

# Organocatalyzed Formal [2 + 2] Cycloaddition of Ketimines with Allenates: Facile Access to Azetidines with a Chiral Tetrasubstituted Carbon Stereogenic Center

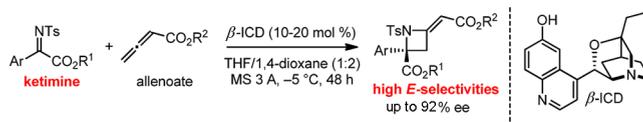
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## ABSTRACT



An enantioselective organocatalyzed aza-MBH-type reaction of ketimines and allenates has been developed. The present formal [2 + 2] cycloaddition produces highly functionalized azetidines with a chiral tetrasubstituted carbon stereogenic center in good to excellent yields and high enantioselectivities.

The simple construction of highly functionalized chiral organic molecules is a subject of intensive research. The aza-Morita–Baylis–Hillman (aza-MBH) reaction between an  $\alpha,\beta$ -unsaturated carbonyl compound and an imine is recognized as one of the most fruitful carbon–carbon bond forming reactions and is catalyzed by nucleophilic amines or phosphines.<sup>1</sup> The products of the aza-MBH reaction are highly functionalized allylic amines which are useful

building blocks for medicinal chemistry.<sup>2</sup> A significant number of works on the asymmetric aza-MBH reactions have been reported,<sup>3</sup> however a few describe the aza-MBH reaction of ketimines<sup>4,5</sup> which can construct tetrasubstituted carbon units. Ketimines, in particular unconjugated ketimines, are considerably less reactive and unstable compared to aldimines, and enantioface differentiation of ketimines is more difficult because of the smaller steric and electronic differences between the two substituents on the prochiral carbon. Therefore, effective enantioselective construction of chiral tetrasubstituted carbon stereogenic centers *via* the aza-MBH reaction of ketimines has been a challenge in asymmetric synthetic chemistry.<sup>6</sup> Herein, we describe the organocatalyzed aza-MBH-type reactions initiated by highly selective  $\gamma$ -addition of allenates to *N*-tosyl  $\alpha$ -ketimine esters, furnishing azetidines with a chiral tetrasubstituted carbon stereogenic center in good to excellent yields and high enantioselectivities.

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Chiral azetidines, which represent an important class of four-membered *N*-heterocycles, have received much attention because of their utilization as ligands<sup>7</sup> and their biological and pharmaceutical activities.<sup>8</sup> However, the synthetic approaches to enantiomerically enriched azetidines are generally multistep processes.<sup>7–9</sup> The [2 + 2] cycloaddition is certainly one of the most powerful methods for the construction of the strained four-membered ring.<sup>10</sup> This strategy was successfully extended to the construction of azetidines *via* diazabicyclo[2.2.2]octane (DABCO) catalyzed formal [2 + 2] cycloaddition as the first aza-MBH-type reaction of allenates with aldimines by Shi<sup>11</sup> in 2003 with further contributions as the enantioselective annulation developed by Masson and Zhu.<sup>12</sup> As the first step in the development of the aza-MBH reaction of ketimines, the reaction of **1a** and ethyl allenate (**2a**) was attempted using 20 mol % of achiral amines (Table 1).

Among the achiral amines we tested, DABCO and *N,N*-dimethyl-4-aminopyridine (DMAP) effectively promoted the reaction of ketimine **1a** with **2a** to give the desired

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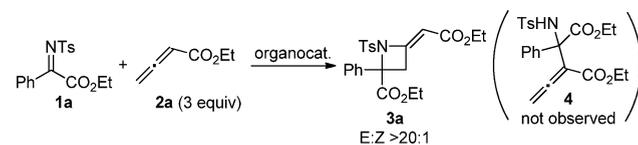
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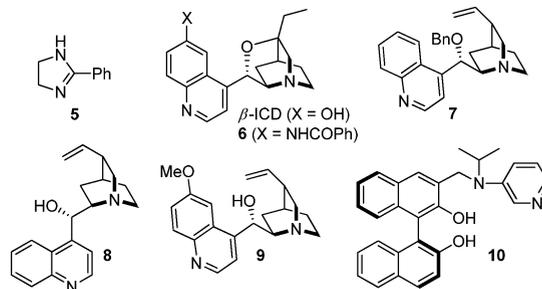
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**Table 1.** Formal [2 + 2] Cycloaddition of **1a** with **2a**<sup>a</sup>



