Enantioselective Conjugate Addition of N-Heterocycles to α,β-Enones Mediated by Diarylprolinols

Ling Fang[a], Aijun Lin[a], Xuefeng Jia[a], Jie Meng[a], Yangnian Wang[a] and Chengjian Zhu*[,a,b]

[a]*School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, China*

[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

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Abstract: Enantioselective conjugate addition of benzotriazole to α,β-enones catalyzed by prolinol derivatives with moderate yields and enantioselectivities was reported. Studies of stereoelectronic effects of the catalyst showed that the transition state could be of a hydrogen bonding activation mode, and fine tuning of the substituents on the aryl moiety of the catalyst is important for the reaction stereoselectivities.

Keywords: Organocatalysis, conjugate addition, diarylprolinols, enones, asymmetric, benzotriazole.

Asymmetric organocatalysis has emerged as an attractive field in organic synthesis for recent years [1]. More and more chiral small molecules could be used as the catalysts in various reactions with excellent results. *L*-proline and its derivatives, as the representative one, have been widely developed in enantioselective construction of C-C [2] and C-hetero [3] bond. However, optically active C-N bond forming has always been challenging, and there are only a few reports with regard to the asymmetric conjugate addition of nitrogen nucleophiles to α,β-unsaturated carbonyl compounds in an organocatalytic manner [4]. Moreover, compounds containing alkylated benzotriazole exhibit important biological and pharmaceutical activities [5], whereas reports related to enantioselective synthesis of these compounds are limited [6]. Recently, Wang developed chiral thiourea derivatives in the addition of benzotriazole to α,β-enones, with up to 64% *ee*, and it was the only example for this organocatalytic process to our knowledge [7]. Therefore, we were interested in seeking other alternative catalysts for this transformation.

We report herein the enantioselective conjugate addition of benzotriazole to α,β-enones catalyzed by diarylprolinols (Fig. **1**). Initially, we studied the reaction of benzotriazole (**2**) with chalcone (**3a**) in the presence of 20 mol% diphenylprolinol (**1a**). Solvent screening revealed that toluene and *p*-xylene could afford the product **4a** with 25% *ee* and 29% *ee*, respectively (Table **1**, entries 1, 2). Meanwhile, the region-isomer **5a** also could be isolated in lower yield, thus its *ee* value was not detected. Some polar solvents such as acetonitrile, dichloromethane, THF and methanol, gave nearly racemic adducts. Several other prolinol derivative catalysts **1b**-**1g** were then examined using toluene as the solvent (Table **1**, entries 3-8, 11). In general, electronic properties of the catalyst aromatic ring had an impact on its performance. The catalyst bearing an electron-donating group on the aromatic ring (**1d**) exhibited higher reactivity than one bearing an electron-withdrawing group (**1c**), albeit with comparable enantioselectivities (Table **1**, entries 4, 5). The highest enantioselectivity was achieved with **1d** at 0 ºC, giving the product **4a** in 53% yield and 42% *ee* after 72 h (Table **1**, entry 10). However, when the trimethylsilyl ether **1e** was examined (Table **1**, entry 6), both the reactivity and enantioselectivity (40% yield and 20% *ee* even after 72h) were even lower than that in the presence of **1a** (Table **1**, entry 1). This is in contrast with the result of asymmetric conjugate addition of **2** to the α,β-unsaturated aldehydes: excellent enantioselectivities were obtained when **1e** was tested [4c]. Meanwhile, we synthesized a new prolinol derivative **1g** [8], bearing an electron-donating group at C(4) position of the prolinol backbone. Disappointedly, **4a** was obtained with 11% *ee* (Table **1**, entry 8). This result suggested that the previous enantioselective attack was partly blocked by the increased steric hindrance on the prolinol backbone.

