệu quả nhất, có thể cho ra các sản phẩm cộng aza-MBH mong muốn với sản lượng cao và độ chọn lọc đối quang tuyệt vời.

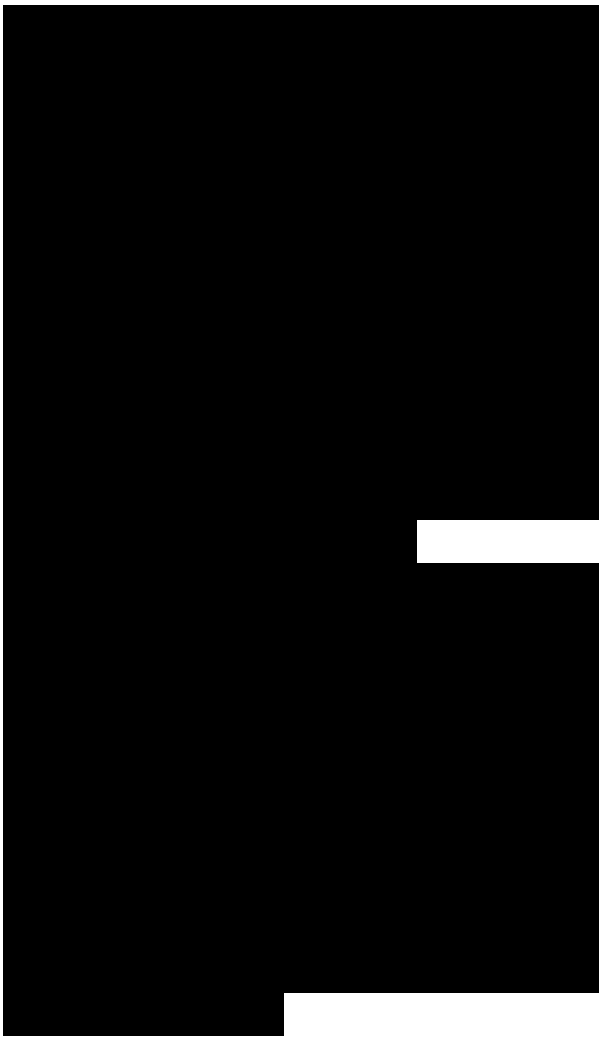
Các chất xúc tác hữu cơ ái nhân dùng các phosphine hóa trị ba làm bazơ Lewis được sử dụng rộng rãi trong quá trình tổng hợp hóa hữu cơ.1 So với các amin thế tương tự, nói chung các phosphine ít tính bazơ hơn và ái nhân hơn; vì thế các phosphine chiral thường thể hiện các hoạt tính xúc tác độc đáo trong quá trình tổng hợp bất đối xứng. Mặc dù có nhiều ứng dụng to lớn trong các phản ứng xúc tác bằng phosphine trong tổng hợp hữu cơ, sự phát triển của các chất xúc tác phosphine chiral vẫn còn ở giai đoạn rất nguyên sơ và các phosphine chiral hiện tại vẫn còn nhiều trở ngại lớn. Nhóm chúng tôi đã khảo sát các phương pháp tổng hợp chất xúc tác hữu cơ bất đối xứng dựa trên axit amin bậc nhất trong vài năm qua ,2p,3 và xúc tác amin bất đối xứng qua các amin bậc nhất chiral đã thể hiện là một công cụ mạnh và linh hoạt trong quá trình tổng hợp bất đối xứng.

in asymmetric catalysis. We envisioned that novel bifunctional phosphine catalysts can be easily derived from natural amino acids, and the designing principles are summarized in Figure 1.

Figure 1. Novel bifunctional phosphine catalysts based on natural primary amino acids.

Simple functional group transformations convert the acid group into a phosphine, and the Br0nsted acid site necessary for the bifunctional catalysts can be easily derived from the amine moiety. Proper selection of side chains then provides either steric or electronic tuning to the structures of the catalysts. Moreover, by connecting the phosphorus atom to a primary carbon, we anticipate higher nucleo- philicity of the resulting chiral phosphines.

