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Enantioselective Michael addition catalyzed by chiral tripodal oxazoline–*t*BuOK complexes

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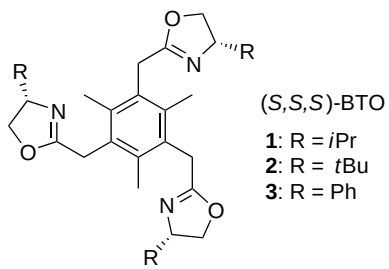
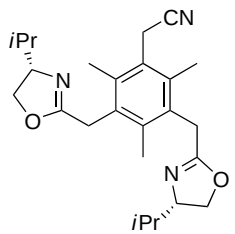
Abstract—Benzene-based tripodal oxazolines are found to be novel chiral ligands for the catalytic enantioselective Michael addition via potassium enolates. Thus, methyl phenylacetate undergoes 1,4-addition to methyl acrylate using a catalytic amount of a *t*BuOK–oxazoline complex in toluene at −78°C, and up to 82% ee is obtained.

Conjugate addition reactions are some of the fundamental organic reactions, which are widely used for carbon–carbon bond forming reactions. Their asymmetric versions have been intensively investigated in recent years catalyzed by various organometallic species.[1,2] Among them, the conjugate additions of enolates generated from carbonyl or nitro compounds, usually called Michael addition reactions, have been widely studied with catalysts such as alkali metal and transition metal complexes. For the alkali metal complexes, chiral ligands such as *Cinchona* alkaloids, alkoxides, phenoxides, crown ethers, and their derivatives have been used as the ligands.[2] For the title reaction, several crown ether derivatives[3,4] have been studied since the early report of Cram.[5] Herein, we wish to report that a new class of ligands, the benzene-based tripodal oxazoline (BTO) system, is potentially useful chiral ligands for the potassium complexes,[6] which is demonstrated for the title reaction.

In the course of our study on the selective molecular recognition of NH_4^+ over K^+ using BTOs as artificial receptors,[7] we have found that they have significant affinities toward K^+ ion. This finding led us to evaluate the compounds as chiral ligands in the catalytic asymmetric reactions that involve complexes of K^+ such as potassium enolates.

An initial experiment, the Michael reaction between methyl phenylacetate and methyl acrylate, with 10 mol% of *t*BuOK–valinol-derived *i*Pr-BTO **1**[7] in toluene at −78°C yielded the addition product in 75% yield after 3 h and with an enantioselectivity of 35% ee.[8] To find optimal conditions with the BTO we varied the reaction conditions including solvents and the molar ratio of the base to the ligand, the results of which are listed in Table 1. Toluene and dichloromethane are found to be good solvents, but the former is favored over the latter in terms of enantioselectivity. As





Keywords: Michael addition; tripodal oxazoline; asymmetric catalyst; potassium enolate.

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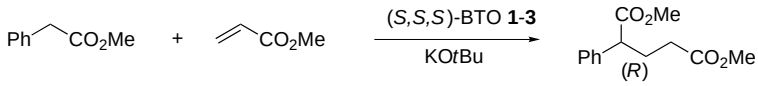
Table 1. Enantioselective Michael addition catalyzed by BTO–*t*BuOK complexes



Entry	BTO (mol%)	KO*t*Bu (mol%)	Condition[a]	Solvent	Time	Ee (%)[b]	Yield (%)[c]
1	**1** (10)	10	A	Toluene	3 h	35	75
2	**1** (5)	10	A	Toluene	6 h	36	51
3	**1** (10)	20	A	Toluene	3 h	46	86
4	**1** (10)	50	A	Toluene	15 min	31	55
5	**1** (10)	20	B	Toluene	3 h	56	80
6	**1** (10)	20	A	CH_2Cl_2	6 h	47	80
7	**1** (10)	20	A	Wet toluene	[d]	–	–
8	**1** (10)	20	A	THF	3 h	3	17
9	**2** (10)	20	A	Toluene	3 h	64	63
10	**2** (10)	20	B	Toluene	8 h	82[e]	83
11	**3** (10)	20	A	Toluene	3 h	41	85

[a] Condition A: a mixture of *t*BuOK and BTO in toluene was stirred at room temperature for 1 h, then the mixture was cooled to −78°C followed by the addition of the ester and methyl acrylate. Condition B: a mixture of *t*BuOK and the ester in toluene was stirred for 15 min at −78°C followed by the addition of BTO, and the resulting mixture was further stirred for 15 min before the dropwise addition of methyl acrylate in toluene.

[b] Determined from optical rotation data (Ref. 8).

[c] Isolated by SiO_2 chromatography.

[d] Very slow.