Having established the optimal protocol for the reaction, we then explored the conjugate addition of benzotriazole with various aromatic α,β-enones. The reaction was carried out with 20 mol% catalyst **1d** in toluene at 0 ºC. As shown in Table **2**, for *para*- and *meta*- position substituted α,β-enones (**3b**-**3c**, **3e**-**3k**), either electron-donating or electron-withdrawing group on the phenyl rings were found to be tolerated in this transformation. Products **4b**-**4c**, **4e**-**4k** could be obtained with moderate yields and enantioselectivities (Entries 1-2, and 4-10). Unfortunately, probably due to a steric effect, a sharp drop in enantioselectivity was observed with the α,β-enone bearing substitution at *ortho*- position of the Ar_1 group (Entries 3, 11). Clearly, compared with chalcone, most α,β-enones regioselectively afforded the N-1 adducts while their N-2 isomers were only in trace amounts. Additionally, the absolute configuration of the addition adduct **4g** [9] was determined to be *R* according to the

*Address correspondence to this author at the School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China; Tel: +86 25 83594886; Fax: +86 25 83317761; E-mail: cjzhu@nju.edu.cn

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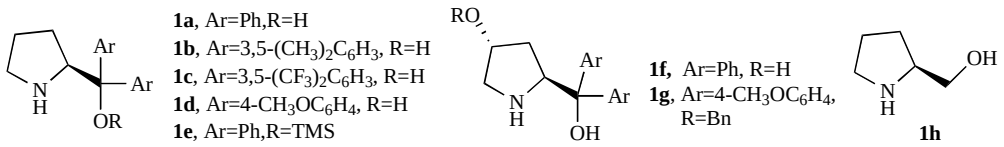
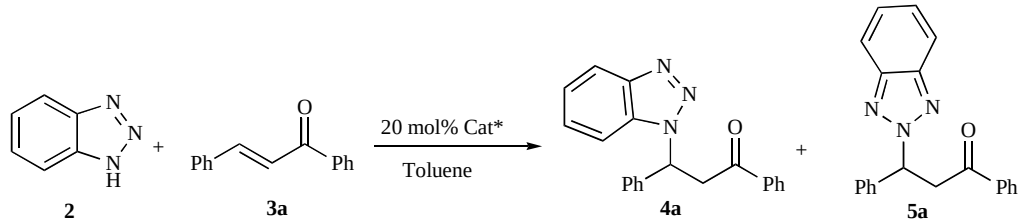


Fig. (1). Prolinol derivative catalysts.

Table 1. Screening of Reaction Conditions for the Conjugate Addition of Benzotriazole (2) to Chalcone (3a)[a]

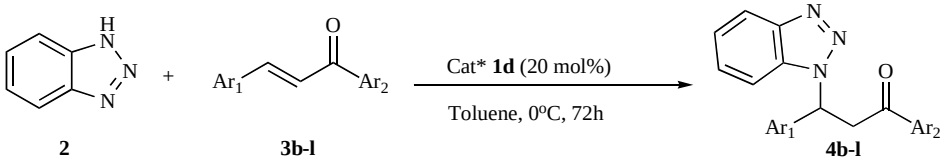


2 **3a** **4a** **5a**

Entry	Cat.	T/°C	Time/h	Yield/%[b] of 4a	Yield/%[b] of 5a	Ee/%[c] of 4a
1	**1a**	rt	48	54	14	25
2[d]	**1a**	15	48	52	15	29
3	**1b**	rt	48	68(82[e])	11	24
4	**1c**	rt	72	48	18	33
5	**1d**	rt	48	55	13	34
6	**1e**	rt	72	40	n.d.[f]	20
7	**1f**	rt	72	50	15	27
8	**1g**	15	72	45	10	11
9[d]	**1d**	15	48	52	n.d.[f]	36
10	**1d**	0	72	53	n.d.[f]	42
11	**1h**	rt	48	46	n.d.[f]	0

[a]The reaction was carried out with 1.3 equiv of **2**. [b]Isolated yields. [c]Determined by Daicel Chiralpak AD-H column. [d]*p*-xylene was used as the solvent. [e]Isolated yield after 5 days. [f]Not determined.