The Morita—Baylis—Hillman (MBH) reaction and its aza counterpart (Aza-MBH reaction) are among the most valuable reactions for the construction of densely functio- nalized products from simple precursors in a highly atom economic fashion. Considerable efforts have been devoted to the development of enantioselective versions of these reactions, and most successful examples are usually



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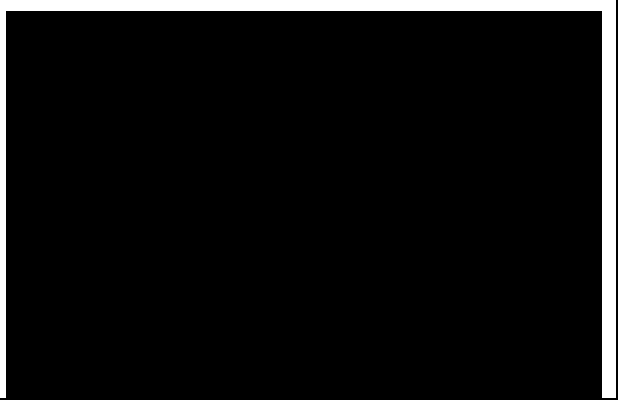

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based on chiral amine catalysts. Hatakeyama et al. reported highly enantioselective MBH and aza-MBH reactions with hexafluoroisopropyl acrylate (HFIPA) catalyzed by a tertiary amine catalyst fi-isocupreidine (fi-ICD). Shi and co-workers employed the same catalyst in the aza-MBH reactions with diverse activated olefins. Later, the group of Sasai applied BINOL-derived amine to promote the aza-MBH reaction. Raheem and Jacobsen also reported a thiourea-mediated aza-MBH reaction. More recently, Zhu et al. disclosed that a modified fi-ICD bearing amide functionality (fi-ICD amide) could be applied in the aza-MBH reaction in the presence of fi-naphthnol and excellent enantioselectivity was achieved with both aromatic and aliphatic sulfinyl imines. On the other hand, chiral phosphine-mediated enantioselective aza-MBH reactions are rather limited. In this context, elegant utilization of BINOL-derived phosphines by the groups of Shi, Sasai, and Ito clearly demonstrated the enormous potential of chiral phosphines in asymmetric MBH reactions. Our research group recently showed that dipeptide-derived novel phosphines

were powerful catalysts for the enantioselective allene—acrylate [3 + 2] cycloadditions (phản ứng cộng hợp đóng vòng) ;2p herein, we demonstrate that amino acid based bifunctional phosphines could effectively catalyze aza-MBH of acrylates with excellent enantiomeric control.

We began our investigation by preparing a number of L-valine-derived bifunctional chiral phosphines with different hydrogen bond donors (catalysts 4 to 7 in Figure 2). In particular, thioureas and sulfonamides are known to be remarkably useful in hydrogen-bonding (H-bond) interactions. The aza-MBH reaction between imines and acrylates was chosen as a model reaction, and the results

