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A Novel Enantioselective Catalytic Tandem Oxa-Michael–Henry Reaction: One-Pot Organocatalytic Asymmetric Synthesis of 3-Nitro-2*H*-chromenes

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Abstract: An enantioselective oxa-Michael–Henry reaction of substituted salicylaldehydes with nitroolefins that proceeds though an aromatic iminium activation (AIA) has been developed by using a chiral secondary amine organocatalyst and salicylic acid as a co-catalyst. The corresponding 3-nitro-2*H*-chromenes were obtained in moderate-to-good yields with up to 91% *ee* under mild conditions. Based on the experimental results and ESI-mass spectrometric detection of the intermediates, a plausible transition state has been proposed to explain the origin of the activation and the asymmetric induction.

Keywords: asymmetric catalysis; Henry reaction; Michael reaction; reaction mechanisms; tandem reactions

Introduction

Chromenes, or benzopyrans, are an important class of scaffolds found in numerous naturally occurring and synthetic molecules possessing a broad spectrum of biological activities.[1] Accordingly, interest in developing syntheses of these privileged structures continues to grow,[2] especially concerning condensations between salicylaldehyde derivatives and Michael acceptors such as α,β-unsaturated aldehydes (ketones) and nitroalkenes which have proven to be a versatile strategy to the benzopyan moiety.[3] Furthermore, for obtaining chiral chromenes, an enantioselective tandem Michael-aldol reaction of salicylaldehyde derivatives with α,β-unsaturated aldehydes (ketones) catalyzed by proline derivatives was developed by Wang, Arvidsson, Córdova and their co-workers, respectively.[4] Nevertheless, a chiral amine catalytic tandem oxa-Michael–Henry reaction of salicylaldehyde derivatives with nitroolefins for chiral 3-nitro-2*H*-chromene derivatives has not been researched. The importance of 3-nitro-2*H*-chromenes is recognized due to their versatile modifiability, for example, they could serve as precursor for flavonols, amines and other biological targets.[5] Some representative examples are shown in Figure 1.

Enantioselective organocatalysis, in which an asymmetric reaction proceeds with small oganic molecules as catalysts, has witnessed tremendous developments due to its efficiency and capacity to extend the scope of chiral organic synthesis in recent years, although its scope is mainly limited to carbonyl systems.[6] Until recently, four different methods to activate carbonyl compounds have been known using amine catalysis:

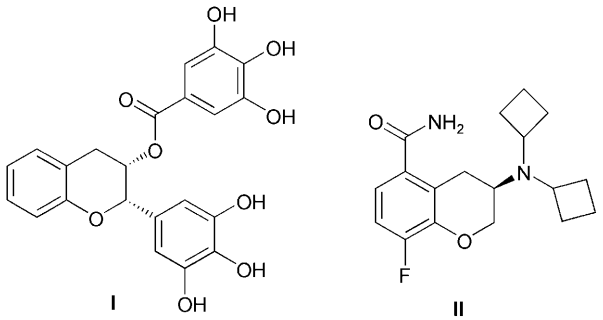


Figure 1. Some representative examples of biologically active compounds derived from 3-nitro-2*H*-chromenes.

