Asymmetric Catalysis

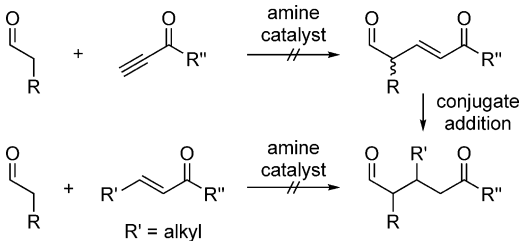
International Edition: DOI: 10.1002/anie.201500225
German Edition: DOI: 10.1002/ange.201500225

Regio- and Stereoselective Conjugate Addition of Aldehydes to β-Tosyl Enones under the Catalysis of a Binaphthyl-Modified Chiral Amine**

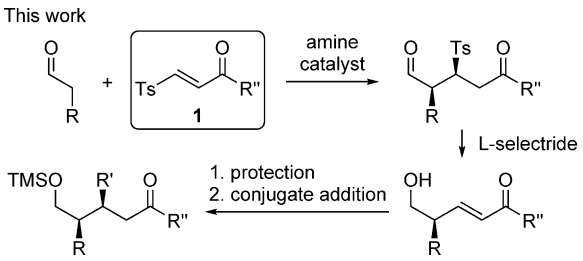
*Taichi Kano, Hisashi Sugimoto, Hiroki Maruyama, and Keiji Maruoka**

Abstract: *A simple axially chiral amine catalyst promoted the regio-, diastereo-, and enantioselective conjugate addition of aldehydes to β-tosyl enones, which serve as ynone surrogates. The adducts were readily converted by treatment with L-selectride into less accessible enones with a γ stereogenic center. Such compounds cannot be prepared through the amine-catalyzed conjugate addition of aldehydes to ynones. The obtained enones underwent further conjugate addition of diorganozinc compounds in the presence of a copper catalyst.*

The conjugate addition of carbon nucleophiles to electron-deficient alkenes is one of the most fundamental and reliable C–C bond-forming reactions in synthetic organic chemistry.[1] In the area of organocatalysis, a large number of chiral-amine-catalyzed conjugate addition reactions of aldehydes to various electron-deficient alkenes have been developed to date.[2,3] Among α,β-unsaturated ketones, alkyl vinyl ketones have been successfully employed in the chiral-amine-catalyzed conjugate addition of aldehydes.[4] To the best of our knowledge, however, amine-catalyzed conjugate addition reactions of aldehydes to ynones or β-alkyl-substituted enones are unprecedented, despite their synthetic utility (Scheme 1).[5–7] In particular, the conjugate addition to ynones, which would be equivalent to an α-alkenylation of aldehydes, could give the synthetically less accessible chiral enone with a γ stereogenic center;[7,8] however, the product is prone to epimerization, thus rendering the asymmetric synthesis of this type of compound very challenging. We became interested in β-tosyl enones **1**[9,10] as synthetic equivalents of ynones. The conjugate addition of aldehydes to **1** was expected to be accelerated by the electron-withdrawing tosyl group. The resulting adducts can be converted into enones with a γ stereogenic center by the elimination of the tosyl group[11] and used for further conjugate addition (Scheme 2). Herein, we report a highly regio- and stereoselective conjugate addition of aldehydes to β-tosyl enones **1** under the catalysis of an axially chiral secondary amine and synthetic applications of this transformation.



Scheme 1. Unprecedented amine-catalyzed conjugate addition reactions of α,β-unsaturated ketones.



Scheme 2. Conjugate addition of aldehydes to β-tosyl enones **1** and application of the transformation. TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

We first investigated the conjugate addition of 3-phenylpropanal to β-tosyl enone **1a** in toluene in the presence of various secondary-amine catalysts (10 mol%) at room temperature (Table 1). Whereas the use of pyrrolidine as a catalyst afforded the desired conjugate adduct **5a** in low yield with excellent regio- and diastereoselectivity (Table 1, entry 1), the chiral pyrrolidine-based catalyst (*S*)-**2**[12] did not promote the conjugate addition, but instead an insoluble precipitate derived from **1a** and (*S*)-**2** was formed (entry 2; see the Supporting Information). In both cases, undesired consumption of **1a** was observed. To our surprise, the reaction catalyzed by the simple binaphthyl-based secondary amine (*S*)-**3**[13] gave the conjugate adduct **5a** in high yield with high stereoselectivity (Table 1, entry 3). The more nucleophilic biphenyl-based amine (*S*)-**4a** gave a similar result (Table 1, entry 4). However, the introduction of substituents at the 3,3′-positions completely shut down the catalytic activity of the biphenyl-based amine (Table 1, entry 5).[13e] Both carbonyl groups of **5** were protected at once by treatment with 1,3-propanediol and a catalytic amount of *p*-toluenesulfonic acid,