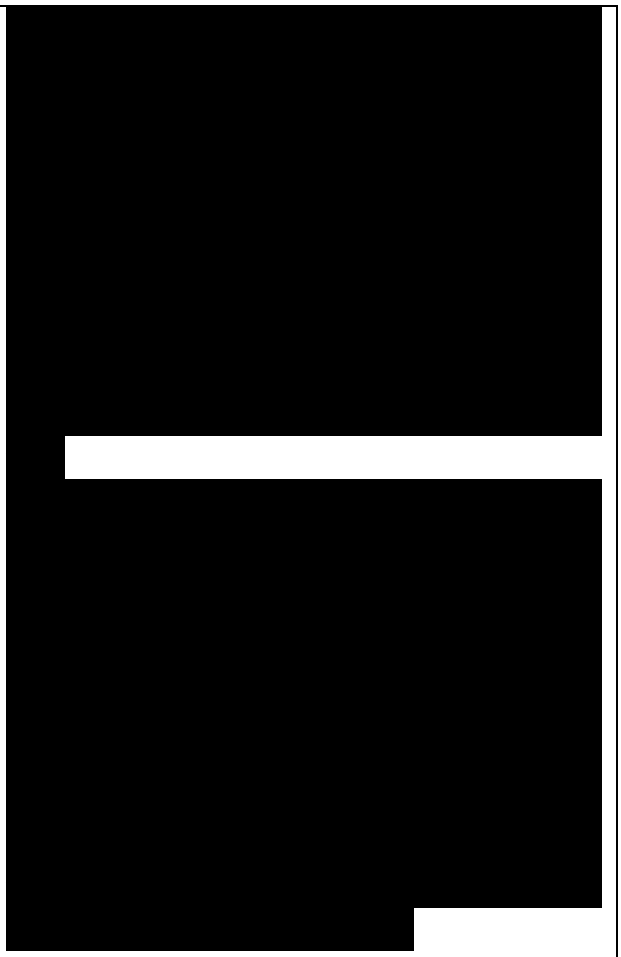


Figure 2. Stuctures of bifunctional phosphine catalysts.

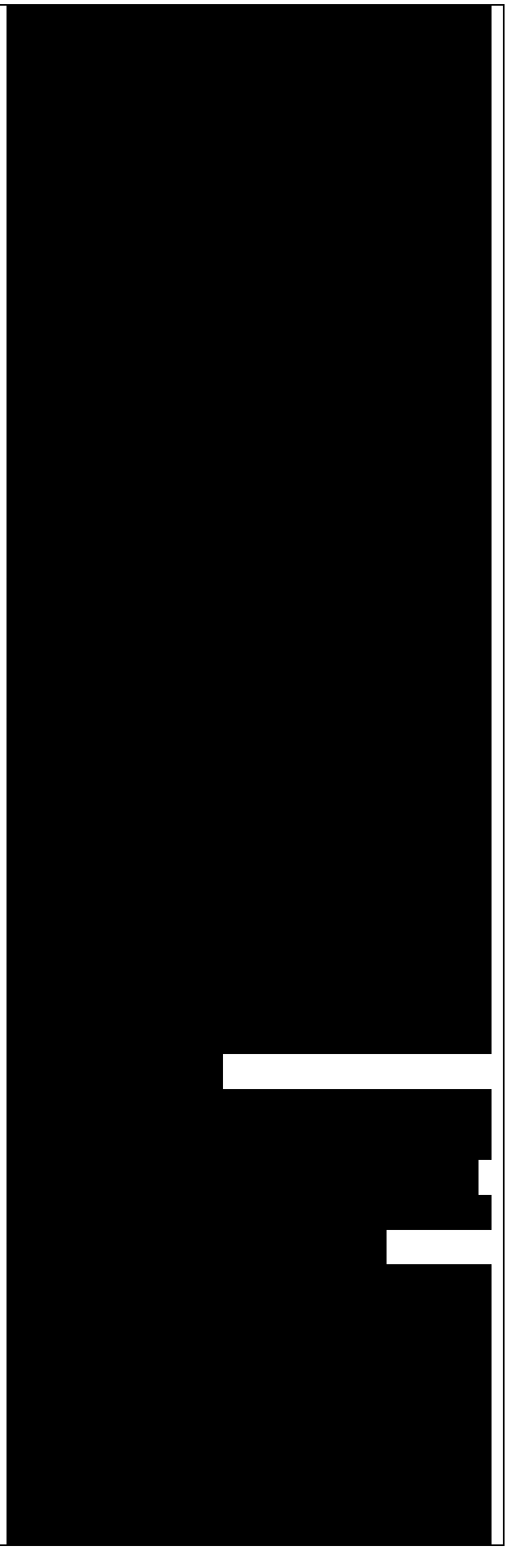
are summarized in Table 1. Phosphine-thiourea 4 gave poor results (entry 1). While catalyst 5 with a Boc group was completely ineffective, phosphine-amide 6 was able to catalyze the reaction, although in very low ee (entries 2 and 3). Phosphine-sulfonamide catalyst 7 was found to display certain reactivity and selectivity (entry 4). We next varied sulfonamide protection on the imine nitrogen and also employed different acrylates (entries 5 to 7). To our delight, by combining N-(p-methoxybenzenesulfonyl)imine and 2-naphthyl acrylate, phosphine-sulfonamide 7 led to the formation of an

