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Recyclable Tertiary Amine Modified Diarylprolinol Ether as Aminocatalyst for the Sequential Asymmetric Synthesis of Functionalized Cyclohexanes and Chromenes

Hao Shen,[a] Ke-Fang Yang,*[a] Zi-Hui Shi,[a] Jian-Xiong Jiang,[a] Guo-Qiao Lai,*[a] and Li-Wen Xu*[a,b]

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The one-pot, organocatalytic Hayashi sequential reaction (HSR) of β-nitroacrylate, aldehyde, toluenethiol, and ethyl 2-(diethoxyphosphoryl)acrylate allowed the synthesis of almost stereoisomerically pure, highly functionalized polysubstituted cyclohexanes with very high diastereo- and enantioselectivity (up to > 99 % *ee*). The one-pot synthesis consists of the tertiary amine modified diarylprolinol silyl ether-mediated asymmetric Michael reaction, a domino Michael reaction/Horner–Wadsworth–Emmons reaction, and a sulfa-Michael reaction. In addition, we have also demonstrated an improved protocol for the domino oxa-Michael/aldol reaction of salicyladehydes with α,β-unsaturated aldehydes with recyclable tertiary amine-modified diarylprolinol silyl ether **3d** as an effective organocatalyst, which results in the formation of chiral chromenes with good enantioselectivities (up to 94 % *ee*). UV/Vis and CD spectroscopy provide a cross-validation method to elucidate the slight difference between electron-withdrawing **3d** and diphenylprolinol silyl ether **3a**, which can give indirect evidence for the enhancement of enantioselective induction with **3d** in the above transformations.

Introduction

The sequential reaction can be considered as one of the most powerful and reliable tools for the one-pot construction of complicated molecules from simple and commercially available substrates.[1] The development of sequential one-pot enantioselective reactions is a new direction in organocatalysis.[2] Furthermore, asymmetric organocatalytic sequential reactions catalyzed by chiral amines,[3] especially secondary amines, have grown rapidly to become one of the most exciting topics in asymmetric organocatalysis, as secondary amines are capable of both enamine and iminium catalysis.[4] In particular, the incorporation of silyl groups in aminocatalysts, which allow steric and electronic modifications, has led to the enhancement in enantioselectivity and reactivity.[5] Since the first example of the use of amino alcohol derived silyl ethers (diarylprolinol silyl ethers) in asymmetric synthesis was independently developed by Jørgensen[6] and Hayashi[7] in 2005, this class of silyl organocatalysts (Jørgensen–Hayashi catalysts) has emerged as a powerful enamine organocatalyst in many organic transformations,[8] including Michael reactions, cycloaddition, domino reactions, and total syntheses, through the activation of aldehydes either by enamine formation (raising the highest occupied molecular orbital)[9] or α, β-unsaturated aldehydes by iminium ion formation (lowering the lowest unoccupied molecular orbital).[10] Herein, we present our recent results on the tertiary amine-modified diarylprolinol ether as a water soluble, recyclable organocatalyst to promote one-pot sequential addition of aldehydes, β-nitroacrylate compounds, and ethyl 2-(diethoxyphosphoryl)-acrylate, in which the sequential reaction affords functionalized cyclohexanes, a similarly basic six-membered backbone or intermediate of (–)-oesltamivir phosphate (Tamiflu), a neuraminidase inhibitor used in the treatment of both type A and type B human influenza.[11] Furthermore, we also report the one-pot, enantioselective domino oxa-Michael/aldol reaction for the facile preparation of benzopyranes in the presence of the same water soluble tertiary amine or ammonium salt-modified diarylprolinol silyl ether.

Results and Discussion

The asymmetric Michael reaction of aldehyde and β-nitroacrylate catalyzed by diphenylprolinol silyl ether is the

[a] Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University,
Hangzhou 310012, P. R. China
Fax: +86-571-28865135
E-mail: liwenxu@hznu.edu.cn
licpxulw@yahoo.com
[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences,
Lanzhou 730000, P. R. China

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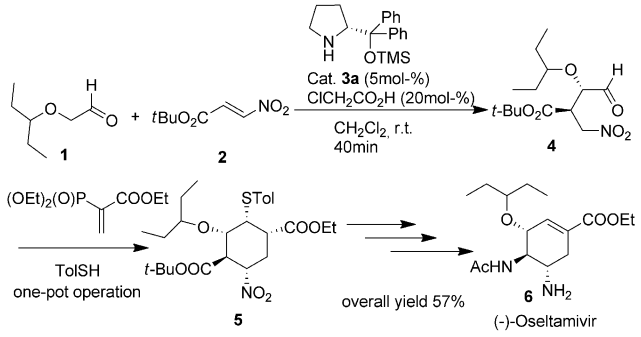
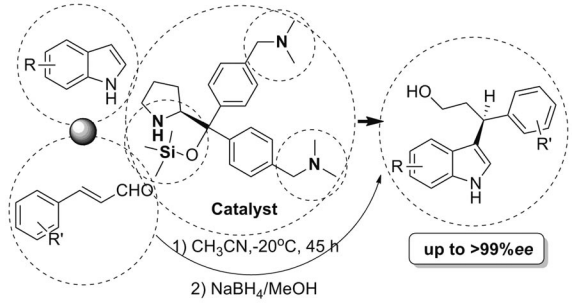
first step that we have investigated. In 2008, Ma et al.[12] reported the excellent asymmetric induction ability of diphenylprolinol silyl ether in the Michael reaction of aldehydes to β-nitroacrylate. In 2009, Hayashi et al.[13] applied this key reaction in the three-step total synthesis of (–)-oseltamivir using alkoxyaldehyde, nitroalkene, and subsequent treatment with diethyl vinylphosphonate. Although there are many important protocols for the synthesis of (–)-oseltamivir,[14] one of the most efficient is that of Hayashi et al.[13] with diphenylprolinol silyl ether as an organocatalyst (Scheme 1). In this procedure, the sequential reaction was mainly composed of an asymmetric Michael reaction, a Horner–Wadsworth–Emmons reaction, and a sulfa-Michael reaction.



