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Chiral amine-catalyzed asymmetric conjugate addition of aldehydes to α-phenylselenoenones as formal *Z*-allylating agents

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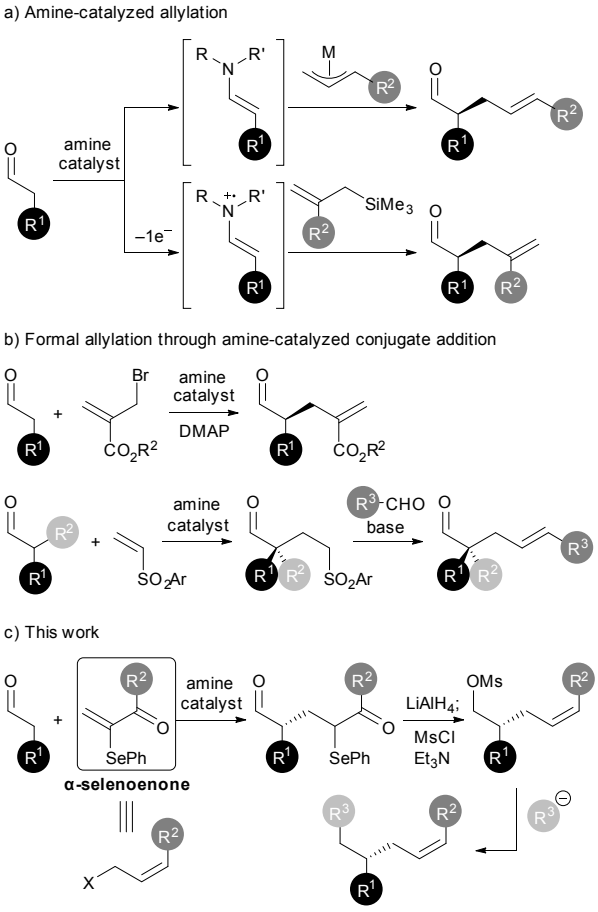
α-Selenoenones could be employed as *Z*-allyl precursors in the chiral amine-catalyzed asymmetric conjugate addition of aldehydes. The obtained formal allylation product, a *Z*-olefin having a sulfonate leaving group, was employed as a synthetically useful chiral alkylating agent.

Organocatalysis is a highly promising tool for the rapid construction of chiral building blocks in the asymmetric synthesis of natural products and biologically active compounds.[1] Chiral amine organocatalysts promote various asymmetric carbon–carbon bond forming reactions such as aldol reactions, Mannich reactions and conjugate additions through enamine intermediates.[2] However, the asymmetric alkylation of aldehydes and ketones remains a challenge due to the undesired *N*-alkylation and deactivation of the amine organocatalyst.[3-6] On the other hand, the amine-catalyzed asymmetric allylation of aldehydes proceeds with the aid of transition metal co-catalysts to give allylation products with *E*-geometry (Scheme 1a).[7] Asymmetric allylation of aldehydes using SOMO (singly occupied molecular orbital) activation gives the β-branched allylation products.[8] Alternatively, optically enriched allylation products can be prepared through chiral amine-catalyzed conjugate additions (Scheme 1b).[9] However, the enantioselective introduction of *Z*-allyl groups has not been developed to date.[10] In this context, we became interested in the possibility of using α-phenylselenoenones[11] as new synthetic equivalents to *Z*-allylating agents. Conjugate addition of aldehydes to α-selenoenones will provide α-selenoketones,[12,13] which can be converted to *Z*-olefins by reduction and treatment with a sulfonyl chloride as shown in Scheme 1c.[14] The obtained *Z*-olefins, formal allylation products have a chiral tertiary carbon atom with three different carbon chains and a sulfonate leaving group derived from the aldehyde moiety as a useful synthetic handle for further elaboration into valuable compounds. Herein we report the chiral amine-catalyzed asymmetric conjugate addition of aldehydes to α-phenylselenoenones as formal *Z*-allylating agents.



Scheme 1 Stereoselective introduction of allyl groups.