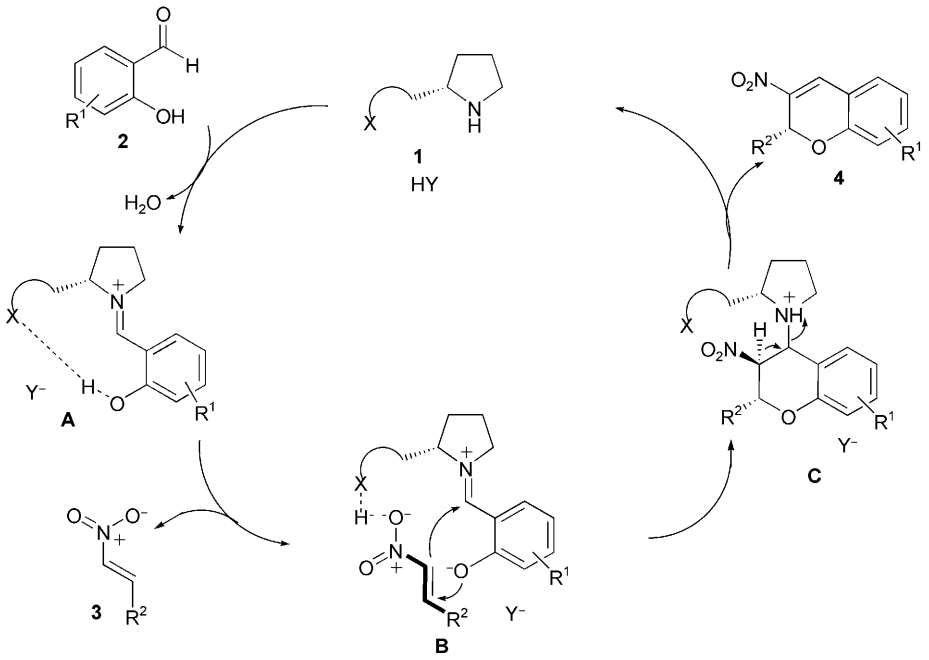


Figure 2. proposed mechanism of aromatic iminium activation for the organocatalyzed asymmetric tandem oxa-Michael–Henry reaction.

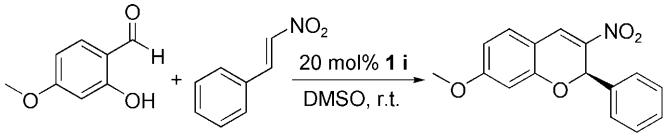
enamine, iminium ion, dienamine activation and SOMO (singly occupied molecular orbital)-enamine activation which was introduced by the research groups of Sibi and Macmillan more recently.[7] However, to our best knowledge, the asymmetric reactions reported through all these activation modes have not involved the activation of aromatic aldehydes. Inspired by the previous study of organocatalytic mechanisms, and based on our research interest in organocatalysis,[8] herein, we report the first example of aromatic iminium activation (AIA) in the field of asymmetric organocatalysis.

As shown in Figure 2, iminium-activated salicylaldehyde[9] **A** which is also activated by the Lewis base moiety **X** of the organocatalyst **1** would be attacked through a domino oxa-Michael–Henry reaction by a β-nitrostyrene which is induced finely by the complex **B**. The intermediate **C** undergoes an elimination process to afford the enantioselective 3-nitro-2*H*-chromenes and recover the catalyst **1** and co-catalyst **HY**.

Results and Discussion

Initially, to explore this possibility of the proposed domino oxa-Michael–Henry process, a model reaction between 4-methoxysalicylaldehyde and β-nitrostyrene was performed in DMSO at room temperature in the presence of an organocatalyst. Firstly, a pyrrolidine-thioimidazole was chosed as an organocatalyst because its structure was suited for the proposed mechanism and it exhibited an efficient catalytic activity for the highly asymmetric Michael additions of ketones and nitroolefins in our previous study.[8] Previous work has shown that carefully chosen acidic cocatalysts could enhance the efficiency and selectivity for the Michael addition catalyzed by chiral secondary amines,[10] and we therefore examined the cocatalyst effects on this domino reaction at the same time (Table 1). The reaction was fast when treated with 20 mol% **1i** (Figure 3) alone without any cocatalysts in DMSO at room temperature, but the product was almost racemic (Table 1, entry 1). However, use of 20 mol% of **1i** along with 10 mol%, 15 mol%, or 20 mol% of hydrobromic acid (Table 1, entries 2–4) as cocatalyst, respectively, gave the products in moderate to high enantioselectivity (Table 1, entry 3, 78% *ee*), although the yields of the product fell in the presence of the cocatalyst. These observations suggest that the acidic component is vitally important for constituting the aromatic iminium intermediate and the Lewis base moiety of the organocatalyst **1i** also enhances the nucleophilicity by deprotonation of the OH moiety of salicylaldehyde. Based on these initial results, we chose the conditions of entry 3 for the further screening of various acids cocatalysts, including HBF_4, HBF_6, TsOH and other organic acids. The best result (67% yield, 85% *ee*) was obtained with 15 mol% salicylic acid as cocatalyst (Table 1, entry 13). The results were in accord with the results of Michael additions of ketones and nitroolefins, probably the salicylic acid contributed a synergistic effect in the reactions in which nitroolefins were involved.[8b,11]