entry	organocat.	solvent	°C	h	yield, % <sup>b</sup>	ee, % <sup>c</sup>
1	DABCO	THF	25	96	43	–
2	DMAP	THF	25	96	20	–
3	DBU or <b>5</b>	THF	25	96	0	–
4	$\beta$ -ICD	THF	25	24	42	80
5	$\beta$ -ICD	1,4-dioxane	25	24	58	82
6	$\beta$ -ICD	CH <sub>2</sub> Cl <sub>2</sub>	25	24	36	66
7	$\beta$ -ICD	toluene	25	24	28	80
8	$\beta$ -ICD	THF	0	24	45	84
9	$\beta$ -ICD	THF/1,4-dioxane (1:1)	0	24	49	89
10	<b>6</b>	THF/1,4-dioxane (1:1)	0	24	10	65
11	<b>7</b>	THF/1,4-dioxane (1:1)	0	24	23	59
12	<b>8, 9, or 10</b>	THF/1,4-dioxane (1:1)	0	24	0	–

<sup>a</sup> Reaction conditions: **1a** (0.06 mmol), **2a** (0.18 mmol), and catalyst (20 mol %) in solvent (0.3 mL). <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Determined by HPLC (Daicel Chiralpak AD). <sup>d</sup> With MS 4 A. <sup>e</sup> With 20 mol % of 2-naphthol. nd: not determined.



azetidine **3a** (Table 1, entries 1 and 2). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 2-phenyl-4,5-dihydro-1*H*-imidazoline (**5**) exhibited no catalytic activity (entry 3). Next, various chiral amine catalysts were tested.  $\beta$ -Isocupreidine ( $\beta$ -ICD), an acid–base organocatalyst known to mediate enantioselective MBH processes,<sup>13</sup> afforded **3a** in moderate yield with 80% ee (entry 4). Using of 1,4-dioxane (entry 5) or lowering the reaction temperature (entry 8) had positive effects on the chemical yields and enantioselectivities. Furthermore, the mixed solvent of THF/1,4-dioxane (1:1 ratio) achieved good outcomes in terms of enantioselectivity (entry 9). On the other hand, amide-type  $\beta$ -ICD **6** (with or without 20 mol % of 2-naphthol),<sup>14</sup> cinchonine

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benzyl ether **7**, cinchonidine (**8**), quinidine (**9**), and 3-(*N*-isopropyl-*N*-3-pyridinylaminomethyl)BINOL (**10**)<sup>15</sup> exhibited low or no catalytic activity (entries 10–12). Notably, neither formation of aza-MBH adduct **4**<sup>12</sup> nor the *Z*-configuration of azetidine **3a** was observed in any reaction; however, ethyl 2-oxo-2-phenylacetate was formed as a side product formed *via* hydrolysis of **1a**. To suppress the decomposition of the moisture-sensitive ketimine, 4 Å molecular sieves (MS 4 A) were added to the reaction media. The addition of MS 4 A improved the chemical yield (69%) and maintained high enantioselectivity (87% ee) (entry 9).

To our delight, the optimal result was obtained when the reaction of **1a** with **2a** was performed in a mixed solvent of THF/1,4-dioxane (1:2) at  $-5^{\circ}\text{C}$  in the presence of MS 3 A (Table 2, entry 1). Under the optimal conditions, the highly *E*-selective and (*R*)-configured azetidines **3** were obtained in good to excellent yields with high enantioselectivities (92–83% ee) irrespective of the electronic nature of substituent groups on the aromatic ring of **1**.<sup>16</sup> When 1-naphthyl ketimine **1b** was utilized as a substrate, the mixture of *E*- and *Z*-**3b** were obtained in a ratio of 6:1 (entry 2). The reactions of **1e** and **1i–j** (entries 5, 10, and 11) using benzyl allenoate (**2b**) (entry 18) led to the formation of the corresponding *E*-**3** (79–70% yields) along with the acyclic  $\gamma$ -adduct **11** (18–6% yields). Finally, optically pure azetidine **3i** could be obtained after a single recrystallization (entry 13).

To demonstrate the synthetic utility of highly functionalized azetidine **3**, various transformations were performed (Scheme 1). Allyl alcohol **12** was produced by DIBAL-H reduction of **3h** without over-reduction.  $\beta$ -Lactam **13** was obtained in 96% yield by oxidation with  $\text{O}_3$ . Subsequently, treatment of lactam **13** with Mg/MeOH cleaved the amide bond to provide acyclic  $\alpha,\alpha$ -disubstituted amino acid derivative **14** in good yield. Finally, **3k** could react with phenylboronic acid *via* Suzuki–Miyaura cross-coupling to quantitatively give biphenyl compound **15**.

