SHORT COMMUNICATION

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Enantioselective Organocatalytic Conjugate Addition of Alkenes to α,β-Enones

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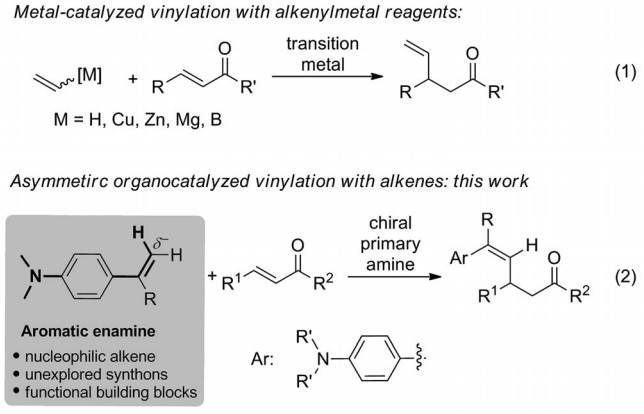
Keywords: Synthetic methods / Organocatalysis / Conjugate addition / Enamines / Alkenes / Enantioselectivity

We report the first example of the enantioselective conjugate addition of alkenes (aromatic enamines) to enones catalyzed by chiral primary amines. The reactions encompass a plethora of α,β-enones including difficult α-substituted vinyl ketones to give vinylation adducts in high yields with good enantioselectivity. The methodology is of synthetic potential in accessing chiral functional materials.

Introduction

Conjugate addition to α,β-unsaturated carbonyl compounds is among the most utilized organic reactions for C–C bond formation.[1] Simple alkenes are less employed in conjugate addition reactions owing to their low nucleophilicity as well as difficulties in controlling the chemo- and stereoselectivity. Alternatively, vinylated organometallics such as Grignard reagents, organocopper reagents, organozinc reagents, and organoboron compounds have been widely employed in conjugate addition reactions to afford vinylated adducts [Scheme 1, Equation (1)].[2] Recently, notable progress was achieved in the direct conjugate addition of simple alkenes to enones by the aid of transition-metal catalysts[3] and Lewis acids catalysts.[4] In this context, organocatalytic versions are still rare,[5] and the catalytic asymmetric direct conjugate addition of alkenes to α,β-unsaturated carbonyls has not been reported so far.



Scheme 1.

Recently, we found that *para*-vinylanilines underwent smooth C–C coupling with aldehydes to afford bisallylic adducts through Knoevenagel-type 1,2-addition.[6] The *para*-vinylanilines demonstrated nucleophilic reactivity closely resembling that of typical enamines [Scheme 1, Equation (2)] as a result of the conjugated *para*-amino groups. These electron-rich anilines have also been widely utilized as functional building blocks in organic electronics.[7] This feature, together with the now extensively explored C–H/C–X functionalization of anilines,[8] underlies enormous synthetic potential for *para*-vinylanilines, which remain largely unexplored. In this context, we have challenged these aromatic enamines as nucleophilic synthons in enantioselective C–C bond formation. Herein, we wish to report the enantioselective conjugate addition of vinylaniline to enones catalyzed by chiral primary amine catalysts to result in unprecedented organocatalytic direct addition reactions with alkenes.

Results and Discussion

Our studies started with the examination of the nucleophilic addition of vinylaniline **1a** to enone **2a**. After extensive screening of different diamine catalysts (see the Supporting Information for the screening results), we eventually identified chiral primary-tertiary diamine **3** derived from quinine[9,10] as the optimal aminocatalyst, which delivered the desired adducts in 97% yield with 76%*ee* (Table 1, entry 1). During the extensive screening, we noticed that acidic additives had a dramatic influence on the reaction outcome, and in this regard, aryl sulfonic acids were found to be the optimal acids in terms of both activity and enantioselectivity. Variations on the aryl ring were then examined to further improve the enantioselectivity (Table 1, entries 1–5). 2,4,6-Trimethylbenzenesulfonic acid (**5d**) was