Scheme 1.

The HSR is valuable in the search for molecules effective against Tamiflu-resistant viruses. However, major problems associated with this organocatalytic system are high catalyst loading (5–10 mol-%) and the difficulty of recovering the catalyst from the reaction mixture. Therefore, it is important to develop a convenient method to facilitate the recovery and reuse of the expensive organocatalysts. Ni et al.[15] have provided a simple example of a modified organocatalyst using a tertiary amine-modified diarylprolinol silyl ether and its salt as efficient, water soluble, recyclable organocatalysts for asymmetric Michael addition. The hypothesis is based on the ability of the dimethylamine group of the catalyst to form water soluble ammonium salts with a Brønsted acid. Their strategy proved to be efficient in the asymmetric Michael addition of aliphatic aldehydes to nitroolefins in water, which provided the Michael adducts with excellent diastereo- and enantioselectivities (> 98 %*ee*, > 95:5 *dr*). Moreover, the catalytic system can be easily recovered and reused at least six times without significant loss of catalytic activity.

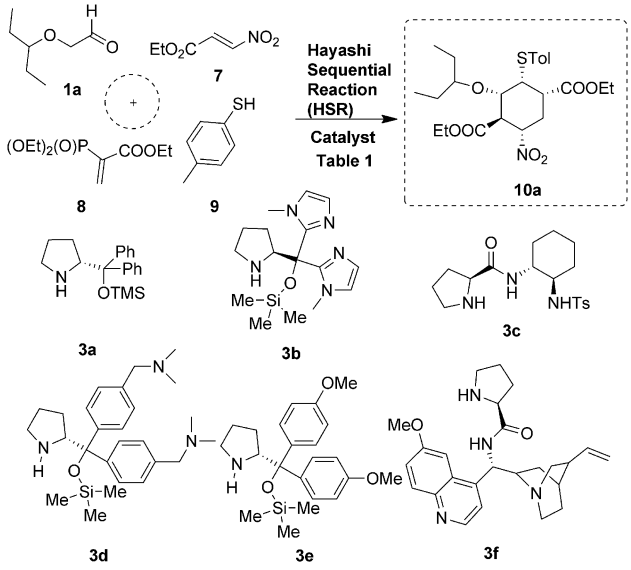
We have recently reported the use of a tertiary amine-modified diarylprolinol silyl ether in the catalytic, asymmetric Friedel–Crafts alkylation of indoles (Scheme 2),[16] which resulted in the highly enantioselective Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes with excellent enantioselectivities (up to > 99 %*ee*). This improved method offers substantial advantages over traditional approaches, not only by avoiding the use of acids and bases, but also the high level of stereoselectivity. In addition, on the basis of experimental results and ^{29}Si NMR spectroscopy, we have demonstrated that the role of the silicon group in the diaryl prolinol silyl ethers (Jørgensen–Hayashi catalyst) is not only as a bulky group to induce the steric repulsion but also as a weak Lewis acidic promoter to facilitate the formation of the iminium intermediate derived from the secondary amine and the substrate (α,β-unsaturated aldehyde). According to ^{29}Si NMR analysis, it was expected that the presence of the tertiary amine on the aromatic ring of the diaryl prolinol silyl ether resulted in a higher level of stereoselectivity, perhaps due to the suppression of a possible intramolecular hypervalent conformer. Although we failed to observe the obvious differences between the tertiary amine-modified diarylprolinol silyl ether and the unmodified diphenylprolinol silyl ether with NMR and other spectra analysis, the design and modification of efficient chiral organocatalysts that lead to enhanced enantioselectivity is not an easy task and could be one of the major challenges in the growing field of asymmetric organocatalysis.



Scheme 2. Catalytic asymmetric Friedel–Crafts alkylation of indoles.

Previous findings led us to continue to hypothesize that the water soluble, recyclable tertiary amine-modified diarylprolinol silyl ether and some other chiral secondary amines could act as effective organocatalysts in the important HSR for the synthesis of functionalized cyclohexanes, a possible intermediate of (–)-oesltamivir phosphate. We started our investigation with a set of experiments to identify the most efficient secondary amine catalysts for the domino–tandem reaction as a model reaction (Scheme 3). Therefore, the search for another excellent organocatalyst and optimal conditions for the domino–tandem addition of aldehydes, β-nitroacrylate compounds, and ethyl 2-(diethoxyphosphoryl)acrylate to the enantioselective construction of optically active functionalized cyclohexanes was performed using the well known diphenylprolinol silyl ether as the starting organocatalyst.