aza-MBH adduct in excellent yield and with moderate enantioselectivity (entry 7). We reasoned that the isopropyl side chain from valine may not provide enough steric control in the asymmetric induction, and with our success in threonine-based catalytic systems,3b—d,g we decided to synthesize serine-derived catalyst 8 and a number of threonine-based phosphine—sulfonamides 9a to 9i, in which various siloxy groups15 were introduced. The threonine core proved to be superior to that of serine (entry 9 versus entry 8). Similar enantioselectivities were observed with bulky siloxy groups, and the thexyldi- methylsilyl (TDS) group was chosen as it gave marginally better results (entries 9—13). Exploration of different sulfonamides in the catalyst structures failed to improve the results (entries 14—17). The enantiomeric excess could be further improved by lowering the reaction temperature (entry 18). When the reaction was performed at —30 °C for 2 days, the desired aza-MBH adduct was obtained in 89% yield and with 91% ee (entry 19).

Table 2. Enantioselective Aza-MBH Reactions of Various Imi- nes 1 and Acrylate 2c Catalyzed by 9b

Table 1. Catalyst Screening and Optimization of Reaction Conditions

a Reactions were carried out with 1 (0.05 mmol), 2 (0.1 mmol for 2a and 0.06 mmol for 2b, 2c), and catalyst (0.005 mmol) in dry THF (0.1 mL at rt or 0.2 mL at —20 °C or 0.25 mL at —30 °C) under N2. b Isolated yield. c Determined by HPLC analysis on a chiral stationary phase. d Reaction was



performed with 20 mol % catalyst at — 20 °C for 48 h. e Reaction was performed with 20 mol % catalyst at — 30 °C for 48 h.

a Reactions were performed with imine 1 (0.05 mmol), 2-naphthyl acrylate 2c (0.06 mmol) and catalyst 9b (0.01 mmol) in dry THF (0.25 mL) under N2. b Isolated yield. c Determined by HPLC analysis on a chiral stationary phase.

With the optimized reaction conditions in hand, the scope of the aza-MBH reaction was evaluated (Table 2). The reaction is applicable to a wide range of aromatic imines; excellent chemical yields and very high enantioselectivities were attainable within 2 days. Notably, the ortho-substituted aromatic imines, which are well-known to be difficult sub-strates for the aza-MBH reaction, were found to be suitable,

and the products were obtained in nearly quantitative yields and with up to 97% ee (entries 11 — 14). These results represent by far the best enantioselectivities attainable for the ortho-substituted substrates in the aza-MBH reaction. In addition, imines with heterocyclic rings were also applicable; 95% and 96% ee were observed (entries 15—16). A less satisfactory result was obtained for a cyclohexyl imine.

The Br0nsted acidic sulfonamide and nucleophilic phosphine in our bifunctional catalysts are indispensable and work cooperatively in promoting enantioselective aza- MBH reactions. When N-methylated sulfonamide 10 was employed as the catalyst, the reaction became slower and enantioselectivity was dramatically decreased [eq 1]. This result suggested

that the H-bond donor moiety in the catalyst contributes significantly to the reaction and is crucial for the asymmetric induction. Surprisingly, phosphine 11 containing N-trifluoromethanesulfonamide was found to be a very poor catalyst, giving the product in low yield and with virtually no enantioselectivity, which may be attributed to the overstabilization of the enolate intermediate by highly acidic N—H in the sulfonamide or formation of a protonated form of the enolate intermediate.