We first examined the chiral amine-catalyzed asymmetric conjugate addition of an aldehyde to α-phenylselenoenone **1a** (Table 1). In the presence of 10 mol% of Hayashi-Jørgensen

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catalyst (*S*)-**2**[15] and benzoic acid as cocatalyst, the conjugate addition of 3-phenylpropanal to **1a** proceeded in toluene to give the desired adduct **5a** in 72% yield with low diastereoselectivity (entry 4). While the major diastereomer was obtained with good enantioselectivity (84%), the ee of the minor diastereomer was low (24%). The ees of both diastereomers are required to be high enough, since they are averaged after the elimination of the seleno group in conversion to the olefinic compound. By using tritylpyrrolidine (*S*)-**3**[16] as catalyst, both diastereomers were obtained with high enantioselectivity (entry 5). Very recently, we have developed novel tritylpyrrolidine catalysts (*S*,*R*)-**4a** and (*R*,*R*)-**4a** that are readily synthesized from L-hydroxyproline.[17] The reaction catalyzed by (*S*,*R*)-**4a** gave a low yield of **5a** with higher enantioselectivity (entry 6). On the other hand, use of diastereomeric catalyst (*R*,*R*)-**4a** improved the yield of **5a** without loss of enantioselectivity (entry 7). When the modified catalyst (*R*,*R*)-**4b** was employed, the product was obtained in higher yield, albeit with slightly lower enantioselectivity (entry 8). Among the solvents tested, the best enantioselectivity was obtained in dichloromethane (entry 12). Use of 2,4,6-trimethylbenzoic acid cocatalyst instead of benzoic acid resulted in an increase of yield (entry 13).

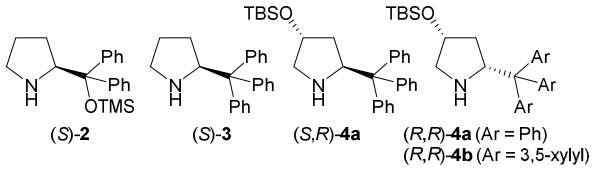
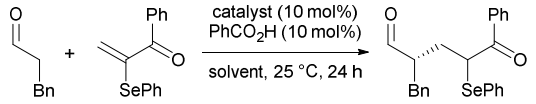


Table 1 Optimization of reaction conditions[a]

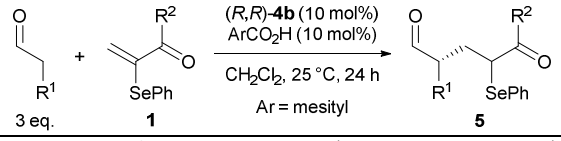


Entry	Catalyst	Solvent	Yield (%)[b]	dr[c]	ee (%)[d]
1	L-proline	toluene	trace	-	-
2[e]	pyrrolidine	toluene	6	2.0/1	-
3	pyrrolidine	toluene	66	1.4/1	-
4	(*S*)-**2**	toluene	72	1.9/1	–84/–24 (63)
5	(*S*)-**3**	toluene	55	2.2/1	–93/–86 (91)
6	(*S*,*R*)-**4a**	toluene	20	1/1.1	–90/–97 (94)
7	(*R*,*R*)-**4a**	toluene	48	3.7/1	97/89 (95)
8	(*R*,*R*)-**4b**	toluene	64	5.2/1	98/69 (93)
9	(*R*,*R*)-**4b**	DMF	n.d.	-	-
10	(*R*,*R*)-**4b**	MeCN	66	3.4/1	96/81 (93)
11	(*R*,*R*)-**4b**	THF	n.d.	-	-
12	(*R*,*R*)-**4b**	CH_2Cl_2	66	3.8/1	99/85 (96)
13[f]	(*R*,*R*)-**4b**	CH_2Cl_2	75	2.2/1	98/88 (95)

[a] Reactions were performed on a 0.1 mmol scale in 0.1 mL of a solvent. [b] ^{1}H-NMR yield utilizing mesitylene as an internal standard. [c] Determined by ^{1}H-NMR. [d] Determined by HPLC analysis using a chiral column. Numbers in parentheses are averaged ee values of two diastereomers. [e] Reaction performed without benzoic acid. [f] Use of 2,4,6-trimethylbenzoic acid instead of benzoic acid. n.d. = not detected.

With the optimized conditions in hand, we explored the reaction scope (Table 2). The reaction of a branched aldehyde, 3-methylbutanal also gave the conjugate adduct in excellent enantioselectivity (entry 3). Use of phenylacetaldehyde led to a decrease in yield, probably due to the low nucleophilicity of the enamine intermediate (entry 4). The lower stereoselectivity can be attributed to product epimerization. Replacing R^2 (Ph) on α-selenoenone **1a** with other aryl groups did not affect the enantioselectivity (entries 5–7). In the reaction of α-selenoenones bearing alkyl groups, the yield decreased slightly as the alkyl groups were longer (entries 8–10), but an increased yield was observed with a longer reaction time (entry 11). The moderate yields might be attributed to the instability of **1** under the reaction contidions.[18]