As shown in Scheme 3 and Table 1, we prepared several secondary amine-based organocatalysts **3a**–**f**, and the reaction results under optimized conditions are shown in Table 1. However, the diphenylprolinol silyl ether is not perfect for this example: the enantiomeric excess of this reaction is only 87 %*ee* when (*E*)-ethyl 3-nitroacrylate was used a model substrate in this domino reaction. Although other aminocatalysts, such as **3b**, **3c**, **3e**, and **3f**, did not lead to a significant improvement in enantioselectivity (up to



Scheme 3. Screening of organocatalysts for the asymmetric HSR of β-nitroacrylate, aldehyde, toluenethiol, and ethyl 2-(diethoxyphosphoryl)acrylate.

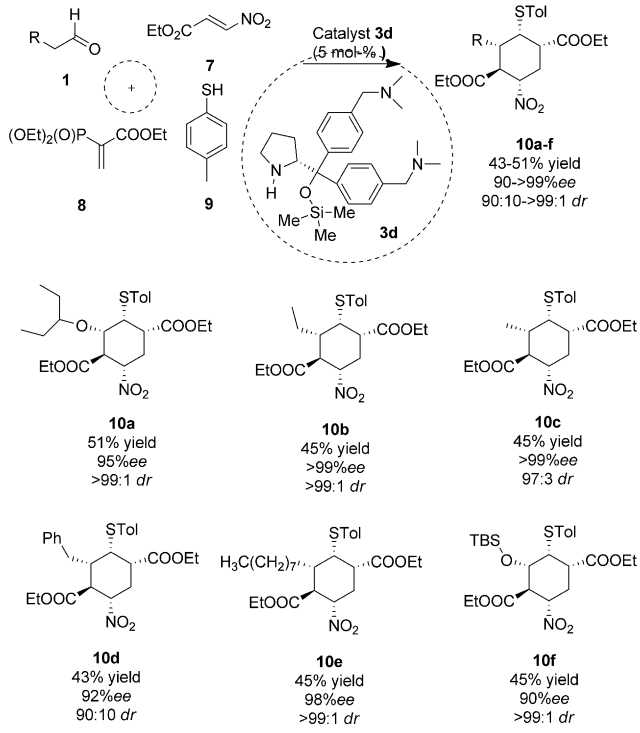
65 %*ee*) and conversion (up to 32% yield), we found that diarylprolinol silyl ether **3d** containing a tertiary amine moiety catalyzed the domino–tandem reaction very efficiently to afford the functionalized cyclohexane **10a** with five chiral centers in an acceptable yield as a single isomer and with excellent enantioselectivity (95 %*ee*). This is in accordance with a previous report that the presence of a tertiary amine in diarylprolinol silyl ether is important for the enhancement of enantioselectivities in different Michael reactions.[16] In addition, the HSR of β-nitroacrylate, aldehyde, toluenethiol, and ethyl 2-(diethoxyphosphoryl)acrylate, was chosen as the model to examine the recyclability of **3d**. After the three-step sequential reaction was completed, 1 N HCl was added to the reaction solution. The desired product, along with starting reagents and side-products of the reaction, was extracted into mixed solvent (Et_2O/hexane, 1:8).[15] The recovered aqueous phase containing **3d**-HCl was neutralized with aqueous K_2CO_3 and the majority of **3d** was obtained by simple extraction and evaporation. Although diarylprolinol silyl ether is an expensive organocatalyst (about 1200 RMB/1 g or 130 EUR/1 g), this procedure demonstrates that **3d** is recyclable and would be beneficial for the large scale preparation of the intermediate of (–)-oesltamivir phosphate.

Table 1. Effect of chiral secondary amine-based organocatalysts in the HSR (Scheme 3).[a]

Entry	Cat. (5 mol-%)	Total yield [%][b]	*ee*[c]
1	**3a**	46	87
2	**3b**	< 10	–
3	**3c**	18	–59
4	**3d**	51	95
5	**3e**	trace	–
6	**3f**	32	–65

[a] Reaction conditions: aldehyde **1a** (3 mmol), β-nitroacrylate **7** (2 mmol), (*R*) or (*S*)-diarylprolinol trimethylsilyl ether **3d** (44 mg, 5 mol-%), 2-(diethoxyphosphoryl)acrylate **8** (708 mg, 3 mmol), and toluenethiol (10 mmol). The reaction was carried out according to ref.[13] [b] Total isolated yield for the one-pot domino operation. [c] Enantiomeric excess (%) was determined by chiral HPLC analysis.