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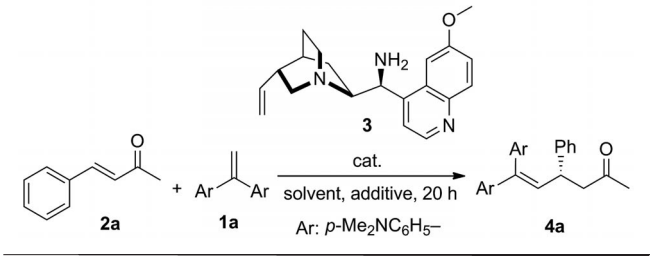
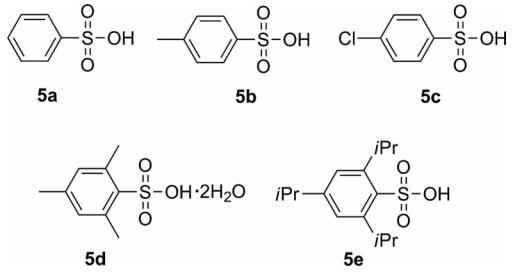
finally reached with a balance of activity and enantioselectivity (Table 1, entry 4). Optimization of the reaction parameters revealed that the reaction was more efficient with chloroform as the solvent (Table 1, entry 4 vs. entries 7 and 8), and the addition of molecular sieves (MS, 4 Å) led to a further improvement in the enantioselectivity (85% yield, 90%*ee*; Table 1, entry 10).

Table 1. Optimization of the reaction conditions.[a]



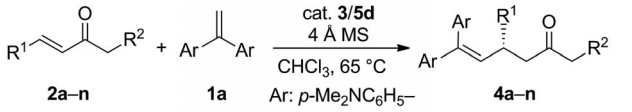
Entry	Acid	Solvent	*T* [°C]	Additive	Yield[b] [%]	*ee*[c] [%]
1	**5a**	$CHCl_3$	65	–	97	76
2	**5b**	$CHCl_3$	65	–	68	87
3	**5c**	$CHCl_3$	65	–	99	70
4	**5d**	$CHCl_3$	65	–	82	87
5	**5e**	$CHCl_3$	65	–	30	77
6	**5d**	CH_2Cl_2	40	–	41	68
7	**5d**	PhCl	65	–	66	81
8	**5d**	THF	65	–	47	80
9[d]	**5d**	$CHCl_3$	65	PPh_3	71	81
10[e]	**5d**	$CHCl_3$	65	4 Å MS	85	90
11[e]	**5d**	$CHCl_3$	25	4 Å MS	<5	68
12[e]	**5d**	$CHCl_3$	65	3 Å MS	88	88



[a] General conditions: **2a** (14.6 mg, 0.1 mmol), **1a** (53.2 mg, 0.2 mmol), solvent (0.5 mL), **3** (20 mol-%), acid (20 mol-%). [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Additive (10 mol-%). [e] MS (2 mg).

With the optimized conditions in hand, we next probed the scope of the conjugate addition for a variety of enones, and the results are presented in Table 2. The scope of the enones is quite general. Enones bearing either electron-donating (Table 2, entries 2, 6, and 7) or electron-withdrawn (Table 2, entries 3–5) groups were equally applicable in the reactions. Additionally, heterocyclic enones bearing furyl, thiophenyl, and benzofuryl substituents all worked very well to afford the desired products in good yields with good enantioselectivity (Table 2, entries 9–11). Notably, phenyl and ethyl ketones could also be used in the reactions, and they gave high yields of the desired adducts with moderate to good enantioselectivities (Table 2, entries 12 and13). Cyclohexenone was also examined in the reaction with vinylaniline **1a**; it provided the product in high yield but with low enantioselectivity (Table 2, entry 14).

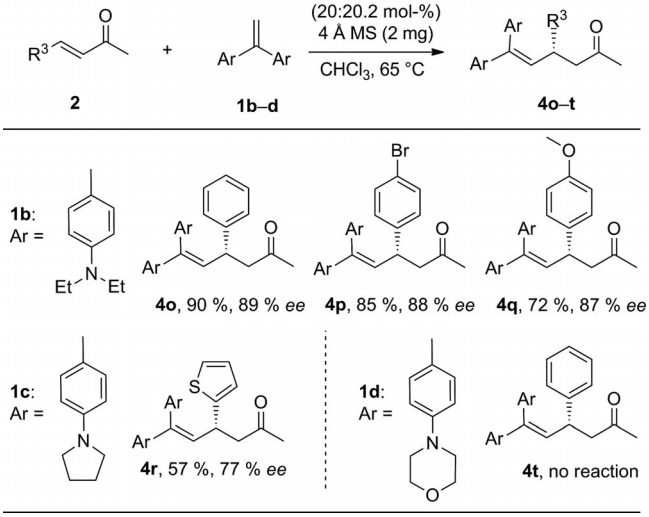
Table 2. Survey of different substituted enones in the primary amine catalyzed conjugate addition.[a]



