



Dipeptide-derived multifunctional phosphonium salt as a catalyst to synthesize highly functionalized chiral cyclopentanes



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ABSTRACT

Asymmetric tandem Michael–Michael reactions between 2-substituted malonates and low reactive enones have been achieved by using novel dipeptides-derived phosphonium salts, affording the synthetically useful and highly functionalized chiral cyclopentanes with good yields, diastereoselectivities and high enantioselectivities.

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1. Introduction

Asymmetric cascade reactions have emerged as powerful tools in organic synthesis¹ as they provide efficient, green chemical approaches to construct complex molecules with multiple stereocenters in one-pot manipulation. With rapid development of organocatalysis in recent years, numerous studies have focused on the asymmetric organocatalytic cascade reactions.² So far, most of these progresses are achieved via the covalent or hydrogen bond promoted cascade reactions,³ in which the low reactive substrates such as chalcone are difficult to proceed. The phase transfer catalysis (PTC), which attracts the chemists with the potentials to accelerate the reaction rate by improving the solubility of the reactive intermediate through the ion pair and enhance the reactivity with base additives by forming ion pair from metal salts (e.g., Na, K, Cs), has made continuous breakthrough in the field.⁴ However, tandem reactions catalyzed by PTCs remain a challenge⁵ probably due to the lack of definite orientation in space of the ion-pair formed between catalyst and substrate, comparing to the covalent or hydrogen-bond catalysis.

In the past few years, several groups have reported asymmetric tandem Michael–Michael ring closure procedure using covalent, hydrogen-bond or NHC catalysts for the preparation of synthetically useful and highly functionalized five or six-membered carbocycles (Fig. 1).⁶ They exclusively employed the, β -unsaturated aldehydes or nitroolefins as the substrates. To the best of our knowledge, no reports have been discovered by using the low reactive enone substrates so far.

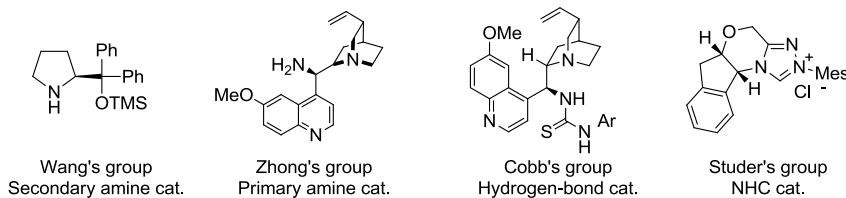
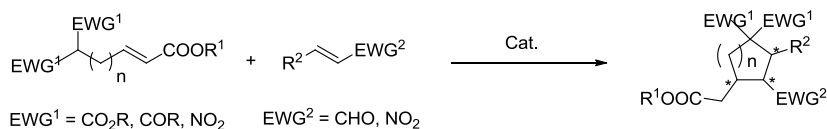
Our group has great interests in the development of amino acid-derived catalysts. Recently, we have firstly developed amino acid derived phosphonium salts as phase transfer catalyst to provide excellent activities and enantioselectivities in aza-Henry reaction and Michael addition.⁷ We postulated that these powerful catalysts can also be used in the challenging tandem Michael–Michael reactions between steric hindered nucleophiles and low reactive enones. Herein, we describe here a novel dipeptide-derived phosphonium salt as catalyst in the asymmetric tandem Michael–Michael reactions to construct synthetically useful five-membered rings with multiple stereocenters.

2. Results and discussion

Initially, the reaction between (*E*)-trimethyl but-3-ene-1,1,4-tricarboxylate **1a** and chalcone **2a** were selected as model reaction

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Previous work



This work

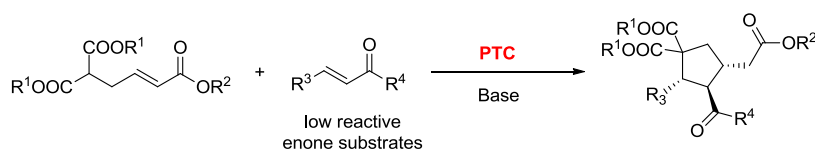


Fig. 1. Related asymmetric cascade cyclizations.

to evaluate the catalyst. The reaction was carried out in the presence of 5 mol% catalyst **4** and 2 equiv of base in toluene at $-10\text{ }^{\circ}\text{C}$, a series of phosphonium salts listed in Fig. 2 were tested and the results were summarized in Table 1.

catalyst, affording the ring closure product with 94% yield, 6:1 dr. and 95% ee value (Table 1, entry 9).

In phase transfer catalysis, base usually plays an important role in the catalytic efficiency. So a series of different bases was exam-

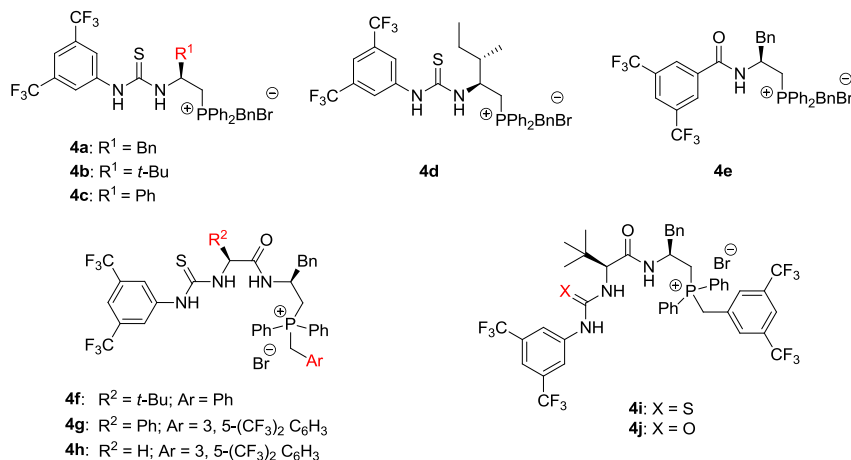


Fig. 2. Structures of the catalysts studied.

In general, only two diastereomers were observed in this reaction. Catalysts bearing single or two hydrogen-bond which worked well in previous studies^{7a,b} did not give satisfactory results in this reaction (Table 1, entries 1–5), while the multiple hydrogen-bond catalyst with *L*-phenylalanine skeleton afforded relatively better enantioselectivity (Table 1, entry 1). To our delight, the catalyst in possession of dipeptide core with one more hydrogen-bond tremendous enhanced the enantioselectivities and diastereoselectivities of the reaction (Table 1, entry 6). Then, a series of dipeptide-derived phosphonium catalysts with *L*-phenylalanine skeleton were prepared and the results revealed that the catalyst **4i** which bearing sterically hindered *t*-Bu group on R² and strong electron-withdrawing group on the salt section was the optimal

ined (Table 1, entries 11–14). Under low basic conditions, the reactions were slow with no contribution to enhance the enantioselectivities, while using strong base such as NaOH, total racemization of the product occurred due to the overwhelming background reaction. Reaction conditions such as solvent, temperature and catalyst loading amount were further evaluated but no better results were obtained (for details, see the Supplementary data). Thus, the best reaction conditions are a combination of catalyst **4i** (5 mol%) and base Cs₂CO₃ (2 equiv) in toluene at $-10\text{ }^{\circ}\text{C}$, which provided the product with 94% yield, 6:1 dr., and 95% ee.

With the optimized reaction conditions in hand, the scope of the tandem Michael–Michael reaction was investigated and the results were summarized in Table 2.

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