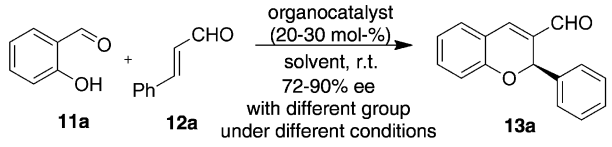
Having established an optimal protocol for the domino reaction, we examined the scope and limitations of the **3d** catalyzed sequential transformation with regard to different aldehydes (Scheme 4). To our delight, in all cases, the domino–tandem reaction proceeded smoothly to furnish the desired functionalized cyclohexanes in moderate overall yields and with excellent enantioselectivities (up to > 99 %*ee*) under the optimized conditions. Both linear and branched apliphatic aldehydes, as well as aldehydes with an aryl or silicon-based bulky groups, were found to be suitable substrates in the domino–tandem reaction.



Scheme 4. Direct organocatalytic asymmetric sequential reactions of different aldehydes under optimized conditions.

Inspired by our work on diarylprolinol silyl ether catalysis, and having established the **3d**-catalyzed HSR of β-nitroacrylate, aldehyde, toluenethiol, and ethyl 2-(diethoxyphosphoryl)acrylate, we then considered improving the enantioselectivity of another sequential transformation with **3d** as the organocatalyst. Asymmetric domino oxa-Michael/aldol sequences constitute a very effective and straightforward entry to enantioenriched benzopyranes, also known as chromenes, widespread constituents in natural products with proven pharmacological activity. Since 2006, several groups,[19] have reported their findings on pyrrolidine silyl ether-catalyzed oxa-Michael initiated domino reactions. A series of secondary amine organocatalysts and the combination of different organocatalysts have been tested for the conjugate addition of salicylaldehyde to *trans*-cinnamaldehyde. Most methods reported gave considerable turnover

and promising levels of enantioselectivity (72–90 %*ee*) under different conditions (Scheme 5). Despite the fact that **3a** was employed as an efficient organocatalyst in the domino oxa-Michael/aldol condensation, enhanced enantioselectivity is still highly desired and there is much room for improvement. Herein, we report an improved protocol for the domino oxa-Michael/aldol reaction of salicyladehydes with α,β-unsaturated aldehydes using **3d** as an effective organocatalyst, resulting in the formation of chiral chromenes with comparable and superior enantioselectivities (up to 94 %*ee*).

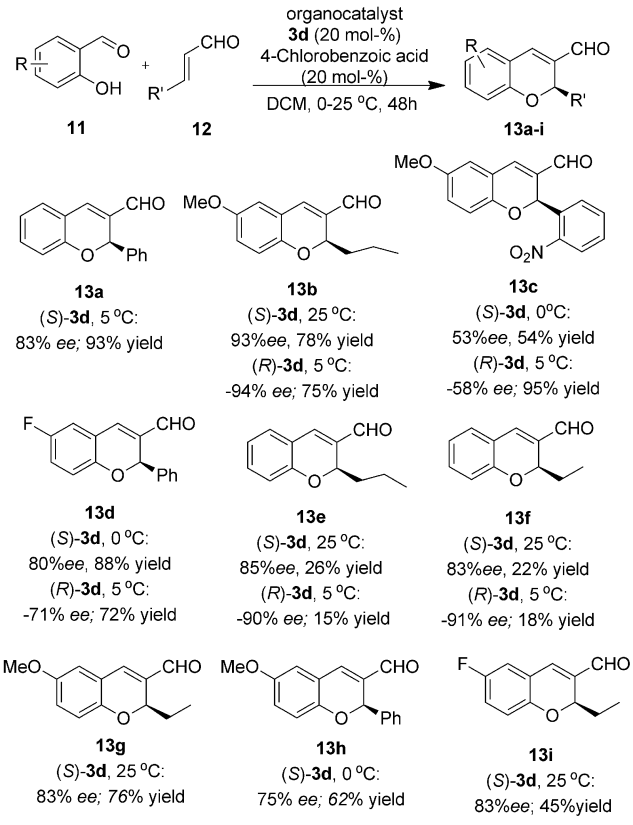


Scheme 5. Direct organocatalytic asymmetric domino oxa-Michael/aldol reactions of salicylaldehyde and *trans*-cinnamaaldehyde reported by different groups.[19]

Initially, we set out to investigate the catalytic activity of (*S*)-**3d** in the sequential addition of salicylaldehyde and *trans*-cinnamaldehyde under different conditions. An investigation on the effect of acid, base, and Lewis acidic additives on the reaction and extensive optimization of reaction conditions determined that *p*-chlorobenzoic acid and molecular sieves provided the highest enantioselectivity (83 %*ee*) and isolated yield (93 %).

The optimized reaction conditions were applied to several α,β-unsaturated aldehydes **11** and salicylaldehydes **12** to probe the scope of the domino oxa-Michael/aldol process. As the data in Scheme 6 show, the reaction appears to have a broad scope, but efficiencies (15–93 % yield) and enantioselectivities (58–94 %*ee*) varied with the electronic and steric nature of **11** and **12**. We found that the use of 5-methoxysalicyclaldehyde resulted in increased yields, and the use of aliphatic α,β-unsaturated aldehydes led to good to excellent enantioselectivities (83–94 %*ee*). Notably, among the substrates investigated, the organocatalyst (*S*)- or (*R*)-**3d** gave better efficiencies and enantioselectivities compared to those of **3a** in this reaction; for example, for **13b**, **3d** gave 94 %*ee* and 75% yield, and **3a** resulted in 90 %*ee* and a poor yield (21 %).[19a] The results showed that relatively higher *ee* values and yields were consistently observed for **3d** in this reaction.[20] Although the enantioselectivities and yields for several structural motifs were unsatisfactory, it is still one of the most efficient methods for the preparation of chiral chromenes from readily available starting materials and the results show that modifying Jørgensen–Hayashi catalysts with an amino group on the diaryl prolinol silyl ether enhances stereoselectivity in this transformation.