Entry	R^1	R^2	Product	Yield[b] [%]	*ee*[c] [%]
1	Ph	H	**4a**	85	90
2	4-Bu	H	**4b**	70	92
3	4-Br	H	**4c**	94	81
4	2-Br	H	**4d**	95	84
5	2-Cl	H	**4e**	96	84
6	3,5-$(CH_3)_2O$	H	**4f**	93	90
7	3,4,5-$(CH_3)_3O$	H	**4g**	94	91
8	2-naphthyl	H	**4h**	75	91
9	2-furyl	H	**4i**	87	83
10	2-thiophenyl	H	**4j**	89	90
11	2-benzofuryl	H	**4k**	75	76
12	Ph	CH_3	**4l**	75	84
13	Ph	Ph	**4m**	96	54
14	$-(CH_2)_3-$		**4n**	98	30

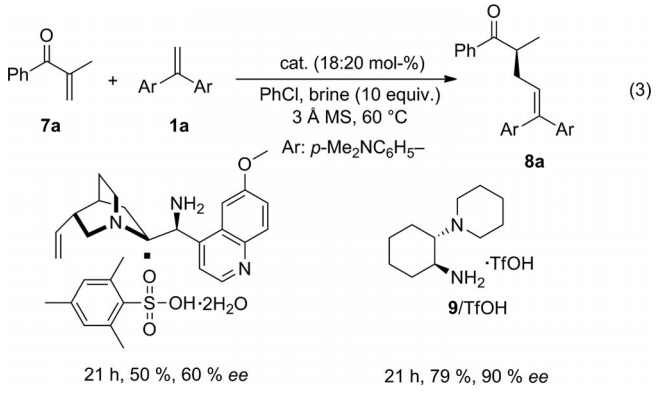
[a] General conditions: **2** (0.1 mmol), **1a** (0.2 mmol), **3/5d** (20:20 mol-%), 4 Å MS (2 mg), $CHCl_3$ (0.5 mL), 65 °C. [b] Yield of isolated product. [c] Determined by HPLC analysis.

The scope of the reaction with respect to the *para*-vinylanilines was next investigated (Scheme 2). Ethyl substituents on the *para*-amino group were tolerated, and corresponding adducts **4o**–**q** were obtained in good yields and high enantioselectivity. Replacement of the dialkylamino group with a pyrrolidine ring reduced the reactivity and the enantioselectivity, as observed with **1c**. Unfortunately, no reaction was observed if the dialkylamino group was replaced by the morpholine group (**1d**), likely a result of its poor electron-donating ability.



Scheme 2. Survey of different *para*-vinylanilines.

We next investigated the reactions with α-substituted vinyl ketones [Scheme 3, Equation (3)]. The enantioselective conjugate addition with α-substituted vinyl ketones remains elusive in asymmetric catalysis, as the stereocenter in this case is not generated in the C–C formation step, but in a rather challenging protonation step.[11] As a continuation of our explorations on asymmetric enamine protonations,[12] we challenged chiral primary amine catalysts in the direct alkene addition to vinyl ketones. Identified β-selective catalyst **3/5d** gave only 50% yield and 60%*ee* in the α-stereogenic reaction (Scheme 3). After screening, our previously developed primary amine catalyst **9**/trifluoromethanesulfonic acid (TfOH)[12d] was found to give the best results (79% yield, 90%*ee*) under the optimized conditions.



