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Biomimetic Asymmetric 1,3-Dioplar Cycloaddition: Amino Acid Precursors in Biosynthesis Serve as Latent Azomethine Ylides

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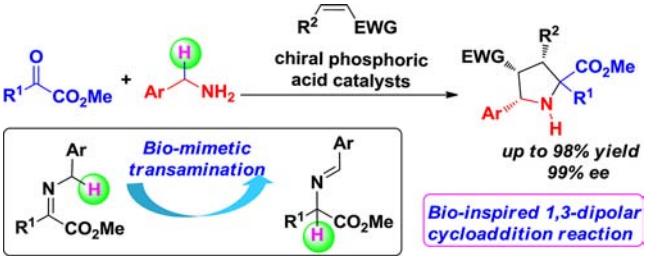
ABSTRACT



The first asymmetric catalytic biomimetic three-component 1,3-dipolar cycloaddition of α-keto esters and benzylamine with electron-deficient olefins, inspired by the transamination of α-keto acids involving pyridoxal phosphate (PLP)-dependent enzymes in biological systems, giving several families of structurally diverse pyrrolidine derivatives in high yields and excellent enantioselectivities (up to 99% ee) under mild conditions is described.

Five-membered nitrogenous heterocycles, in particular, pyrrolidines and spirooxindoles, are key structural motifs prevalent in numerous biologically significant molecules and natural alkaloids.[1] The asymmetric 1,3-dipolar cycloaddition of azomethine ylides with electronically deficient olefins has been accepted as the most straightforward access to optically active pyrrolidine derivative. The past decade has witnessed the explosive emergence of excellent chiral ligands and catalysts capable of affording a highly enantioselective 1,3-dipolar cycloaddition.[2,3] In these reactions, the azomethines, serving as the dipole components, were exclusively generated from the classical condensation reaction of amino esters with either aldehydes or ketones (Scheme 1a).[4] In nature, the biosynthesis of α-amino acids from α-keto acids via transamination reactions catalyzed by pyridoxamine phosphate (PLP)-dependent enzymes suggests that the aldimine intermediates, analogues of azomethine ylides, could be smoothly generated from a 1,3-proton shift reaction of ketimines formed from α-keto acids and corresponding amines (Scheme 1b).[5] The recent biomimetic transaminations have led to an

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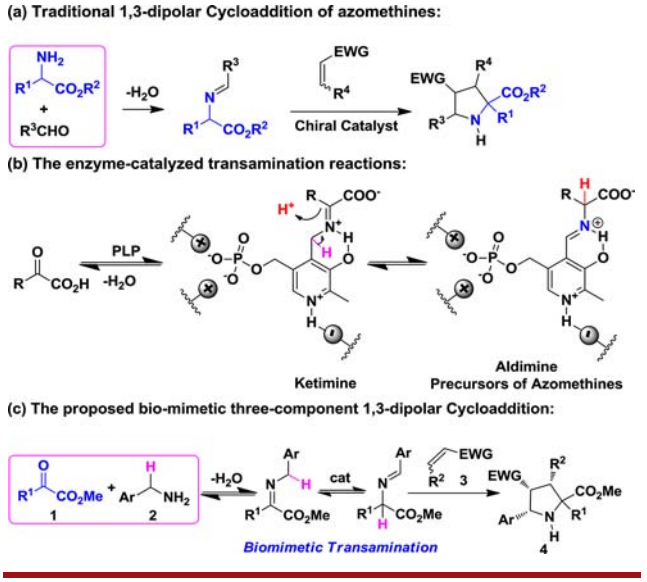
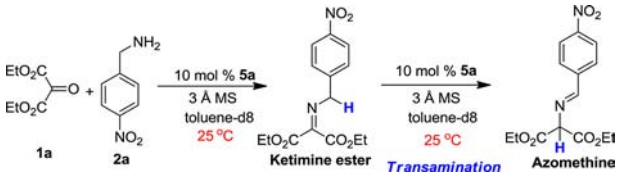
attractive synthesis of optically active amino acids, wherein the imino esters, precursors of azomethine ylides, existed as key intermediates.[6−9] Inspired by the biosynthetic mechanism[10] and biomimetic procedures, we proposed a biomimetic 1,3-dipolar cycloaddition, rendering assembly of α-keto esters, amines and electron-deficient olefins into pyrrolidine derivatives in a structurally diverse manner (Scheme 1c).

