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The Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Ynones with Azomethine Ylides

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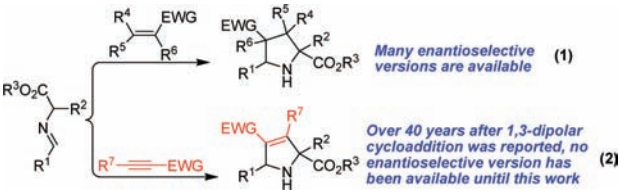
ABSTRACT

The first catalytic asymmetric 1,3-dipolar cycloaddition of electron-deficient carbon−carbon triple bonds with azomethine ylides has been established. This reaction provides an unprecedented approach to access novel 2,5-dihydropyrrole derivatives with potential bioactivities in perfect enantioselectivities of up to >99% *ee*.

Recent decades have witnessed the great importance of 1,3-dipolar cycloaddition in organic chemistry.[1] Particularly, those of azomethine ylide dipoles with unsaturated carbon−carbon bonds represent important processes in organic synthesis and their enantioselective versions have offered a robust method to access chiral pyrrolidine structural motifs, which present frequently in natural alkaloids and artificial molecules with vital bioactivities.[2] Consequently, elegant developments have been described in the field of asymmetric 1,3-dipolar cycloadditions of azomethine ylides to electron-deficient olefins by using either chiral metal-based catalysts[3] or organocatalysts (eq 1).[4] However, more than 40 years after Huisgen pioneered the 1,3-dipolar cycloaddition,[5] no catalytic asymmetric variants have been found for the electronically poor carbon−carbon triple bond dipolarophiles (eq 2). More surprisingly, even racemic 1,3-dipolar cycloadditions of azomethine ylides with alkynes are rather limited with the exception of a few intramolecular versions, which have sporadically been described in past decades.[2b−e,6] Thus, this transformation, in particular, its enantioselective version, has remained a formidable challenge.



The 2,5-dihydropyrrole skeleton, which can be constructed by 1,3-dipolar cycloaddition of azomethine ylides with alkynes, not only constitutes the core structural element of many natural alkaloids[7] but also serves as a key building block for a variety of natural products.[8] More importantly, a number of 2,5-dihydropyrrole derivatives exhibit important bioactivities such as antioxidant,[9] antitumor,[10] anti-inflammatory,[11] and quinone-dependent amine oxidase inhibitory activity.[12] The significance of 2,5-dihydropyrrole motifs relevant to synthetic and medicinal

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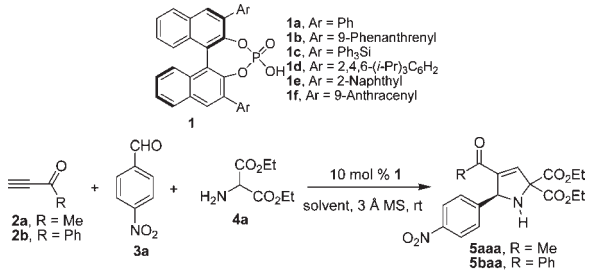
applications has led to a demand for efficient synthesis of related compounds, especially those with high enantioselectivity. We have recently established a series of 1,3-dipolar cycloadditions between azomethine ylides and electron-deficient olefins in excellent enantioselectivity using chiral phosphoric acids as catalysts wherein a chiral Brønsted acid bonded dipole is involved.[13] Encouraged by this success and in view of no enantioselective version of the 1,3-dipolar cycloadditions of alkynes with azomethine ylides as well as the importance of 2,5-dihydropyrroles, we decided to use a chiral Brønsted acid[14] to control the stereoselectivity of the titled reaction. Herein, we report the first asymmetric version of this reaction with exquisite levels of enantioselectivity (up to >99% *ee*).

Table 1. Screening of Catalyst and Optimization of Conditions[a]



entry	5	1	solvent	yield (%)[b]	ee (%)[c]
1	**5aaa**	**1a**	CH_2Cl_2	77	<5
2	**5aaa**	**1b**	CH_2Cl_2	75	7
3	**5aaa**	**1c**	CH_2Cl_2	91	<5
4	**5aaa**	**1d**	CH_2Cl_2	73	<5
5	**5aaa**	**1e**	CH_2Cl_2	65	<5
6	**5aaa**	**1f**	CH_2Cl_2	79	13
7	**5aaa**	**1f**	$CHCl_3$	76	26
8	**5aaa**	**1f**	toluene	74	94
9	**5baa**	**1f**	toluene	62	>99
10	**5baa**	**1f**	toluene	69	>99[d]

[a] The reaction was carried out in 0.1 mmol scale in solvent (1 mL) with 3 Å MS (100 mg) for 12 h (**2a**) or 36 h (**2b**), and **2**/**3a**/**4a** was 2.5/1.2/1. [b] Isolated yield. [c] Determined by HPLC. [d] **2b**/**3a**/**4a** was 2.5/2/1.