Table 1. Tandem oxa-Michael–Henry reaction catalyzed by organocatalyst **1i** and different acids as cocatalysts.[a]



Entry	Co-catalyst	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	none	48	93	5
2	HBr (0.5 equiv. of **1i**)	96	32	56
3	HBr (0.75 equiv. of **1i**)	96	22	78
4	HBr (1.0 equiv. of **1i**)	96	10	62
5	HBF_4	96	17	53
6	HPF_6	96	23	46
7	CH_3COOH	96	15	51
8	CF_3COOH	96	34	57
9	CH_3SO_3H	96	47	62
10	C_6H_5COOH	96	42	51
11	*p*-CH_3-C_6H_4COOH	96	40	52
12	*p*-NO_2-C_6H_4COOH	96	44	72
13	*p*-CH_3-$C_6H_4SO_3H$	96	25	70
14	2-(naphthalen-1-yl)acetic acid	96	35	73
15	naphthalene-1-sulfonic acid	96	33	62
16	**salicylic acid**	**96**	**67**	**85**

[a] Unless otherwise specified, all reactions were carried out with 4-methoxy salicylaldehyde (1 mmol), β-nitrostyrenes (0.5 mmol), the catalyst **1i** (0.1 mmol, 20 mol%) and the specified co-catalyst (0.075 mmol, 15 mol%) in DMSO (0.5 mL) at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 90/10).

To search for more optimal catalysts, we synthesized and screened a number of structurally related amines (Figure 3). However, we found that pyrrolidine-thioimidazole was the most effective catalyst in terms of stereocontrol, providing a relatively high yield and good enantioselection. In contrast to results obtained with diamine catalysts, except **1e**, reactions with L-proline and L-prolinol, as well as diphenylprolinol **1c** and its derivative **1d** only provided racemic products (Table 2, entrie 1–4).

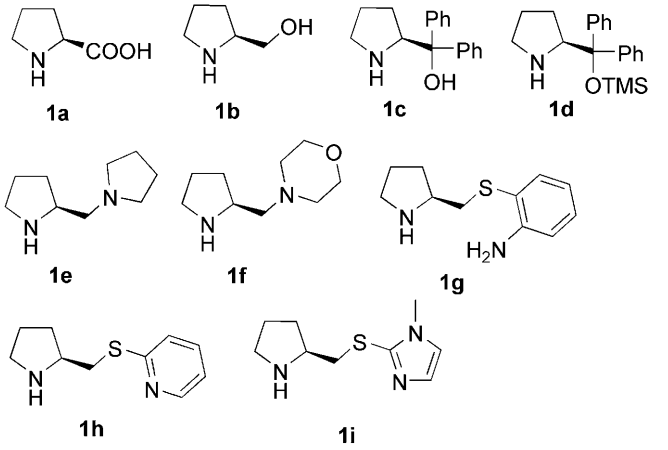
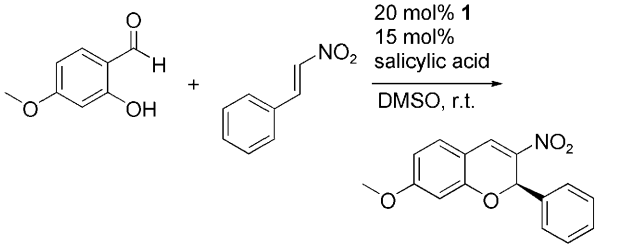


Figure 3. Screened organocatalysts.

Table 2. Tandem oxa-Michael–Henry reaction catalyzed by organocatalyst **1** and salicylic acid.[a]

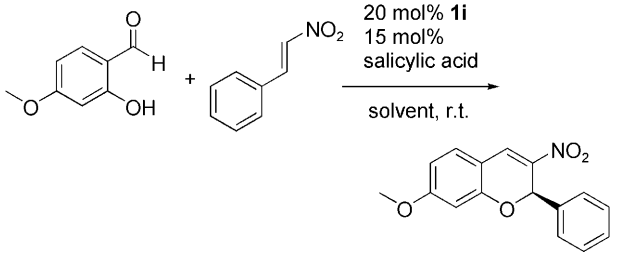


Entry	Catalyst	Time[h]	Yield[b] [%]	*ee*[c] [%]
1	**1a**[d]	96	13	0
2	**1b**	96	21	0
3	**1c**	96	17	0
4	**1d**	96	14	0
5	**1e**	96	<5	nd[e]
6	**1f**	96	30	70
7	**1g**	96	47	76
8	**1h**	96	36	72