Scheme 1. Design of Bio-mimetic Cycloaddition Reaction



As long as azomethine ylides are formed, the 1,3-dipolar cycloaddition with electronically deficient olefins could occur in the presence of either organocatalysts or Lewis acids.[2,3] Thus, the identification of an appropriate chiral catalyst for the efficient transamination process of keto esters with amine turned out to be key element of the proposed biomimetic 1,3-dipolar cycloaddition (Scheme 1c). Previously, we demonstrated that chiral phosphoric acids are excellent catalysts for 1,3-dipolar cycloaddition;[11] therefore, we initially investigated if the phosphoric acid was able to catalyze the transamination of keto esters. The ^{1}H NMR studies on the measurement of a mixture of diethyl 2-oxomalonate (**1a**) and 4-nitrobenzylamine (**2a**) with 10 mol % of **5a** in toluene-d_8 indicated that the transamination proceeded smoothly to give azomethine ylide at room temperature (Scheme 2).[12] These findings essentially permit the direct use of α-keto esters, the amino acid precursors, as latent azomethine ylides to participate in the enantioselective 1,3-dipolar cycloaddition with dipolarophiles **3** under the catalysis of chiral phosphoric acids. However, the use of either chiral Lewis acids or other organocatalysts that were typically applied to asymmetric 1,3-dipolar cycloaddition[2,3] failed to afford smooth transamination, and thus they are impossible to catalyze the three-component biomimetic 1,3-dipolar cycloaddition reaction.

Scheme 2. Brønsted Acid Catalyzed Transamination



Consequently, the feasibility of the three-component biomimetic 1,3-dipolar cycloaddition was explored by evaluating a reaction of diethyl 2-oxomalonate (**1a**), 4-nitrobenzylamine (**2a**), and dimethyl maleate (**3a**) in the presence of 10 mol % of BINOL-derived phosphoric acids[13] at room temperature (Table 1). As expected, the enantioselective cycloaddtion reaction proceeded smoothly to furnish the desired product **4a** in a 62% yield, but with a low ee value (Table 1, entry 1). As reported previously,[11] the structure of the chiral phosphoric acids derived from BINOL still exerted great impact on the enantioselectivity (entries 1−8) and the bisphosphoric acid **6** turned out to be the best catalyst in terms of the stereochemical outcomes, capable of delivering 95% ee (Table 1, entry 8). Further optimization of reaction conditions revealed that the highest level of enantioselectivity (98% ee) could be achieved in DCM at 50 °C (Table 1, entry 11).

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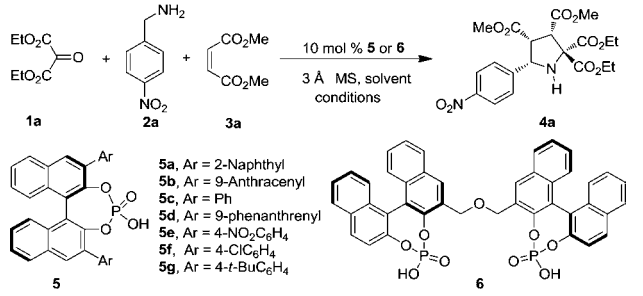
Table 1. Optimization of Reaction Conditions[a]



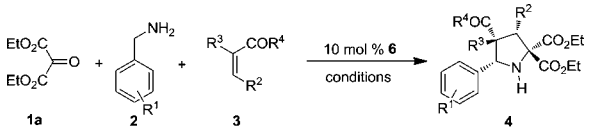
entry	catalyst	conditions	yield[b] (%)	ee[c] (%)
1	**5a**	toluene, rt, 3 days	62	8
2	**5b**	toluene, rt, 3 days	68	4
3	**5c**	toluene, rt, 8 days	93	13
4	**5d**	toluene, rt, 3 days	68	10
5	**5e**	toluene, rt, 3 days	88	6
6	**5f**	toluene, rt, 3 days	69	8
7	**5g**	toluene, rt, 3 days	59	5
8	**6**	toluene, rt, 3 days	71	95
9	**6**	toluene, 0 °C, 8 days	-	-
10	**6**	CH_2Cl_2, rt, 8 days	70	98
11	**6**	CH_2Cl_2, 50 °C, 8 days	90	98

[a] Reactions were carried out on a 0.2 mmol scale with 3 Å MS (300 mg) in the presence of phosphoric acid **5** or **6**, and the ratio of **1a**/**2a**/**3a** was 2.0/2.0/10.0. [b] Isolated yields. [c] Determined by chiral high-performance liquid chromatography (HPLC), and the absolute configuration was determined by comparison with literature data.[11] rt = room temperature.