Our proposed mechanism of the [2 + 2] cycloaddition of ketimine with allenoate using  $\beta$ -ICD is shown in Scheme 2. Addition of  $\beta$ -ICD to allenoate **2** affords the resonance-stabilized zwitterionic intermediate **I**, which could react with ketimine **1** according to two different pathways. Addition of the  $\gamma$ -carbanion to **1** would yield intermediate **IIa**, which upon [2 + 2] cyclization would give intermediate **III**. To avoid steric interactions between the aryl substituent of ketimine and the quinoline backbone in the catalyst, the reaction using  $\beta$ -ICD would favor the (*R*)-configuration product. Finally, *E*-azetidine **3** would be provided by the steric repulsion of the Ts-group and  $\text{CO}_2\text{R}^2$  functionality in

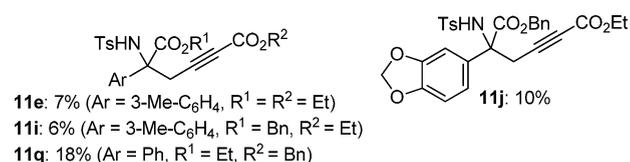
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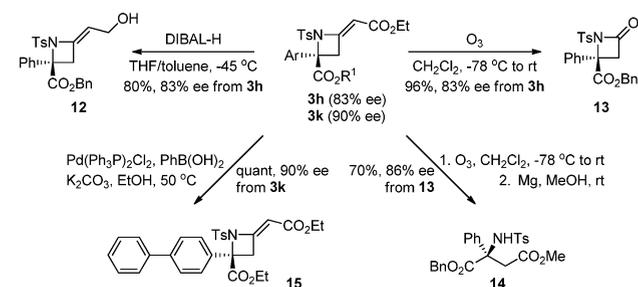
**Table 2.** Azetidine Formation from **1** with **2** Using  $\beta$ -ICD<sup>a</sup>

entry	Ar	R <sup>1</sup>	<b>1</b>	R <sup>2</sup>	yield of <i>E</i> - <b>3</b> % <sup>b</sup>	<i>E</i> : <i>Z</i> ratio <sup>c</sup>	ee of <i>E</i> - <b>3</b> % <sup>d</sup>
1	Ph	Et	<b>1a</b>	Et, <b>2a</b>	82, <b>3a</b>	>20:1	87
2	1-naphthyl	Et	<b>1b</b>	<b>2a</b>	70, <b>3b</b>	6:1	88
3	2-naphthyl	Et	<b>1c</b>	<b>2a</b>	71, <b>3c</b>	>20:1	90
4	2-Me-C <sub>6</sub> H <sub>4</sub>	Et	<b>1d</b>	<b>2a</b>	93, <b>3d</b>	>20:1	86
5	3-Me-C <sub>6</sub> H <sub>4</sub>	Et	<b>1e</b>	<b>2a</b>	74 <sup>h</sup> , <b>3e</b>	>20:1	88
6	4-Me-C <sub>6</sub> H <sub>4</sub>	Et	<b>1f</b>	<b>2a</b>	72, <b>3f</b>	>20:1	83
7	4-Br-C <sub>6</sub> H <sub>4</sub>	Et	<b>1g</b>	<b>2a</b>	quant (44) <sup>e</sup> , <b>3g</b>	>20:1	90 (92) <sup>e</sup>
8	4-Br-C <sub>6</sub> H <sub>4</sub>	Et	<b>1g</b>	<b>2a</b>	64 <sup>f</sup> , <b>3g</b>	>20:1	90 <sup>f</sup>
9	Ph	Bn	<b>1h</b>	<b>2a</b>	83, <b>3h</b>	>20:1	83
10	3-Me-C <sub>6</sub> H <sub>4</sub>	Bn	<b>1i</b>	<b>2a</b>	71 <sup>h</sup> , <b>3i</b>	>20:1	87
11		Bn	<b>1j</b>	<b>2a</b>	79 <sup>h</sup> , <b>3j</b>	>20:1	84
12	4-Br-C <sub>6</sub> H <sub>4</sub>	Bn	<b>1k</b>	<b>2a</b>	98 (44) <sup>e</sup> , <b>3k</b>	>20:1	90 (92) <sup>e</sup>
13	4-Cl-C <sub>6</sub> H <sub>4</sub>	Bn	<b>1l</b>	<b>2a</b>	79, <b>3l</b>	>20:1	88 (>99) <sup>g</sup>
14	2-Me-C <sub>6</sub> H <sub>4</sub>	Bn	<b>1m</b>	<b>2a</b>	93, <b>3m</b>	>20:1	84
15	4-Me-C <sub>6</sub> H <sub>4</sub>	Bn	<b>1n</b>	<b>2a</b>	97, <b>3n</b>	>20:1	85
16	Ph	CH <sub>2</sub> CF <sub>3</sub>	<b>1o</b>	<b>2a</b>	75, <b>3o</b>	>20:1	83
17	Ph	Me	<b>1p</b>	<b>2a</b>	76, <b>3p</b>	>20:1	86
18	Ph	Et	<b>1a</b>	Bn, <b>2b</b>	70 <sup>h</sup> , <b>3q</b>	>20:1	84