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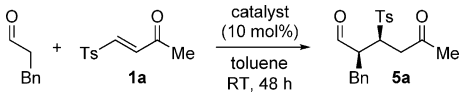
[**] This research was supported by a Grant-in-Aid for Scientific Research from MEXT (Japan). H.S. thanks the Japan Society for the Promotion of Science for a Research Fellowship for Young Scientists. We are grateful to T. Yoneda for performing X-ray crystallographic studies.

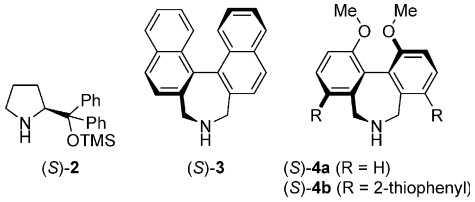
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201500225.

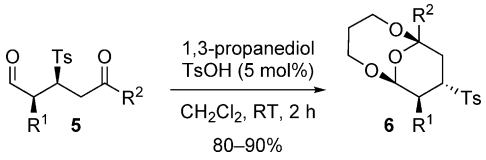
Table 1: Conjugate addition of 3-phenylpropanal to **1a**.[a]



Entry	Catalyst	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1[e]	pyrrolidine	29	>20:1	–
2	(*S*)-**2**	0	–	–
3	(*S*)-**3**	92	>20:1	91
4	(*S*)-**4a**	83	>20:1	89
5	(*S*)-**4b**	0	–	–

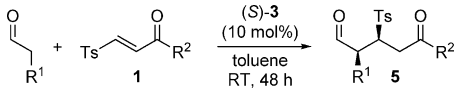
[a] The reaction of 3-phenylpropanal (0.6 mmol) with **1a** (0.2 mmol) was carried out in the presence of a catalyst (0.02 mmol) in toluene (0.2 mL) at room temperature. Bn = benzyl. [b] Yield of the isolated product. [c] The *syn*/*anti* ratio of the product was determined by ^{1}H NMR spectroscopy. [d] The *ee* value of the product was determined by HPLC on a chiral stationary phase after conversion into **6a** (R^1 = Bn, R^2 = Me). [e] The reaction was carried out for 19 h.





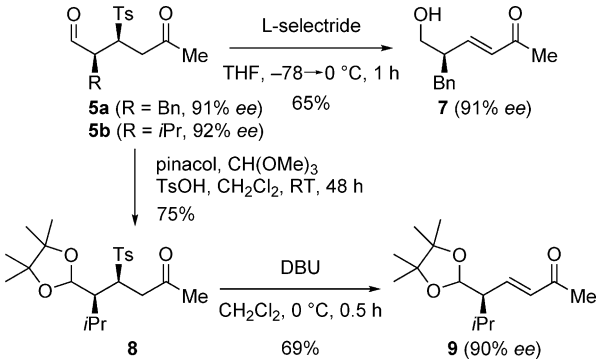
Scheme 3. Protection of the carbonyl groups of **5**.

Table 2: Conjugate addition of aldehydes to **1**.[a]



Entry	R^1	R^2	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	Me	Me	36	>20:1	94
2[e]	Et	Me	68	>20:1	93
3	Bu	Me	74	>20:1	93
4[f]	CH_2Cy	Me	81	>20:1	92
5	CH_2CH_2OBn	Me	77	>20:1	87
6	allyl	Me	82	>20:1	91
7	Bn	Me	92	>20:1	91
8	*i*Pr	Me	87	>20:1	92
9[f]	Bn	Et	80	>20:1	92
10	Bn	Ph	0	–	–

[a] The reaction of 3-phenylpropanal (0.6 mmol) with **1** (0.2 mmol) was carried out in the presence of (*S*)-**3** (0.02 mmol) in toluene (0.2 mL) at room temperature. [b] Yield of the isolated product. [c] The *syn*/*anti* ratio of the product was determined by ^{1}H NMR spectroscopy. [d] The *ee* value of the product was determined by HPLC on a chiral stationary phase after conversion into **6**. [e] The reaction was carried out for 36 h. [f] The reaction was carried out with (*S*)-**3** (0.04 mmol). Cy = cyclohexyl.