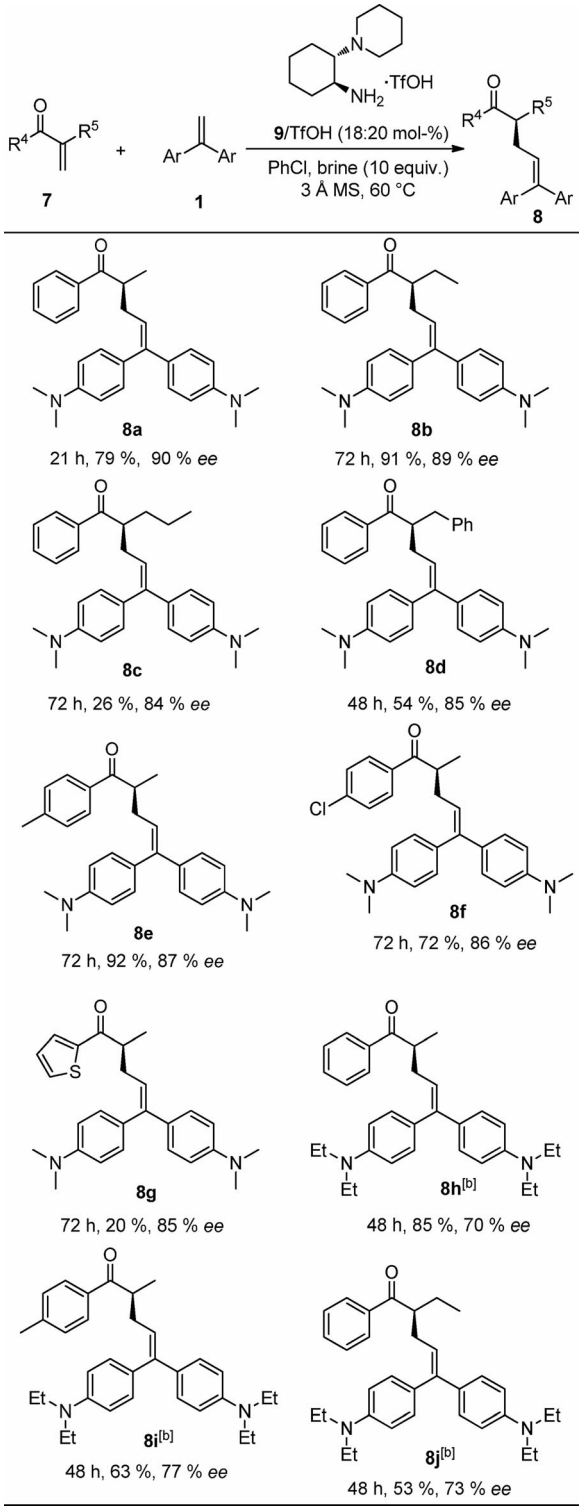
Scheme 3. Enantioselective conjugate addition with α-substituted vinyl ketones.

The substrate scope of the enantioselective protonation reaction was explored (Table 3). α-Methyl and α-ethyl vinyl ketones showed very good yield and high enantioselectivity (Table 3, compounds **8a** and **8b**). Upon changing the methyl substituent to a bulky group, such as propyl or benzyl, the enantioselectivity was maintained, but the reactivity decreased (Table 3, compounds **8c** and **8d**). Enones bearing either electron-donating (Table 3, compound **8e**) and electron-withdrawing (Table 3, compound **8f**) groups were equally applicable in the reactions. Additionally, the reaction with thiophenyl-substituted enones worked well to afford the desired products with good enantioselectivity (Table 3, compounds **8g**). An ethyl-substituted aromatic enamine was also tested in the reaction, and in those reactions, the desired adducts were obtained in moderate to good yields and enantioselectivities (Table 3, compounds **8h** and **8j**).

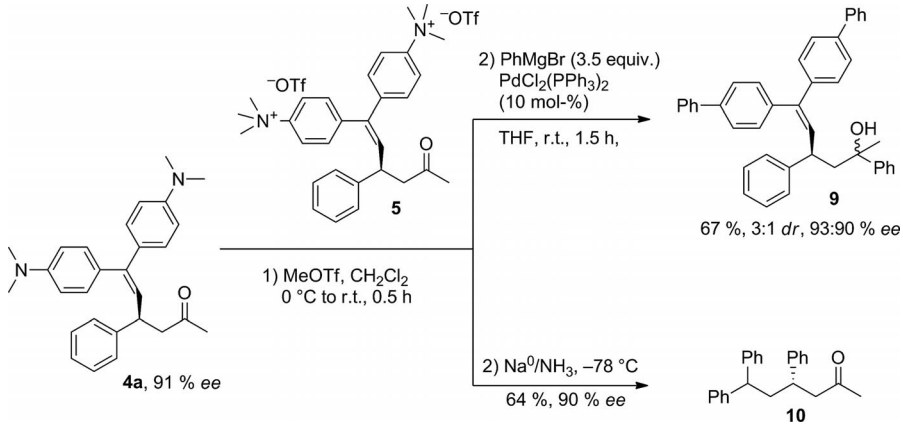
Anilines are very useful synthons in organic synthesis, and they can be transformed into many important molecules by C–H/C–X functionalization. We found that adduct **4a** could be successfully converted into ammonium triflates **5** in nearly quantitative yield.[13]