At the outset of our study, we conducted a reaction of 3-butynone (**2a**) and diethyl 2-aminomalonate (**4a**) with 4-nitrobenzaldehyde (**3a**) in dichloromethane at room temperature in the presence of 10 mol % of chiral phosphoric acids **1**. However, the preliminary screening of the catalysts led to disappointing results (Table 1, entries 1−6). To our delight, the screening of solvents revealed that nonpolar solvents appeared to be more suitable for the reaction and a high enantioselectivity of 94% *ee* could be achieved in toluene (entry 8). More significantly, an exquisite level of enantioselectivity of >99% *ee* was observed for the reaction involving 1-phenylprop-2-yn-1-one (**2b**), but the yield turned out to be moderate (entry 9). The presence of excess amounts of **3a** enabled the reaction to give a higher yield with a maintained enantioselectivity (entry 10 vs 9).

With optimal conditions in hand, we then explored the generality for aldehydes by reaction with 1-phenylprop-2-yn-1-one (**2b**) and 2-aminomalonate (**4a**). As shown in Table 2, the protocol is amenable to a wide scope of aromatic aldehydes including electronically poor and rich ones in excellent enantioselectivities (entries 1−9). Basically, benzaldehydes substituted with an electronically withdrawing group at the *para*-position gave perfect stereoselectivities (entries 1, 4, and 5, up to >99% *ee*). The position of the substituent of benzaldehydes appeared to exert some impact on the stereoselectivity (entries 1−3). Importantly, even if electronically rich benzaldehydes were applied, a high enantioselectivity could also be delivered as exemplified by the reaction with 4-methoxylbenzaldehyde (entry 8). Moreover, disubstituted benzaldehyde appeared to be an excellent substrate, offering a perfect enantioselecitvity of >99% *ee* (entry 9). It is noteworthy that heteroaromatic aldehyde and aliphatic aldehyde can also be applied to this reaction with high enantioselectivity (entries 10 and 11).

The substrate scope with respect to ynones **2** was next explored by reaction with either electronically poor or rich benzaldehydes (Table 3). Both aliphatic and aromatic ynones were capable of undergoing the reaction with high to excellent enantioselectivities, while the former gave a lower enantioselectivity (94% *ee*) than the aromatic ones (entry 9 vs 1−4). When 4-nitrobenzaldehyde was

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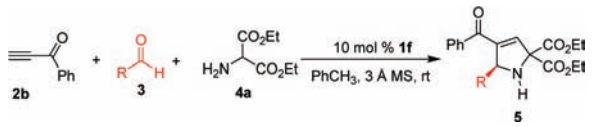
Table 2. Scope of Aldehydes[a]

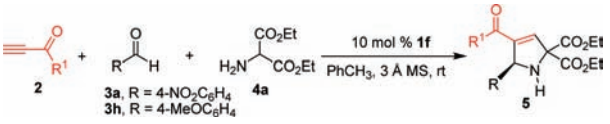


entry	5	R (3)	yield (%)[b]	ee (%)[c]
1	**5baa**	4-$NO_2C_6H_4$ (**3a**)	69	>99
2	**5bba**	3-$NO_2C_6H_4$ (**3b**)	57	>99
3	**5bca**	2-$NO_2C_6H_4$ (**3c**)	80	91
4	**5bda**	4-BrC_6H_4 (**3d**)	79	99
5	**5bea**	4-CNC_6H_4 (**3e**)	78	98
6	**5bfa**	Ph (**3f**)	76	97
7	**5bga**	2-Naphthyl (**3g**)	43	98
8	**5bha**	4-$MeOC_6H_4$ (**3h**)	73	94
9	**5bia**	3,4-$Cl_2C_6H_3$ (**3i**)	67	>99
10	**5bja**	2-Thiophenyl (**3j**)	82	86
11	**5bka**	Isopropyl (**3k**)	41[d]	81[d]

[a] The reaction was carried out in 0.1 mmol scale in toluene (1 mL) with 3 Å MS (100 mg) for 36 h, and **2b**/**3**/**4a** was 2.5/2/1. [b] Isolated yield. [c] Determined by HPLC. [d] Performed for 72 h.

employed, the substitution pattern on the aryl group of **2** has very little impact on the stereoselectivity (entries 1−4). Electronically poor, neutral, rich or heteroaromatic ynones (**2c**−**2f**) gave perfect enantioselectivities (entries 1−4, >99% *ee*'s). When 4-methoxybenzaldehyde was used as the reaction component, the diminished *ee*'s were observed for different 1-arylprop-2-yn-1-ones **2** in comparison with those obtained in cases involving 4-nitrobenzaldehyde, but still reached high levels of enantioselectivity of up to 94% *ee* (entries 5−8).