[a] Unless otherwise specified, all reactions were carried out with 4-methoxy salicylaldehyde (1 mmol), β-nitrostyrene (0.5 mmol), the catalyst **1** (0.1 mmol, 20 mol%) and salicylic acid (0.075 mmol, 15 mol%) in DMSO (0.5 mL) at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Daicel Chiralpak AS-H, hexane/*i*.PrOH = 90/10).
[d] With no acid added.
[e] nd means not determined.

Having established the best catalyst/cocatalyst system for the domino oxa-Michael–Henry reaction, we next investigated the impact of different reaction media on the efficiency of this process. The results indicated that the solvents played a significant role in this reaction (Table 3). Reactions in polar solvents such as CH_3OH, EtOH, *i*-PrOH, DMF, DMSO (Table 3, entries 1–5), generally proceeded in relatively high yields, whereas those in less polar solvents (Et_2O, CH_2Cl-CH_2Cl, CH_3CN, THF and toluene) took place in low yields or even did not react at all (Table 3, entries 6–10). This is presumably due to the polar solvents' ability to stabilize the intermediates possessing partial charges as well as its dissolving power for the reaction system. However, the reaction in more polar medium (such as ionic liquids, Table 3, entries 11 and 12) did not perform as well as expected.

Table 3. Screening of the solvents for the tandem oxa-Michael–Henry reaction catalyzed by organocatalyst **1i** and salicylic acid.[a]



Entry	Solvent	Time[h]	Yield[b] [%]	*ee*[c] [%]
1	CH_3OH	96	25	70
2	EtOH	96	14	76
3	*i*-PrOH	96	10	82
4	DMF	96	20	72
5	**DMSO**	**96**	**67**	**85**
6	Et_2O	96	<10	nd
7	CH_2ClCH_2Cl	96	<10	nd
8	CH_3CN	96	<10	nd
9	THF	96	<10	nd
10	Toluene	96	0	nd
11	$[BMIm]BF_4$	96	<10	nd
12	$[BMIm]PF_6$	96	<10	nd

[a] All reactions were carried out with 4-methoxy salicylaldehyde (1 mmol), β-nitrostyrene (0.5 mmol), the catalyst **1i** (0.1 mmol, 20 mol%) and salicylic acid (0.075 mmol, 15 mol%) in the specified solvent (0.5 mL) at room temperature.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 90/10).

The scope and limitation of this catalytic system were explored next by using a wide range of salicylaldehydes and β-nitrostyrenes. Use of salicylaldehyde with no substitution gave the chromene derivatives in relatively high yields and moderate enantioselectivities (Table 4, entries 1–4). When introducing the substituted salicylaldehydes (Table 4, entries 5–8), the domino reactions afforded the corresponding products with higher enantioselectivites, which demonstrated the reactions were more selective with the steric interaction increasing. For example, 4-methoxysalicylaldehyde was found to be a competent substrate for this transformation to give the products in a good selectivity. The corresponding products were in fact obtained in good enantioselectivites (61–91%), irrespective of the electronic properties of the substituents at the aromatic ring of the β-nitrostyrene (Table 4, entries 9–14).

To determine the absolute configuration, TD-DFT calculations of the electronic circular dichroism (ECD) spectra were implemented in the Gaussian 03 program.[12] As show in Figure 4, the theoretical ECD

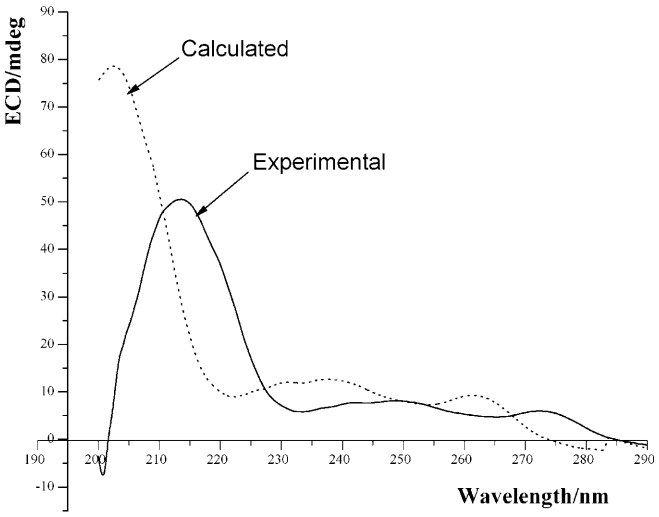


Figure 4. The theoretical simulated ECD spectrum (dotted trace) for the *R*-configuration of compound **4f** by the means of the TD-DFT/B3LYP/6-31+G* method, compared to the experimental spectrum (full trace).