In situ generated ammonium salt **5** smoothly underwent Kumada-type coupling with a Grignard reagent, and in this instance, Grignard addition also occurred to the ketone moiety. The triphenylated adduct was isolated in 67% yield with 3:1 *dr* and maintained enantioselectivity (Scheme 4). The ammonium moiety was also be reduced to reveal a phenyl group under Birch reduction conditions (64% yield, 90%*ee*; Scheme 4).[14] Vinylation adduct **4c** was also readily

Table 3. The adducts of the enantioselective protonation reaction catalyzed by primary amines.[a]

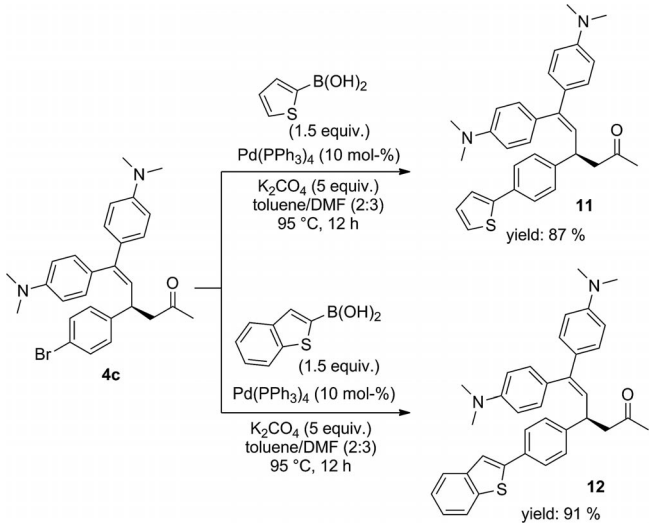


[a] General conditions: **7** (0.1 mmol), **1** (0.12 mmol), **9**/TfOH (18:20 mol-%), 3 Å MS (2 mg), brine (10 equiv.), PhCl (0.5 mL), 60 °C. [b] **7** (0.1 mmol), **1** (0.12 mmol), **9**/TfOH (18:20 mol-%), PhCl (0.5 mL), 60 °C.



Scheme 4. Further transformation of the aniline moiety.

derivatized with thiophene and benzothiophene through typical Suzuki coupling, which led to conjugated aromatics (Scheme 5).[15]

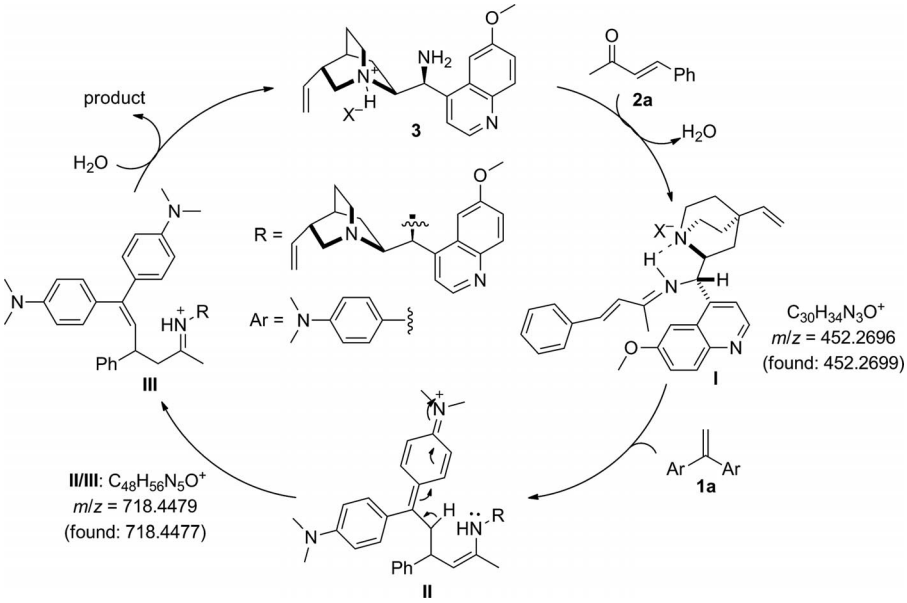


Scheme 5. Further functionalization of adduct **4c**.