Table 3. Scope of Ynones[a]

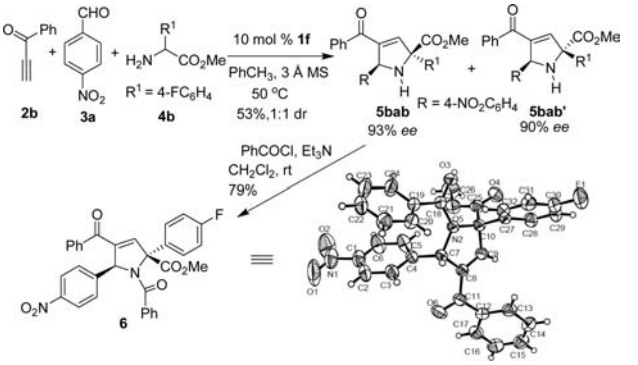


entry	5	R^1	3	yield (%)[b]	ee (%)[c]
1	**5caa**	4-FC_6H_4 (**2c**)	**3a**	64[d]	>99[d]
2	**5daa**	4-$MeOC_6H_4$ (**2d**)	**3a**	61[e]	>99[e]
3	**5eaa**	2-Naphthyl (**2e**)	**3a**	50	>99
4	**5faa**	2-Thiophenyl (**2f**)	**3a**	69	>99
5	**5cha**	4-FC_6H_4 (**2c**)	**3h**	72	90
6	**5dha**	4-$MeOC_6H_4$ (**2d**)	**3h**	78	94
7	**5eha**	2-Naphthyl (**2e**)	**3h**	55	91
8	**5fha**	2-Thiophenyl (**2f**)	**3h**	88	83
9	**5aaa**	CH_3 (**2a**)	**3a**	74[f]	94[f]

[a] The reaction was carried out in 0.1 mmol scale in toluene (1 mL) with 3 Å MS (100 mg) at rt for 36 h, and **2**/**3**/**4a** was 2.5/2/1. [b] Isolated yield. [c] Determined by HPLC. [d] Performed at 50 °C for 58 h. [e] Performed at 50 °C for 84 h. [f] Performed for 12 h and **2a**/**3a**/**4a** was 2.5/1.2/1.

More interestingly, α-aryl amino esters proved to be a reactive component and afforded high enantioselectivity as exemplified by **4b** (Scheme 1). In addition, the absolute

Scheme 1. Reaction Using α-Aryl Amino Ester As Substrate and Absolute Configuration of Products



configuration of products **5** was assigned to be 5*S* by X-ray structures of compounds **5aaa** and **6** (>99% *ee*'s after recrystallization),[15] which was derived from benzoylation of **5bab** in 79% yield (Scheme 1).

To understand the stereochemistry experimentally observed, theoretical calculations were performed on the transition state (TS) of the **1f**-catalyzed 1,3-dipolar cycloaddition of ynone **2b** to the azomethine ylide by the hybrid density functional theory (DFT) method.[16] The

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(14) For a Brønsted acid catalyzed 1,3-diploar addition of nitrones: (a) Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411. For reviews:(b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Terada, M. *Chem. Commun.* **2008**, 4097. (e) Terada, M. *Synthesis* **2010**, 1929.

(15) CCDC 824305 for compound **5aaa**, CCDC 824305 for compound **6**. See the Supporting Information for details.

(16) The calculations were performed with the Gaussian 03 program: Frisch, M. J. et al. *Gaussian 03*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2004 (for complete ref 16, see Supporting Information)

(17) The details on bioscreen of **5** are in the Supporting Information.

BINOL-derived phosphoric acid **1f** again served as a Brønsted acid/Lewis base bifunctional catalyst[13c] to accelerate the cycloaddition between the ynone and the azomethine ylide by H-bonding interactions. Basically, the located TS structures (Figure 1) indicated that the triple bond of ynones would become more electron-deficient by a H-bond formed between the carbonyl oxygen of the ynone and the phosphoric OH of the catalyst to render the β-carbon more electrophilic and, simultaneously, the carbon anion of the dipole of azomethine ylide would become more reactive due to the H-bonding interaction between the H−N of the ylide and the Lewis basic phosphoryl oxygen.[13c] Such a dual activation mode facilitates a smooth conjugate addition of the azomethines to the ynones as shown in **Ts-I**, wherein the predicted forming bond distances indicated this conjugate addition step occurs much earlier than the Mannich-type reaction. Therefore, the 1,3-dipolar cycloaddition proceeded via a sequential Michael addition and Mannich-type cyclization rather than a concerted pathway.