With the optimal conditions in hand, we investigated the generality for the scope of primary amines and electron-deficient olefins (Table 2). Significantly, the biomimetic enantioselective 1,3-dipolar cycloaddition showed excellent substrate generality, which is basically required for the diversity-oriented synthesis. For example, a wide spectrum of benzylamine derivatives including those bearing either electron-withdrawing or electron-donating substituents could be nicely tolerated and afforded pyrrolidine derivatives with 92−99% ee (Table 2, entries 1−8). Moreover, the exploration of the substrate scope focused on dipolarophiles revealed that a structurally diverse range of electronically deficient functionalized olefins, such as methyl vinyl ketone (MVK, **3j**), methyl acrylate (**3k**) and 2-substituted methyl acrylate (**3l**) were all able to undergo the 1,3-dipolar cycloaddition, furnishing the desired products with excellent levels of stereoselectivity (Table 2, entries 9−11).

We next turned our attention to explore the scope and generality of α-keto esters (Table 3). Although the aryl α-keto esters **1** are basically less reactive toward the amine and the corresponding imines are much more difficult to undergo the transamination than 2-oxomalonate and its imines, they could also participate in the enantioselective 1,3-dipolar cycloaddition. The variation of the substituent on phenyl group in the aryl α-keto esters **1** could be tolerated to give the corresponding pyrrolidine derivatives **4** in high yields and with very high levels of enantioselectivity

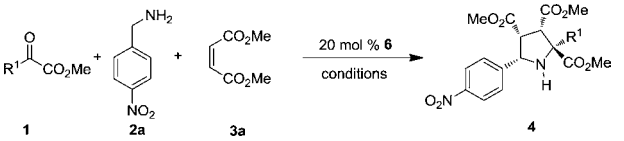
Table 2. Scope of Substituted Benzylamines and the Electron-Deficient Olefins of the Bio-mimetic Asymmetric Three-Component 1,3-Dipolar Cycloaddition[a]



entry	4	R^1	R^2	R^3	R^4	yield[b] (%)	ee[c] (%)
1	**4b**	3-NO_2	COOMe	H	OMe	80	92
2[e]	**4c**	2-NO_2	COOMe	H	OMe	76	92
3	**4d**	4-CN	COOMe	H	OMe	69 (93[e])	94 (92[e])
4	**4e**	4-Br	COOMe	H	OMe	73	98
5[e]	**4f**	4-Cl	COOMe	H	OMe	82	99
6	**4g**	4-F	COOMe	H	OMe	64	97
7[e]	**4h**	H	COOMe	H	OMe	83	92
8[e]	**4i**	4-MeO	COOMe	H	OMe	79	96
9[e]	**4j**	4-NO_2	H	H	Me	60	94
10[e]	**4k**	4-NO_2	H	H	OMe	76	93
11	**4l**	4-NO_2	H	Ph	OMe	71	94

[a] Reactions were carried out on a 0.2 mmol scale with 3 Å MS (300 mg) in the presence of phosphoric acid **6** at 50 °C for 8 days, and the ratio of **1a**/**2**/**3** was 2.0/2.0/10.0. [b] Isolated yields. [c] Determined by chiral high-performance liquid chromatography (HPLC) and the absolute configuration was determined by comparison with literature data.[11] [e] In toluene.

Table 3. Scope of α-Phenyl Keto Esters of the Bio-mimetic Asymmetric Three-Component 1,3-Dipolar Cycloaddition[a]



entry	4	R^1	yield[b] (%)	ee[c] (%)
1	**4m**	C_6H_5	90	91
2[d]	**4n**	4-BrC_6H_4	75	92
3[d]	**4o**	4-ClC_6H_4	74	99
4[d]	**4p**	4-FC_6H_4	78	90
5[d]	**4q**	4-$CF_3C_6H_4$	86	93
6[d]	**4r**	3-BrC_6H_4	67	94

[a] Reactions were carried out on a 0.1 mmol scale with 3 Å MS (150 mg) in the presence of phosphoric acid **6** at 50 °C for 6 days, and the ratio of **1**/**2a**/**3a** was 6.0/4.0/1.0. [b] Isolated yields. [c] Determined by chiral high-performance liquid chromatography (HPLC), and the absolute configuration was determined by comparison with literature data.[11] [d] Performed at 70 °C.