Although the origin of the enantioselectivity in the diarylprolinol silyl ether-catalysed transformation through enamine or iminium catalysis has been investigated spectroscopically and with DFT calculations,[21] it is still difficult



Scheme 6. Organocatalytic asymmetric oxa-Michael/aldol reactions.

to explain the slight steric difference between diphenylprolinol silyl ether **3a** and tertiary amine-modified diarylprolinol silyl ether **3d** on enantioselective induction. However, as the initial screening of catalysts showed the importance of the tertiary amine group, we believe that the electronic effect of the amine enhances the enantioselective activity of the chiral seconary amine. Considering the small structural and electronic differences between **3a** and **3d**, the study of the enhanced enantioselectivity with **3d** is surprising. In an effort to demonstrate the structural discrepancies between **3a** and **3d**, the electronic properties of **3a** and **3d** with different groups (H and CH_2NMe_2, respectively) were investigated by UV/Vis and CD spectroscopy. The structural information obtained from these methods appear quite indirect, but they present many advantages compared to more conventional spectroscopy in the elucidation of electronic properties.

The electronic absorption spectra of **3a** and **3d** display several intense absorption bands between 220 and 300 nm (Figure 1). The spectrum of **3d** is redshifted compared to that of **3a**, which indicates the presence of a different π-conjugated system within the aryl ring that is though to arise from a p orbital conjugated, electron-withdrawing CH_2NMe_2 group and n→π* transition.

CD spectroscopy has been shown to be a sensitive and powerful tool for analytical applications.[22] To elucidate the difference between **3a** and **3d**, we have investigated and compared the chiroptical properties of the chiral **3a** and **3d**

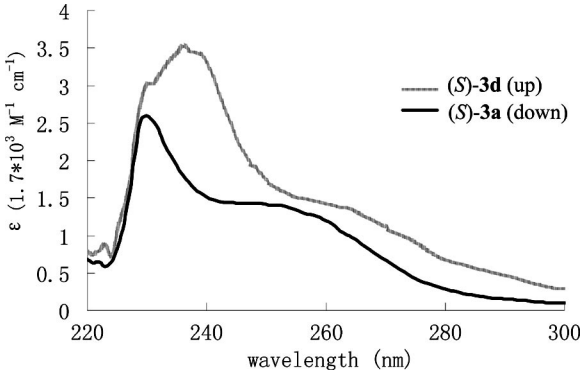


Figure 1. UV/Vis spectra of (*S*)-**3d** and (*S*)-**3a** in CH_2Cl_2.

by CD in CH_2Cl_2. As shown in Figure 2, we can see that the chiroptical properties of diarylprolinol silyl ethers appear to be dominated by the two geminal aryl rings that reflect n–π* and π–π* transitions due to the existence of the H and CH_2NMe_2 groups, respectively. Moreover, the differences between **3a** and **3d** reflect the electronic nature of the CH_2NMe_2 group in **3d**. UV/Vis and CD spectroscopy provide a cross-validation method to elucidate the slight difference between the electron-withdrawing **3d** and **3a**, which gives indirect evidence for the enhancement of enantioselective induction with catalyst **3d** in the above transformations. Very recently, Zeitler and Gschwind et al.[23] demonstrated that the electronic contributions of electron-donating groups and electron-withdrawing groups should have the opposite effect on the enamine amounts and the stability of enamine intermediates. Therefore, in analogy to this new investigation and on the basis of experimental results, we

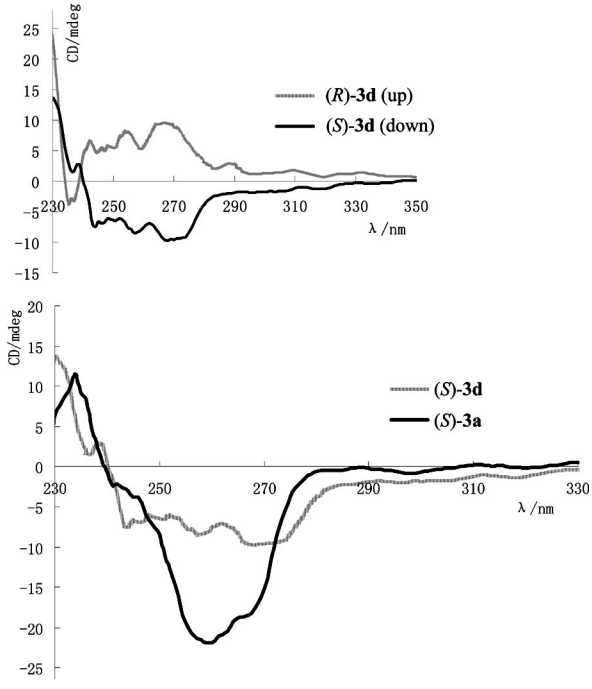


Figure 2. CD spectra of (*R*)-**3d** and (*S*)-**3d** (top) and (*S*)-**3d** and (*S*)-**3a** (bottom) in CH_2Cl_2.

can conclude that the enantioselective induction and the rate of diarylprolinol silyl ether-catalyzed transformations are largely dependent on the electronic effect of the aryl substitutents.