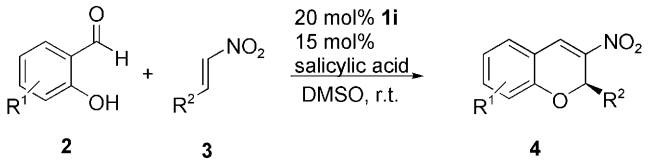
spectra of **4f** matched with the experimental data very well when it was assumed as *R*.

Based on the observed absolute configurations of the products and the discussion above, a mechanism as shown in Figure 2 was proposed to explain the observed results. For the proof of its rationality, the existence of intermediates **A** and **C** in the reaction mixture was confirmed using the ESI-MS method (Figure 5).

Among the two possible orientations of the aromatic iminium, the **TS-B** is favored (Figure 6), as the unfavorable steric interaction between the phenyl group of salicylaldehyde and the catalyst backbone is avoided, which constitutes the chiral environment for the oxa-Michael addition to the *re* face of the β-nitrostyrene, leading to the observed *R* products, while the disfavored **TS-B′** may lead to the *S* products.

The involvement of both the organocatalyst and the cocatalyst in this asymmetric tandem oxa-Michael–Henry reaction was quite crucial as neither **1i** nor salicylic acid alone could catalyze the formation of chiral 3-nitro-2*H*-chromenes efficiently. The organocatalyst **1i** may not only serve in the role of asymmetric iminium activation, but also in the role of a Lewis base to facilitate the deprotonation of the salicylaldehyde so as to promote the Michael addition to the β-nitrostyrene. The salicylic acid may also have a dual role in the process, which might favor the formation of the aromatic iminium as well as serve for a hydrogen-bonding interaction between the nitro oxygen of **3** and its hydroxy group (Figure 6, **TS-B**).

Table 4. Scope of tandem oxa-Michael–Henry reactions.[a]



Entry	R^1	R^2	Product **4**	Yield[b] [%]	*ee*[c] [%]
1	H	Ph	**4a**	72	51
2	H	4-MeC_6H_4	**4b**	81	45
3	H	4-MeOC_6H_4	**4c**	87	52
4	H	naphthalen-2-yl	**4d**	51	53
5	3-MeO	Ph	**4e**	78	77
6	4-MeO	Ph	**4f**	67	85
7	5-MeO	Ph	**4g**	32	48
8	5-Cl	Ph	**4h**	72	62
9	4-MeO	4-ClC_6H_4	**4i**	57	69
10	4-MeO	4-BrC_6H_4	**4j**	46	61
11	4-MeO	2-MeOC_6H_4	**4k**	37	91
12	4-MeO	3-MeOC_6H_4	**4l**	52	71
13	4-MeO	4-MeOC_6H_4	**4m**	47	72
14	4-MeO	naphthalen-2-yl	**4n**	35	70

[a] All reactions were carried out with **2** (1 mmol), **3** (0.5 mmol), the catalyst **1i** (0.1 mmol, 20 mol%) and salicylic acid (0.075 mmol, 15 mol%) in DMSO (0.5 mL) at room temperature for 96 h.
[b] Isolated yield.[c] Determined by chiral HPLC analysis (Daicel Chiralpak AS-H or OD-H).