A typical iminium-ion cycle is proposed for the alkene addition reactions (Scheme 6).[16,17] Critical iminium ion intermediate **I** (*m*/*z* = 452.2699) as well as catalyst–product adduct **II/III** (*m*/*z* = 718.4477) can be detected by ESI-MS analysis of the reaction mixture, which verifies the aminocatalytic nature of this reaction.

Conclusions

In summary, we developed an unprecedented enantioselective conjugate addition of alkenes to enones under mild reaction conditions. The reaction is enabled by chiral primary amines through a typical iminium ion cycle, and both β-substituted and unsubstituted α,β-enones can be incorporated to give vinylation adducts in high yields with good enantioselectivity.[18] The obtained conjugated adducts, endowed with their versatile derivatization sites as demonstrated, are of potential as chiral organic electronics. Further exploration of the nucleophilic features of *para*-vinylanilines in catalysis as well as investigations into the applications of the obtained conjugated molecules are ongoing.



Scheme 6. Proposed catalytic cycle for the conjugate addition.

Experimental Section

General Information: Commercial reagents were used as received, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were measured with a NMR instrument (300 MHz for ^{1}H, 75 MHz for ^{13}C). Tetramethylsilane served as the internal standard for the ^{1}H NMR spectra, and $CDCl_3$ served as the internal standard for the ^{13}C NMR spectra. The enantiomeric excess values were determined by HPLC analysis on Chiral Daicel Chiralcel AD-H, IA-H, and OD-H columns. The IR spectra were obtained by using an FTIR spectrometer (Thermo Fisher Nicolet 6700). Optical rotations were measured by using a 0.5 mL cell with a 0.25 dm path length and a high accuracy polarimeter Rudolph Autopl VI. HRMS was recorded with a commercial instrument (EI or ESI Source).

Representative Procedure for the Enantioselective Conjugate Addition of Alkenes to Enones: To a solution of **3/5d** (11.2 mg, 20 mol-%) in $CHCl_3$ (0.5 mL) was added **2a** (0.1 mmol) and **1a** (0.2 mmol). Then, 4 Å MS (2 mg) were added into the tube. The resulting solution was stirred at 65 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was directly separated by flash column chromatography on silica gel (petroleum ether/ethyl acetate). Collected fractions were concentrated, and the product was dried under high vacuum.

Representative Procedure for the Enantioselective Protonation Reactions

Method A: Catalyst **9**/TfOH (18:20 mol-%) and α-substituted vinyl ketone **7** (0.1 mmol) were dissolved in PhCl (0.2 mL) and brine (18 μL), and the mixture was stirred for 15 min under ambient atmosphere at room temperature. To the mixture, aromatic enamine **1a** (0.12 mmol) was added. Then, 3 Å MS (2 mg) were added into the tube. The resulting solution was stirred at 60 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was directly separated by flash column chromatography on silica gel (petroleum ether/ethyl acetate). Collected fractions were concentrated, and the product was dried under high vacuum.

Method B: Catalyst **9**/TfOH (18:20 mol-%) and aromatic enamine **1b** (0.05 mmol) were dissolved in PhCl (0.2 mL), and the mixture was stirred for 5 min under ambient atmosphere at room temperature. To the mixture, α-substituted vinyl ketone **7** (0.1 mmol) was added. The resulted solution was stirred at 60 °C. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was directly separated by flash column chromatography on silica gel (petroleum ether/ethyl acetate). Collected fractions were concentrated, and the product was dried under high vacuum.

Supporting Information (see footnote on the first page of this article): Screening reactions, characterization data, crystallographic data, and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgments

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[17] X-ray crystal structures of compounds **8g** and **10** were determined, and the absolute configurations were assigned accordingly (see the Supporting Information for details). CCDC-989981 (for **8g**) and -989980 (for **10**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[18] The *para*-vinylanilines also reacted with α,β-enals to give mainly 1,2 adducts, see ref.[6]

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