Conclusions

We have shown that the tertiary amine-modified diarylprolinol silyl ether **3d** can be successfully used as an efficient organocatalyst in the sequential reaction of β-nitroacrylate, aldehydes, toluenethiol, and ethyl 2-(diethoxyphosphoryl)-acrylate. Notably, this strategy improved the enantioselectivity from 87–95 %*ee* without affecting the conversion. The reaction proceeds with superior and complete regioselectivity with a very high enantioselectivity to furnish almost stereoisomerically pure, highly functionalized, polysubstituted cyclohexanes. In addition, we have demonstrated an improved protocol for the domino oxa-Michael/aldol reaction of salicyladehydes with α,β-unsaturated aldehydes in which recyclable **3d** was used as an effective organocatalyst. This protocol resulted in the formation of chiral chromenes with comparably good enantioselectivities (up to 94 %*ee*). Finally, UV/Vis and CD spectroscopy provide a cross-validation method, which elucidates the slight difference between electron-withdrawing tertiary amine-modified diarylprolinol silyl ether **3d** and diphenylprolinol silyl ether **3a**. This gives indirect evidence for the enhancement of enantioselective induction with **3d** in these transformations. Although the current organocatalytic route has some limitations in terms of yields and enantioselectivities, the oxa-Michael/aldol reaction constitutes a direct catalytic asymmetric route to chiral chromenes, and modifying Jørgensen–Hayashi catalysts with the introduction of an amino group on the diarylprolinol silyl ether enhances stereoselectivity in certain asymmetric transformations setting the benchmark for further development.

Experimental Section

General Remarks: All reagents and solvents were used directly without purification. Flash column chromatography was performed with silica (200–300 mesh). ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively with an Advance (Bruker) 400 MHz Nuclear Magnetic Resonance Spectrometer, and were referenced to internal solvent signals. TLC was performed using silica gel F254 TLC plates and visualized with ultraviolet light. HPLC was carried out with a Waters 2695 Millennium system equipped with a photodiode array detector. EI and CI mass spectra were performed with a Trace DSQ GC/MS spectrometer. The domino reaction products were confirmed by GC–MS, ^1H NMR, and ^{13}C NMR spectroscopy. The ESI-MS analysis of the samples was performed with an LCQ advantage mass spectrometer (ThermoFisher Company, USA), equipped with an ESI ion source in the positive ionization mode, with data acquisition using the Xcalibur software (Version 1.4). The diarylprolinol silyl ethers were synthesized according to reported procedures.[6–8,15–17]

Typical Procedure for One-Pot Asymmetric Domino-Tandem Reactions: *o*-Nitrobenzoic acid (66.8 mg, 20 mol-%)[18] was added to a

solution of aldehyde **1** (3 mmol), β-nitroacrylate **7** (2 mmol), and (*R*)-diarylprolinol trimethylsilyl ether **3d** (44 mg, 5 mol-%) in CH_2Cl_2 (4 mL) at room temperature. The reaction mixture was stirred overnight at room temperature followed by addition of ethyl 2-(diethoxyphosphoryl)acrylate **8** (708 mg, 3 mmol), and Cs_2CO_3 (6 mmol) at 0 °C. After the resulting suspension was stirred for additional 3 h at 0 °C, the solvent was removed under reduced pressure. EtOH (6 mL) was added, and the resulting mixture was stirred for 15 min at room temperature before addition of toluenethiol (10 mmol) at –15 °C. The resulting mixture was stirred for 36 h at room temperature before being quenched with cold 2 N HCl. The products in the aqueous layer were extracted three times into $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried with $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (silica gel) provided **10a**–**f**.