Moreover, comparison of the located transition structures **Ts-I-*S*** and **Ts-I-*R*** indicated that even in the conjugate addition step, the stereodiscrimination already occurred because **Ts-I-*S*** is predicted to be more stable than **Ts-I-*R***. Further calculaztions on the subsequent Mannich reaction revealed that the stereochemistry of the products were controlled by the steric interactions between the reaction substrates and 3,3′-substituents of the catalyst **1f**. In detail, the 9-anthracenyl rings at the 3,3′-positions of **1f** were oriented paralleling toward the substrates in **Ts-II-*S***, and this geometry is more suitable for establishing interactions between **1f** and the substrates to stabilize the transition state. In contrast, the 3,3′-bulky substituents of **1f** are directed perpendicularly to the substrates in **Ts-II-*R***, resulting in the disfavored orientation of the substrates and thereby destabilizing **Ts-II-*R*** structure. The **Ts-II-*S*** was predicted to be more stable than **Ts-II-*R*** by ∼7 kcal/mol in favor of the generation of the *S*-enantiomer, which is in accordance with the experimentally observed stereochemistry.

Finally, in order to identify potential bioactivity of these novel chiral compounds, some selected 2,5-dihydropyrroles **5** were subjected to an in vitro cytotoxicity test to mammary carcinoma cell line MCF7. The preliminary results reveal that compound **5aaa** exhibits cytotoxicity to the MCF7 cell with an IC_{50} value of 166.92 μg/mL,[17] which indicates this type of 2,5-dihydropyrrole derivatives may find medicinal applications after further structural modulation and biological studies.

In summary, we have established the first asymmetric catalytic 1,3-dipolar cycloaddition of electron-deficient carbon−carbon triple bonds with azomethine ylides. The chiral phosphoric acid catalyzed reaction tolerates a wide range of substrates to furnish novel 2,5-dihydropyrrole derivatives with potential bioactivities[17] in perfect enantioselectivities of up to >99% *ee*. DFT studies on the reaction mechanism suggested that the reaction underwent a sequential conjugate addition and Mannich reaction rather than a concerted pathway, distinct from most variants between electron-deficient olefins and azomethine yildes.[3d−r,13] This reaction not only represents the first enantioselective catalytic 1,3-dipolar cycloaddition involving carbon−carbon triple bond dipolarophiles but also provides a facile approach to access chiral 2,5-dihydropyrrole architecture, which holds great potential in synthetic and medicinal chemistry.

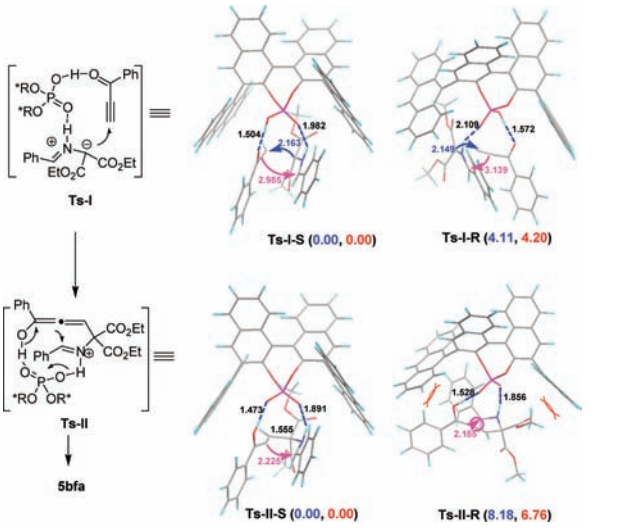

Figure 1. B3LYP/6-31G* optimized transition state structures and partial crucial bond length parameters in angstrom, relative energies in enthalpy (blue) and Gibbs free energy (red), and reaction mechanism.

Acknowledgment. We are grateful for financial support from MOST (973 Project 2009CB82530), Ministry of Education, and NSFC (20732006, 21002083).

Supporting Information Available. Experimental details, characterization of new compounds, and crystal data of **5aaa** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.(16) The calculations were performed with the Gaussian 03 program: Frisch, M. J. et al. *Gaussian 03*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2004 (for complete ref 16, see Supporting Information)