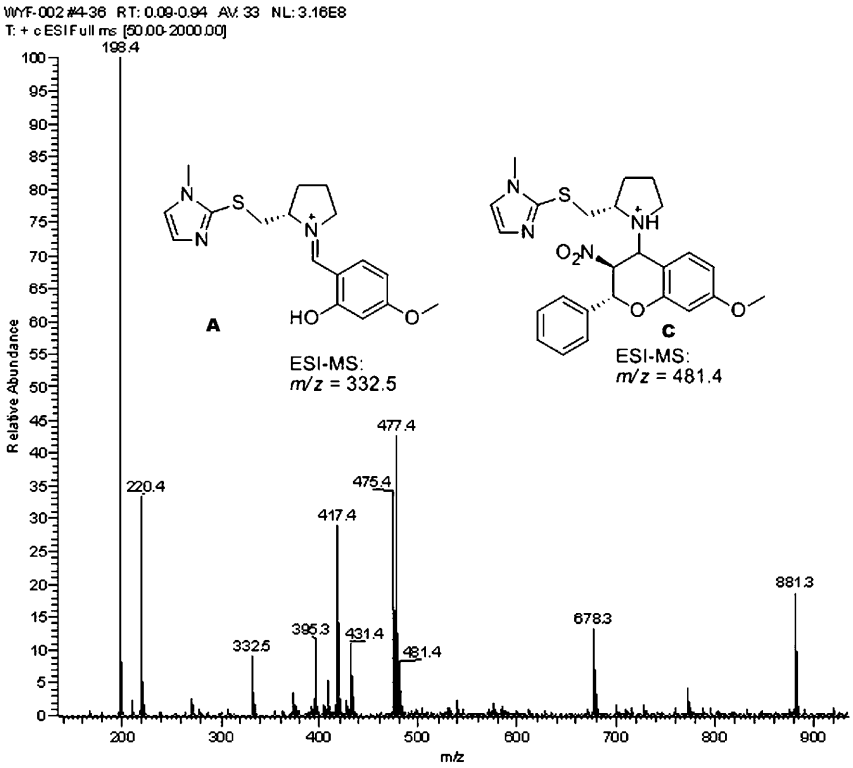


Figure 5. ESI-mass spectra: the existence of intermediates **A** and **C** in the reaction mixture was confirmed.

Conclusions

In summary, the new organocatalytic tandem oxa-Michael–Henry reaction, promoted by organocatalyst **1i** and the cocatalyst salicylic acid through the first reported aromatic iminium activation, serves as an efficient method for the preparation of chiral 3-nitro-2*H*-chromenes with moderate to good enantioselectivites.

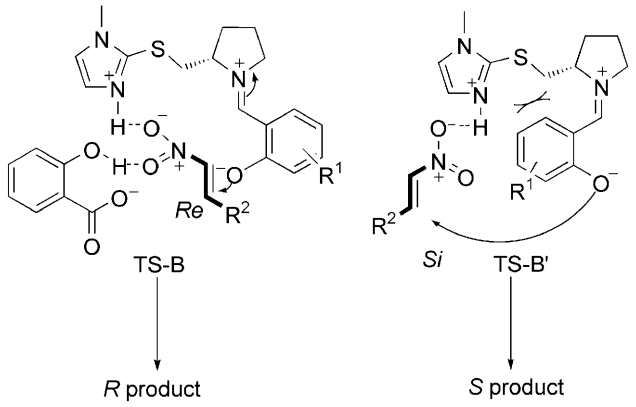


Figure 6. The proposed transition states in the tandem oxa-Michael–Henry reaction.

A broad range of salicylaldehydes and β-nitrostyrenes can be tolerated in the process. A plausible transition pathway has been proposed to explain the origin of the activation and the asymmetric induction. Further studies of the application of AIA on organocatalysis are underway.

Experimental Section

Typical Procedure for the Organocatalytic Asymmetric Oxa-Michael–Henry Reaction

After stirring a solution of catalyst **1i** (0.1 mmol, 20 mol%) and salicylic acid (0.075 mmol, 15 mol%) in DMSO (0.5 mL) at 25 °C for 1 h, 4-methoxysalicylaldehyde (0.152 g, 1 mmol) and β-nitrostyrene (0.075 g, 0.5 mmol) were added sequentially. After being stirred at 25 °C for 96 h, the reaction mixture was quenched with distilled water (10 mL), and extracted with EtOAc (3×10 mL). The organic layer was dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by flash chromatography to furnish a yellow solid in 67% yield. The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane:*i*-PrOH = 90:10; flow rate 1.0 mL min^{-1}; t_R major isomer = 14.2 min, t_R minor isomer = 21.1 min).

Acknowledgements

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