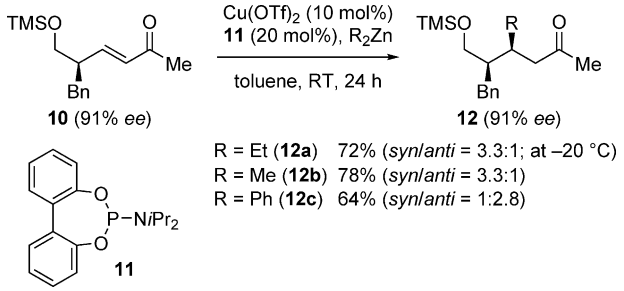
Scheme 4. Conversion of adducts **5** into α,β-unsaturated ketones **7** and **9**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

and the *ee* values of products of **5** were determined from the resulting 1,3,5-trioxocanes **6** (Scheme 3).

Having optimized the reaction conditions, we examined the scope of the reaction with respect to the aldehyde and enone substrates (Table 2). In the presence of (*S*)-**3** (10 mol%), the reactions of various aldehydes with **1a** (R^2 = Me) gave the corresponding conjugate adducts **5** in moderate to good yields with high stereoselectivity (Table 2, entries 1–8). In the reaction of propanal, elimination of tosyl group from the conjugate adduct **5** (R^1 = Me, R^2 = Me) was observed (Table 2, entry 1), which explains the low yield of **5**. Since the reaction of 3-phenylpropanal with **1b** (R^2 = Et) was slower than that with **1a** (R^2 = Me), 20 mol% of (*S*)-**3** was used to obtain **5** (R^1 = Bn, R^2 = Et) in high yield (Table 2, entry 9). In all cases examined, conjugate addition occurred at the β position of **1** exclusively, and only *syn* isomers were obtained.

The obtained conjugate adducts **5a** and **5b** were readily converted into enones **7** and **9**, respectively, through β elimination of the tosyl group (Scheme 4). Treatment of **5a** with L-selectride provided enone **7** without loss of optical purity by chemoselective reduction of the formyl group. After the protection of the formyl group of **5b** with pinacol, treatment of **8** with DBU gave enone **9**, although racemization was observed to a small extent. The obtained optically enriched enones **7** and **9** with a stereogenic center at the γ position cannot be prepared by the amine-catalyzed conjugate addition of aldehydes to ynones, and the present method can be viewed as a formal asymmetric α alkenylation of aldehydes.

After TMS protection of **7** with *N*,*O*-bis(trimethylsilyl)-acetamide, enone **10** was used for the conjugate addition of dialkyl zinc reagents and diphenylzinc (Scheme 5).[14] In the presence of $Cu(OTf)_2$ (10 mol%) and phosphoramidite ligand **11** (20 mol%), the conjugate addition of diethylzinc and dimethylzinc to **10** proceeded without racemization to give the corresponding *syn* adducts **12a** and **12b** predominantly,[15] which cannot be prepared through the amine-catalyzed conjugate addition of 3-phenylpropanal to β-alkyl- or β-phenyl-substituted enones. Interestingly, the reaction of **10** with diphenylzinc gave the *anti* adduct **12c** as the major diastereomer.[16]



Scheme 5. Conjugate addition of diorganozinc reagents to **10**. Tf = trifluoromethanesulfonyl.

Since the conjugate adduct was formed in much lower yield in the reaction catalyzed by pyrrolidine than with the less nucleophilic amine (*S*)-**3** (Table 1, entry 1 versus 3), the consumption of pyrrolidine and (*S*)-**3** in the presence of **1a** (10 equiv) was monitored by ^{1}H NMR spectroscopy in [D_8]toluene. Although pyrrolidine disappeared within 10 min by reaction with **1a**, 60% of (*S*)-**3** remained unchanged even after 7 h. This result suggests that the higher yield observed with less nucleophilic (*S*)-**3** may at least in part be due to the slow catalyst deactivation by conjugate addition to **1**.

In summary, the regio-, diastereo-, and enantioselective conjugate addition of aldehydes to β-tosyl enones, which serve as ynone surrogates, was realized by the use of a simple axially chiral amine catalyst. The conjugate adducts were readily converted into less accessible enones with a γ stereogenic center through β elimination of the tosyl group. The products can thus be used for further conjugate addition.

Keywords: aldehydes · asymmetric catalysis · Michael addition · olefination · organocatalysis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 8462–8465
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Received: January 9, 2015
Revised: May 20, 2015
Published online: June 18, 2015