Despite their enormous applications, the mechanism of the MBH reactions is not entirely clear. Based on recent elegant mechanistic studies and our experimental observations, we propose the mechanism of the 9b-promoted aza-MBH reaction as depicted in Figure 3. The reversible conjugate addition of phosphine to acrylate generates intermediate A. Since enolate A is more basic than the imine substrate, and thus is a better H-bond acceptor, it forms a H-bond with the Br0nsted acid moiety of 9b. We

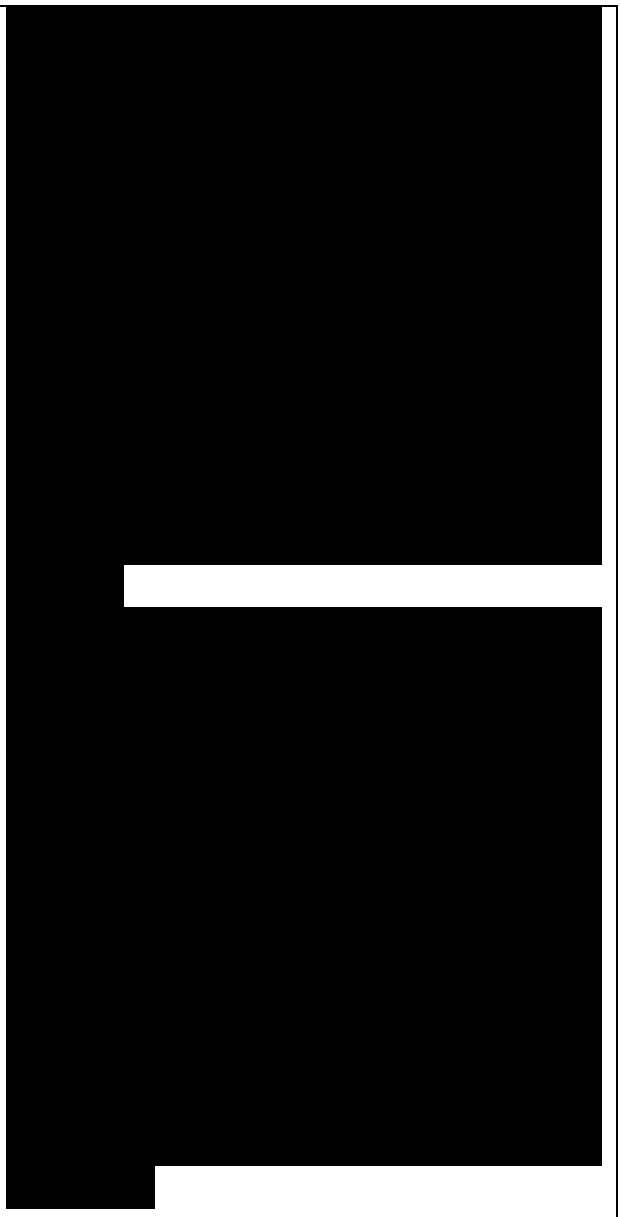


Figure 3. Proposed reaction mechanism.

believe such a H-bond, together with the bulky OTDS group, favors the formation of a structurally well- defined phosphonium enolate intermediate A, providing a confined spatial arrangement for the incoming imine. Had the OTDS be replaced by a less hindered OTMS group, the less rigid intermediate A is anticipated to provide less stereocontrol. This is consistent with experimental observations; the MBH adduct was obtained in 64% ee when OTMS-derived catalyst 9e was employed, in contrast to a 74% ee

attainable with OTDS-derived 9b under otherwise identical reaction conditions (entry 13 versus 10, Table 1). A subsequent Mannich reaction of A with imine yields zwitterionic intermediate B. The proton transfer from the a-carbon atom then takes place to yield enolate C, which undergoes fi-elimination to afford the MBH adduct and regenerate 9b at the same time.

In conclusion, we have introduced a novel class of bifunctional phosphine catalysts. In particular, we have derived a series of phosphine—sulfonamide bifunctional catalysts from natural amino acids. The effectiveness of our catalysts has been demonstrated in highly enantioselective aza-MBH reactions. DFT calculations are ongoing toward to a deeper understanding of the reaction mechanism and will be reported in due course.