<sup>a</sup> Reaction conditions: **1** (0.06 mmol), **2a** (0.18 mmol),  $\beta$ -ICD (20 mol %) in THF/1,4-dioxane (1:2, 0.3 mL) at  $-5^{\circ}\text{C}$ . <sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by HPLC (Daicel Chiralpak AD for **3a**, **3g–p**; Daicel Chiralpak IC for **3b**, **3d–f**; Daicel Chiralpak AD3 for **3c**; Daicel Chiralcel OD3 for **3q**). <sup>e</sup> At  $-20^{\circ}\text{C}$ . <sup>f</sup> 10 mol % of  $\beta$ -ICD was used. <sup>g</sup> After a single recrystallization. <sup>h</sup> Acyclic  $\gamma$ -adducts **11** were obtained.

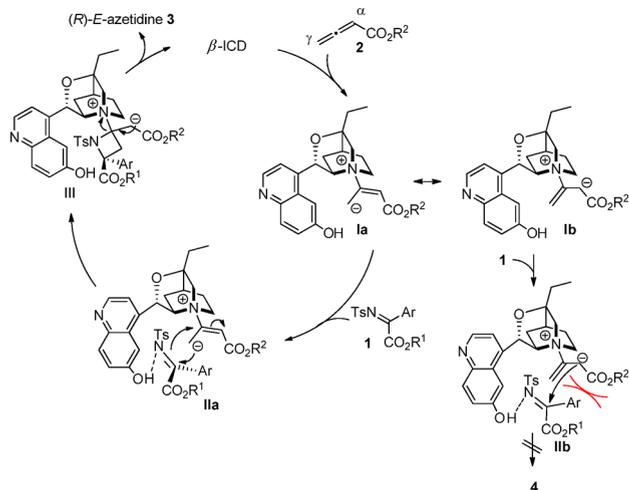


**Scheme 1.** Synthetic Transformations of Azetidine (*R*)-**3**



the fragmentation of **III** with concurrent regeneration of the catalyst. In contrast, the addition of the  $\alpha$ -carbanion to the ketimine to afford aza-MBH product **4** is not supported probably because of the steric hindrance of the ketimine (intermediate **IIIb**).

**Scheme 2.** Our Proposed Reaction Mechanism



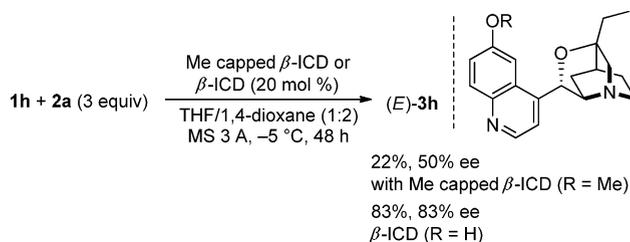
To gain insight into the influence of protic additives on the reaction rate,<sup>14,17</sup> additional control studies were performed. When the reaction of **1p** and **2a** (3 equiv) was performed in the presence of  $\beta$ -ICD (20 mol %) and a Brønsted acid (20 mol %), the yield of product **3p** decreased (from 76% to 45%, 43%, 53%, and 0% using 2-naphthol, (*S*)-BINOL, (*R*)-BINOL, and benzoic acid, respectively); however high enantioselectivities (> 81% ee) were maintained, and the formation of aza-MBH adduct **4** was not observed characteristically.<sup>18</sup> Because using methyl capped  $\beta$ -ICD resulted in low activity and selectivity, the phenolic hydroxyl group in  $\beta$ -ICD could play an important role in the intramolecular activation of the substrates to efficiently promote the aza-MBH-type reaction with high enantiocontrol (Scheme 3).

In summary, we have developed the enantioselective aza-MBH-type reaction of *N*-tosylketimines with allenates promoted by chiral organocatalysts to form azetidines

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(18) When using a Brønsted acid as an external proton source, decomposition of ketimine was observed.

**Scheme 3.** Formal [2 + 2] Cycloaddition of **1h** with **2a** Using the Methyl Capped  $\beta$ -ICD



with a chiral tetrasubstituted carbon stereogenic center in good to excellent yields and high enantioselectivities. The obtained azetidines were readily transformed into various derivatives. To the best of our knowledge, the present transformation is the first example of an enantioselective reaction of ketimines with allenates. Further investigation into the reaction mechanism and scope as well as its application to the enantioselective synthesis of biologically active compounds is currently underway.

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**Supporting Information Available.** Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.