Table 2 Substrate scope[a]



Entry	R^1	R^2	Yield (%)[b]		dr[c]	ee (%)[d]
1	Bn	Ph	**5a**	84	2.2/1	98/88
2	Hex	Ph	**5b**	69	2.2/1	96/75
3	*i*-Pr	Ph	**5c**	74	2.4/1	97/95
4	Ph	Ph	**5d**	38	1.7/1	85/46
5	Bn	4-MeO-C_6H_4	**5e**	59	2.0/1	98/92
6	Bn	4-Br-C_6H_4	**5f**	79	2.8/1	98/90
7	Bn	2-Naphth	**5g**	68	2.3/1	96/88
8	Bn	Me	**5h**	74	3.5/1	98/83
9	Bn	Et	**5i**	56	3.5/1	98/84
10	Bn	Hept	**5j**	48	3.5/1	98/87
11[e]	Bn	Hept	**5j**	60	3.7/1	97/74

[a] Reactions were performed on a 0.1 mmol scale in 0.1 mL of CH_2Cl_2. [b] Isolated yield. [c] Determined by ^{1}H-NMR. [d] Determined by HPLC analysis using a chiral column. [e] Performed for 48 h.

The obtained conjugate adducts **5** were successfully converted to the corresponding olefins (Table 3). The conjugate adducts **5** in diethyl ether or THF were reduced with $LiAlH_4$ and then treated with methanesulfonyl chloride and triethylamine in dichloromethane.[14] In all cases, olefins **6** were obtained in good yields and *Z*-selectivities without loss of enantiopurity. As shown in Scheme 2, addition of hydride ion from $LiAlH_4$ would give *syn*-adducts,[14a] regardless of the stereochemistry at the α-position of ketone **5**, and the following *anti*-elimination after mesylation leads to *Z*-olefins.[14b]

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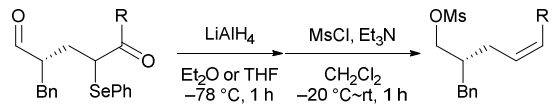
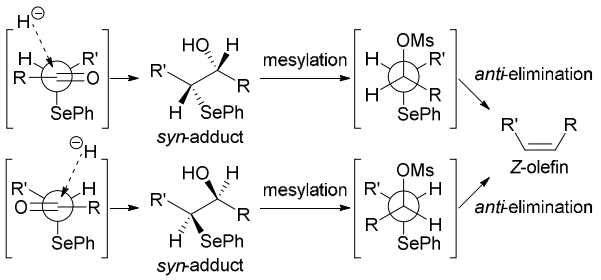
Table 3 Transformation of conjugate adducts **5** to *Z*-olefins **6**[a]



5 **6**

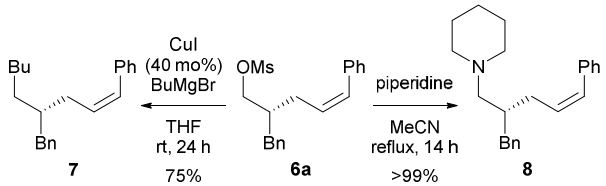
Entry	R	Yield (%)[b]		*Z*/*E*[c]	ee (%)[d]
1	Ph	**6a**	84	>20/1	95
2	4-MeO-C_6H_4	**6e**	81	19/1	95
3	4-Br-C_6H_4	**6f**	82	>20/1	94
4	Me	**6h**	70	10/1	94
5	Et	**6i**	83	11/1	94
6	Hept	**6j**	82	8.1/1	96

[a] See Supporting Information for details. [b] Isolated yield. [c] Determined by ^{1}H-NMR. [d] The ee of *Z*-isomer was determined by HPLC analysis using a chiral column.



Scheme 2 Formation of *Z*-olefins.

The resulting olefin **6a** with the mesylate leaving group was used as an alkylating agent having a stereocenter at the β-position (Scheme 3). In the presence of CuI, the reaction of **6a** with butylmagnesium bromide gave *Z*-olefin **7**. The nucleophilic substitution of **6a** by piperidine afforded the tertiary amine **8** in good yield.



7 **6a** **8**

Scheme 3 Application of **6a** as a chiral alkylating agent.

In summary, we have developed the chiral amine-catalyzed asymmetric conjugate addition of aldehydes to α-phenylselenoenones as synthetic equivalents of *Z*-allyl groups. The obtained olefinic compound having a sulfonate leaving group was employed as a chiral alkylating agent and the synthetic utility was successfully demonstrated.

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