Table 2. Scope of the Conjugate Addition Reaction[a]



2 **3b-l** **4b-l**

Entry	Ar_1	Ar_2	4	Yield/%[b]	Ee/%[c]
1	4-ClC_6H_4	4-$MeOC_6H_4$	**4b**	55	45
2	4-MeC_6H_4	C_6H_5	**4c**	60	35
3	2-ClC_6H_4	C_6H_5	**4d**	43	4
4	4-ClC_6H_4	4-MeC_6H_4	**4e**	62	50
5	4-ClC_6H_4	C_6H_5	**4f**	59	46
6	4-$NO_2C_6H_4$	C_6H_5	**4g**	54(72[d])	50
7	3-BrC_6H_4	C_6H_5	**4h**	61	44
8	3-$NO_2C_6H_4$	C_6H_5	**4i**	58	45
9	4-$MeOC_6H_4$	C_6H_5	**4j**	55	34
10	4-BrC_6H_4	C_6H_5	**4k**	62	32
11	2-BrC_6H_4	C_6H_5	**4l**	55	4

[a]The reaction was carried out with 1.3 equiv of **2**, products **5** were not determined. [b]Isolated yields. [c]Determined by Daicel Chiralpak AD-H or AS-H column. [d]Isolated yield after 5 days.

literature [6, 7]. Although the reaction mechanism is not clear, the catalyst screening results shown above suggested that the α,β-enone substrate and benzotriazole were activated by the catalyst **1d** *via* hydrogen bonding [10].

In summary, we have presented the diarylprolinol-catalyzed enantioselective conjugate addition between benzotriazole and α,β-enones with moderate enantioselectivity. Studies suggested that the transition state could be hydrogen bonding activation mode. Further investigations on the optimization of the catalyst structure to improve the stereoselectivity as well as the development of the scope of various substrates are currently underway.

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[8] Compound **1g,** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 9.0 Hz, 2H), 7.38-7.31 (m, 7H), 6.86-6.80 (m, 4H), 4.50 (dd, *J* = 6.9, 9.9 Hz, 1H), 4.45 (s, 2H), 4.09-4.04 (m, 1H), 3.77 (s, 6H), 3.15-3.14 (m, 2H), 1.80 (ddd, *J* = 5.4, 9.6, 13.5 Hz, 1H), 1.68 (ddd, *J* = 1.2, 6.6, 13.5 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 158.0, 140.3, 138.4, 137.8, 128.5, 127.7, 127.1, 126.6, 113.6, 113.4, 79.6, 76.5, 70.8, 63.6, 55.3, 55.2, 52.0, 33.0

[9] General procedure for the asymmetric conjugate addition of α,β-enones: to a stirred solution of catalyst **1d** (6.3 mg, 0.02 mmol) and α,β-enone **3** (0.1 mmol) in toluene (1 ml) at 0 °C was added benzotriazole **2** (15 mg, 0.13 mmol), and the resulting mixture was stirred for the specified time (Table **2**). The crude reaction mixture was directly purified by flash chromatography on silica gel to afford the corresponding product **4**. Compound **4g:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (dd, *J* = 6.0, 18.0 Hz, 1H), 4.83 (dd, *J* = 8.0, 18.0 Hz, 1H), 6.71 (dd, *J* = 6.9, 7.2 Hz, 1H), 7.38-7.40 (m, 1H), 7.46-7.52 (m, 4H), 7.58-7.63 (m, 3H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.98-8.00 (m, 2H), 8.20-8.18 (m, 2H). HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 50:50, flow rate 0.5 ml/min), retention time, 40.6 min (minor), 54.4 min (major).

[10] Due to the poor reactive nature of the aromatic enones, iminium-ion mechanism was less acceptable.