10a: 51% yield, 95 %*ee*, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, J = 8.0 Hz, 2 H), 7.06 (d, J = 8.0 Hz, 2 H), 4.61–4.68 (m, 1 H), 4.20–4.28 (m, 1 H), 4.06–4.17 (m, 2 H), 3.98–4.00 (t, J = 7.2 Hz, 1 H), 3.84–3.90 (m, 1 H), 3.77–3.81 (dd, J_1 = 3.6, J_2 = 10.8 Hz, 1 H), 3.38–3.44 (t, J = 10.8 Hz, 1 H), 3.12–3.18 (m, 1 H), 2.74–2.79 (dt, J_1 = 3.2, J_2 = 13.2 Hz, 1 H), 2.60–2.65 (dt, J_1 = 3.6, J_2 = 13.6 Hz, 1 H), 2.30–2.36 (m, 4 H), 1.25–1.30 (m, 6 H), 1.16–1.20 (t, J = 7.2 Hz, 4 H), 0.72–0.76 (t, J = 7.2 Hz, 3 H), 0.62–0.65 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 170.1, 137.7, 133.0, 131.4, 129.6, 83.4, 80.4, 76.8, 61.8, 61.6, 52.8, 49.2, 43.5, 27.0, 25.1, 23.7, 21.2, 14.2, 9.0, 8.5 ppm. IR (film): $\tilde{\nu}_{max}$ = 2965, 2937, 2878, 1733, 1557, 1493, 1463, 1376, 1290, 1260, 1197, 1033, 953, 810 cm^{-1}. ESI-MS: m/z = 481.83. The *ee* value of the product was determined by HPLC with a Daicel IA column (hexane/*i*PrOH = 90:10), flow rate 1.0 mL min^{-1}, t_{major} = 5.704 min; t_{minor} = 8.542 min.

10b: 45% yield, > 99 %*ee*, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.38 (d, J = 8.0 Hz, 2 H), 7.05–7.07 (d, J = 8.0 Hz, 2 H), 4.65–4.72 (m, 1 H), 4.07–4.22 (m, 4 H), 3.91 (m, 1 H), 3.80–3.84 (m, 1 H), 3.03–3.09 (t, J = 11.2 Hz, 1 H), 2.77–2.82 (dt, J_1 = 3.2, J_2 = 12.0 Hz, 1 H), 2.65–2.70 (dt, J_1 = 3.2, J_2 = 13.6 Hz, 1 H), 2.28–2.32 (m, 4 H), 1.72–1.87 (m, 2 H), 1.24–1.27 (t, J = 7.2 Hz, 3 H), 1.13–1.67 (t, J = 7.2 Hz, 3 H), 0.59–0.63 (t, J = 7.2 Hz, 3 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 170.5, 137.7, 132.6, 131.0, 129.8, 84.9, 61.5, 61.3, 51.0, 48.2, 46.4, 27.6, 23.4, 21.1, 14.1, 14.0, 11.4 ppm. IR (film): $\tilde{\nu}_{max}$ = 2975, 2940, 1730, 1552, 1491, 1474, 1374, 1320, 1297, 1266, 1201, 1164, 1138, 1103, 1037, 957, 866, 808 cm^{-1}. ESI-MS: m/z = 868.76 (dimer + Na). The *ee* value of the product was determined by HPLC with a Daicel IA column (hexane/*i*PrOH = 90:10), flow rate 1.0 mL min^{-1}, t_{major} = 6.147 min; t_{minor} = 6.553 min.

10c: 45% yield, > 99 %*ee*, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.36 (d, J = 8.0 Hz, 2 H), 7.07–7.09 (d, J = 8.0 Hz, 2 H), 4.67–4.74 (m, 1 H), 4.08–4.23 (m, 4 H), 3.84–3.90 (m, 1 H), 3.73 (m, 1 H), 3.00–3.05 (t, J = 11.2 Hz, 1 H), 2.84–2.89 (dt, J_1 = 3.2, J_2 = 13.2 Hz, 1 H), 2.68–2.73 (dt, J_1 = 3.6, J_2 = 13.6 Hz, 1 H), 2.28–2.34 (m, 4 H), 1.26–1.29 (t, J = 7.2 Hz, 3 H), 1.03–1.12 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 170.2, 137.5, 133.4, 132.2, 129.8, 84.6, 61.5, 61.3, 55.5, 48.5, 46.4, 39.5, 27.4, 21.1, 17.8, 14.2, 13.9 ppm. IR (film): $\tilde{\nu}_{max}$ = 2982, 2906, 1730, 1551, 1492, 1483, 1453, 1379, 1366, 1283, 1260, 1203, 1143, 1085, 1035, 939, 866, 809 cm^{-1}. ESI-MS: m/z = 840.76 (dimer + Na). The *ee* value of the product was determined by HPLC with a Daicel IA column (hexane/*i*PrOH = 90:10), flow rate 1.0 mL min^{-1}, t_{major} = 7.062 min; t_{minor} = 9.660 min.

10d: 43% yield, 92 %*ee*, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.18 (m, 3 H), 7.09–7.11 (d, J = 8.4 Hz, 2 H), 7.00–7.01 (d, J = 7.6 Hz, 2 H), 6.84–6.86 (t, J = 3.2 Hz, 2 H), 4.73–4.80 (m, 1 H), 4.13–4.22 (m, 4 H), 3.84–3.92 (m, 1 H), 3.69 (m, 1 H), 3.18–3.19 (d, J = 3.2 Hz, 1 H), 2.98–3.00 (m, 1 H), 2.68–2.74 (m, 2 H), 2.42–2.49 (m, 2 H), 2.30 (s, 3 H), 1.26–1.27 (m, 3 H), 1.00–1.03 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR(100 MHz, $CDCl_3$): δ = 172.3, 170.1, 137.8, 137.3, 131.8, 130.9, 129.7, 129.3, 129.1, 128.8, 128.5, 126.5, 85.0, 61.7, 61.1, 50.2, 48.2, 46.1, 45.8, 36.3, 27.4, 21.1, 14.2, 13.9 ppm. IR (film): $\tilde{\nu}_{max}$ = 3028, 2980, 2932, 2870, 1730, 1552, 1494, 1455, 1370, 1371, 1290, 1257, 1213, 1163, 1116, 1094, 1029, 952, 866, 810, 739, 700 cm^{-1}. ESI-MS: m/z = 992.73 (dimer + Na). The *ee* value of the product was determined by HPLC with a Daicel AD-H column (hexane/*i*PrOH = 95:5), flow rate 1.0 mL min^{-1}, t_{major} = 9.926 min; t_{minor} = 11.895 min.