[e] $[\alpha]_D^{22} = -73.0$ (*c* 1.0, EtOH).

expected, coordinating solvents such as THF or the presence of water in toluene gave poor reactivity and enantioselectivity. Also, the molar ratio of the base to BTO **1** was found to affect the enantioselectivity. Thus, when we doubled the amount of *t*BuOK, from 10 to 20 mol%, the enantioselectivity was raised from 35 to 46% ee. However, further increasing the base gave worse effects in both the yield and the enantioselectivity. Interestingly, an apparent improvement in the enantioselectivity (increment of 10% ee) was observed when we changed the addition sequence of reactants, from A to B. Thus, an optimized reaction condition is to use 10 mol% of the BTO and 20 mol% of *t*BuOK in toluene under condition B at −78°C. It is notable that the reaction did not proceed at all when the base was replaced with *t*BuONa.

Next, applying the established reaction condition, we evaluated two other ligands, *t*Bu-BTO **2** and Ph-BTO **3**.[9] The former had to be synthesized from (2,4,6-trimethylbenzene)-1,3,5-triacetic acid and *tert*-leucinol, following the procedure used for the synthesis of the others.[†] The bulky *t*Bu groups on the oxazoline rings are expected to provide a highly crowded environment around the potassium ion coordinated to the oxazoline ligands, which may increase the enantioselectivity of the Michael reaction. This expectation was found to be the case: A significant improvement in the enantioselectivity was achieved under the established condition using *t*Bu-BTO **2**, and an enantioselectivity of 82% ee was obtained, a comparable enantioselectivity to the highest ones obtained so far (83–85% ee).[3] In the case of Ph-BTO **3**, a slightly lower enantioselectivity was observed compared to that observed with *i*Pr-BTO **1**. The observed enantioselectivities depending on the BTOs indicate that for better enantioselectivity more tight molecular interactions are required between the Michael acceptor and the potassium enolate, which is presumably coordinated to the BTO.

In regard to the mechanism of the Michael addition, we believe that a potassium enolate of the ester bounds to the BTO through a tripodal coordination of the oxazoline nitrogens to the K^+ ion. A face-selective approach of the Michael acceptor to a π-face of the enolate would result in the addition product enriched in one enantiomer.[‡] Thus, the geometric isomerism of the enolate[3d] as well as the chiral environment around both the enolate and the acceptor would determine the sense and degree of the enantio-discrimination. A reliable description is guaranteed by a further mechanistic study. To answer an important question whether the BTOs coordinate the K^+ ion in the described tripodal mode, not in a bidentate chelated one, we have synthesized a new chiral bis(oxazoline), BBO **4**,[§] and evalu-

[†] *t*Bu-BTO **2**: overall 22% yield in a one-pot reaction; $R_f = 0.45$ (ethyl acetate/hexanes = 3/2, by volume); mp 134–135°C; $[\alpha]_D^{21} = -137.6$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.07 (dd, 3H, $J = 8.6$, 9.9), 3.92 (dd, 3H, $J = 8.0$, 8.6), 3.78 (dd, 3H, $J = 8.0$, 9.9), 3.72 (s, 6H), 2.37 (s, 9H) 0.83 (s, 27H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 136.1, 131.1, 76.0, 69.0, 34.0, 30.5, 26.3, 17.6; MS (FAB): *m*/*z* (rel. intensity) 538 (M+1, 100), 480 (13). Elemental analysis for $C_{33}H_{51}N_3O_3$: calcd: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.53; H, 9.56; N, 7.93.

[‡] Possibility of enantioselective protonation of a potassium enolate as the chiral discrimination mode is excluded by examining the optical purity of reaction mixture at different time intervals, which gave the same optical purity in each case.

§ To be published elsewhere.

ated its effectiveness as the chiral ligand in the Michael addition. The same experiment under otherwise identical condition B, however, did not give any appreciable product after a prolonged reaction time at −78°C and at room temperature, with remaining starting materials and the ligand. This observation along with the unsuccessful result obtained with *t*BuONa indicates that the catalytic reaction proceeds via a tripodal complex between the BTO and *t*BuOK.¶

In summary, we have demonstrated for the first time that tripodal oxazoline compounds are a new class of potentially useful chiral ligands for the asymmetric reactions that involve potassium complexes such as the Michael addition studied here. Applications of BTOs to other catalytic asymmetric reactions are under investigation.

Acknowledgements

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¶ One referee raised a question why TBO gives high enantioselectivity whereas BBO does not at all. We think that the bidentate BBO has a lower binding affinity toward spherical K^+, and furthermore this property would result in poor transportation of the ion from the aqueous phase into the organic layer where the reaction occurs.

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