(up to 99% ee). It is worth mentioning that the protocol was amenable to the phenyl α-keto esters bearing either a bromo or a trifluoromethyl substituent on the benzene ring to give the corresponding pyrrolidines, which were not available from previous methods,[11] in part due to the unavailability of the related amino acids (Table 3, entries 2, 5, and 6). In this regard, the current approach presents some intrinsic advantages over the methods developed

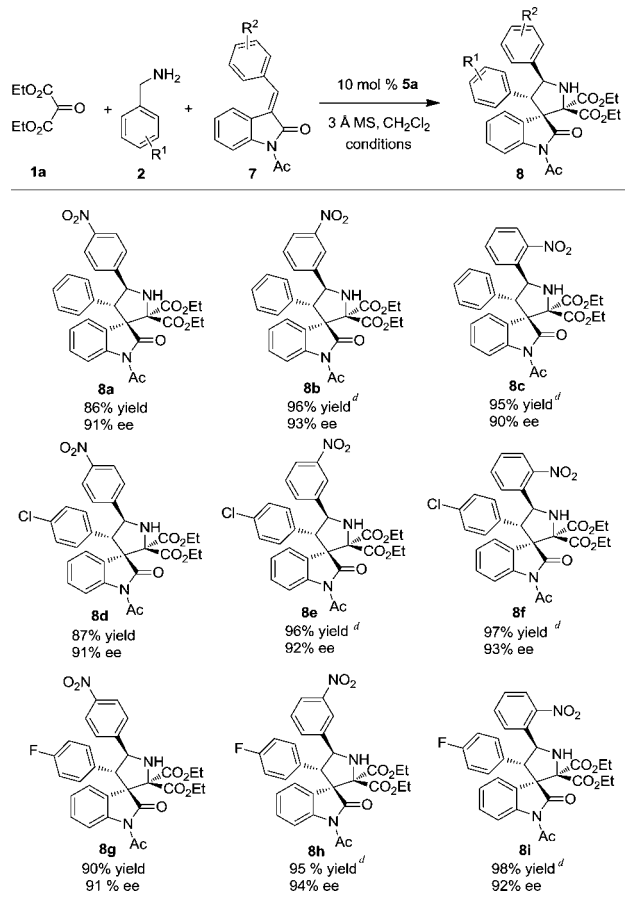


Figure 1. Biomimetic asymmetric three-component 1,3-dipolar cycloaddition for the synthesis of spirooxindole derivatives. (a) Reactions were carried out on a 0.1 mmol scale with 3 Å MS (150 mg) in the presence of phosphoric acid **5a** at room temperature for 2−3 days, and the ratio of **1a**/**2**/**7** was 1.2/1.0/2.0. (b) Isolated yields. (c) Determined by chiral high-performance liquid chromatography (HPLC), and the absolute configuration was determined by comparison with literature data.[11] (d) Performed at 50 °C.

previously for constructing five-membered heterocyclic rings from α-phenylglycine esters.

To demonstrate the pivotal influence of various phosphoric acids on catalytic activity and to further expand the potential of this transformation as a privileged tool, a biomimetic enantioselective organocatalytic approach to rapidly access spirooxindole derivatives was described. The catalyst screening and optimization of conditions were carried out again for the three-component 1,3-dipolar cycloaddition reaction of α-keto esters, benzylamine, and methyleneindolinones **7**. The highest enatioselectivity of spirooxindole derivatives was obtained from the reaction conducted in the presence of 3,3′-*β*-naphthyl phosphoric acid **5a**. A structurally diverse collection of spiro-[pyrrolidin-3,3′-oxindole] derivatives **8** were obtained in excellent yields and enantioselectivities (Figure 1).[11b] Indeed, the protocol provides a significant opportunity for the diversity-oriented synthesis of oxindoles containing quaternary stereogenic centers.

In conclusion, we have developed a highly efficient, so far unique, biomimetic diversity-oriented synthesis of a pyrrolidine derivative collection. This relies on the strategic use of phosphoric acid catalyzed biomimetic transamination of keto esters and amines, the precursors of amino acids, to in situ generate azomethine ylides, which readily participated in a highly enantioselective 1,3-dipolar cycloaddition with a structurally diverse range of dipolarophiles. As a result, highly functionalized pyrrolidines and spirooxindole derivatives were obtained with excellent enantioselectivities. Considering the easier accessibility of α-keto esters than the corresponding amino esters, the unique biomimetic protocol will be more promising for the synthesis of pyrrolidine derivatives in structural diversity than the traditional 1,3-dipolar cycloaddition reactions. In addition, these findings also open a window for the development of new Brønsted acid-catalyzed stereoselective cycloaddition reactions involving ketimine intermediates.

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Supporting Information Available. Detailed experimental details, compound characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.