10e: 45% yield, 98 %*ee*, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.40 (d, J = 8.0 Hz, 2 H), 7.06–7.08 (d, J = 8.0 Hz, 2 H), 4.65–4.72 (m, 1 H), 4.12–4.23 (m, 4 H), 3.94–3.99 (m, 1 H), 3.91 (m, 1 H), 3.07–3.13 (t, J = 11.2 Hz, 1 H), 2.78–2.83 (dt, J_1 = 3.2, J_2 = 13.2 Hz, 1 H), 2.68–2.72 (dt, J_1 = 3.6, J_2 = 13.6 Hz, 1 H), 2.30–2.32 (m, 4 H), 1.21–1.29 (m, 14 H), 0.83–0.87 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 170.6, 137.7, 132.6, 131.3, 129.8, 85.0, 61.5, 61.4, 51.7, 48.2, 46.4, 45.0, 31.9, 30.5, 29.5, 29.4, 29.2, 27.7, 26.9, 22.7, 21.1, 14.2, 14.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 2926, 2852, 1732, 1558, 1493, 1439, 1378, 1366, 1319, 1290, 1261, 1200, 1158, 1135, 1034, 886, 812, 560 cm^{-1}. ESI-MS: m/z = 1036.89 (dimer + Na). The *ee* value of the product was determined by HPLC with a Daicel IB column (hexane/*i*PrOH = 97:3), flow rate 0.5 mL min^{-1}, t_{major} = 13.148 min; t_{minor} = 16.596 min.

10f: 45% yield, 90 %*ee*, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 8.0 Hz, 2 H), 7.06 (d, J = 8.0 Hz, 2 H), 4.61–4.68 (m, 1 H), 4.23–4.31 (m, 1 H), 4.03–4.11 (m, 3 H), 3.81–3.87 (m, 2 H), 3.38–3.43 (t, J = 10.8 Hz, 1 H), 2.78–2.83 (dt, J_1 = 3.2, J_2 = 13.2 Hz, 1 H), 2.60–2.65 (dt, J_1 = 3.6, J_2 = 13.6 Hz, 1 H), 2.29 (s, 3 H), 1.25–1.29 (t, J = 7.2 Hz, 4 H), 1.15–1.19 (t, J = 6.8 Hz, 3 H), 0.75 (s, 9 H), –0.04 (s, 3 H), –0.24 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 169.9, 137.5, 132.7, 131.1, 129.6, 83.1, 73.1, 61.7, 61.5, 61.6, 55.5, 50.4, 43.5, 26.7, 25.5, 21.1, 17.8, 14.0, 13.9, –4.3, –5.6 ppm. IR (film): $\tilde{\nu}_{max}$ = 2960, 2934, 2858, 1737, 1727, 1554, 1490, 1473, 1448, 1380, 1366, 1329, 1290, 1279, 1252, 1196, 1156, 1126, 1138, 1034, 930, 887, 840, 815, 780, 673 cm^{-1}. ESI-MS: m/z = 1072.71 (dimer + Na). The *ee* value of the product was determined by HPLC with a Daicel IA column (hexane/*i*PrOH = 90:10), flow rate 1.0 mL min^{-1}, t_{major} = 4.929 min; t_{minor} = 6.415 min.

General Procedure for the Addition of 2-Hydroxybenzaldehydes to Cinnamaldehyde: To a solution of *trans*-cinnamaldehyde (0.5 mmol) in the presence of catalyst (20 mol-%), acid, and 4 Å molecular sieves (250 mg) in CH_2Cl_2 (2.5 mL) was added salicylaldehyde (1.0 mmol) and the resulting solution was stirred at room temperature for the specified time. The reaction mixture was directly purified by silica gel chromatography and fractions were collected and concentrated in vacuo to give the pure product. This is a known compound with spectroscopic properties in accordance with those reported.[19]

Supporting Information (see footnote on the first page of this article): General remarks and the procedure of the organocatalytic domino reaction, spectroscopic data and HPLC diagrams for the domino adducts **10a**–**f** and **13a**–**i**.

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[20] Under almost the same reaction conditions in the presence of catalyst (*S*)-**3a** (see Table 3 in ref.[19a]), the diphenylprolinol silyl ether **3a** gave the corresponding products **13a**, **13c**, **13e**, and **13h**, in 60 %*ee* (63% yield), 29 %*ee* (54%yield), 69 %*ee* (25% yield), and 44 %*ee* (70% yield), respectively.

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