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Pyrrolidinyl–Camphor Derivatives as a New Class of Organocatalyst for Direct Asymmetric Michael Addition of Aldehydes and Ketones to β-Nitroalkenes

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Abstract: Practical and convenient synthetic routes have been developed for the synthesis of a new class of pyrrolidinyl–camphor derivatives (**7a–h**). These novel compounds were screened as catalysts for the direct Michael addition of symmetrical α,α-disubstituted aldehydes to β-nitroalkenes. When this asymmetric transformation was catalyzed by organocatalyst **7f**, the desired Michael adducts were obtained in high chemical yields, with high to excellent stereoselectivities (up to 98:2 diastereomeric ratio (d.r.) and 99% enantiomeric excess (*ee*)). The scope of the catalytic system was expanded to encompass various aldehydes and ketones as the donor sources. The synthetic application was demonstrated by the synthesis of a tetrasubstituted-cyclohexane derivative from (*S*)-citronellal, with high stereoselectivity.

Keywords: camphor · citronellal · Michael addition · nitroalkenes · organocatalysis

Introduction

Nature is a master of asymmetric synthesis and enzymes are highly efficient biocatalysts in living systems. Besides enzymes and transition-metal complexes, organocatalysis is now renowned as a third powerful tool for the synthesis of potentially important optically active compounds.[1] In recent years, much attention has been paid to the development of asymmetric organocatalysis, with remarkable advances made by means of enamine or iminium catalysis.[2] There are many advantages to using small chiral molecules to catalyze asymmetric reactions: they are often inexpensive and readily available from natural resources (e.g., amino acids, alkaloids), stable in air and water, robust, and more importantly, they are environmentally friendly.[3]

The conjugate (Michael) addition is one of the most efficient and powerful atom-economical carbon–carbon bond-forming reactions in synthetic chemistry.[4] Organocatalytic conjugate addition is one of the most important strategies and broadly applicable asymmetric carbon–carbon bond-forming reactions, with a wide variety of donors and acceptors, can be employed.[5] In recent years, many methods have been developed for the direct asymmetric Michael additions of unmodified carbonyl compounds to nitroalkenes to produce enantiomerically enriched nitroalkanes.[6] Among these reactions, the Michael addition of α, α-disubstituted aldehydes to β-nitrostyrenes is of particular interest due to the all-carbon quaternary stereocenter possessed by the Michael products.[7] The synthesis of quaternary stereogenic centers is considered a challenging task in asymmetric synthesis.[8]

In our continued synthetic efforts toward the development of new organocatalysts,[9] we envision that a well-defined, rigid, bicyclic camphor scaffold can serve as an efficient stereocontrol element.[10] The assembly of pyrrolidine and camphor frameworks with an appropriate linker can constitute a new class of bifunctional organocatalysts.[11] Previously, we have designed and synthesized a series of camphor-based pyrrolidine organocatalysts for direct asymmetric aldol reactions on water.[9a,b] Recently, we have developed camphor-containing pyrrolidine derivatives that could serve as efficient bifunctional organocatalysts in the asymmetric Michael addition of aldehydes with β-nitroalkenes to produce Michael adducts with high chemical yields and stereoselectivities.[9c,d] Minor modifications to the structure of the organocatalysts may contribute significantly to the stereochemical outcome of a reaction. The pyrrolidine structur-

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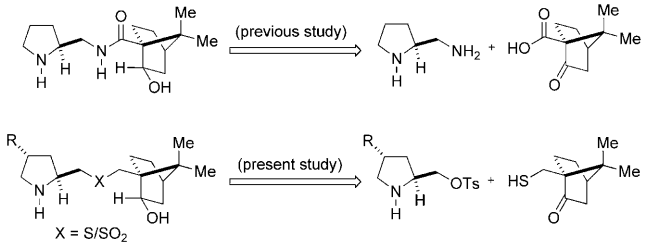
al unit and the camphor scaffold were linked with appropriate functionalities, such as sulfide and sulfone linkers, as illustrated in Scheme 1. In addition, the pyrrolidine C4-posi-

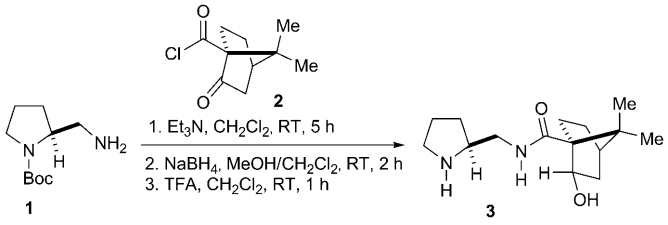


Scheme 1. Retrosynthesis of pyrrolidinyl–camphor-derived organocatalysts.

tion can be substituted with a hydroxyl group or a bulky silyl ether functionality. Furthermore, the camphor C2-carbon atom can be varied as a carbonyl group or an *exo*-hydroxyl group. In this context, we report the synthesis of a new class of organocatalysts, **3** and **7a–h**, and their applications for direct asymmetric Michael addition of a wide range of aldehydes and ketones to various nitroalkenes. The desired Michael products were obtained with high chemical yields and enantioselectivities when organocatalyst **7f** was used.

Results and Discussion

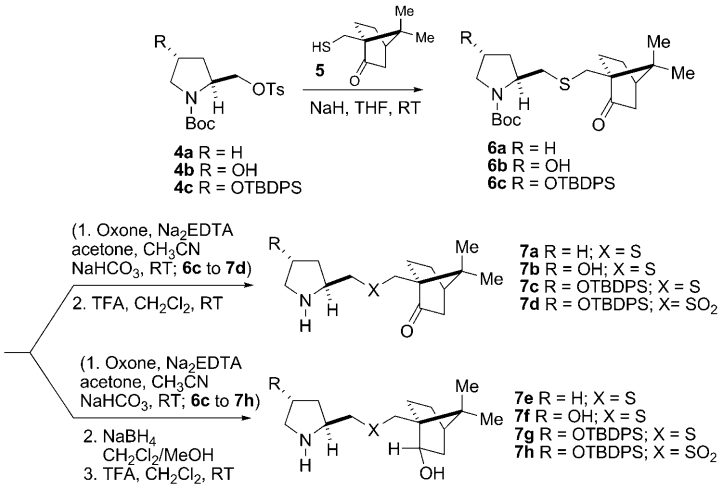
The design and synthesis of a readily accessible, highly stereoselective, and tunable catalyst is always desirable for asymmetric catalysis. We have developed an efficient synthesis of pyrrolidinyl–camphor organocatalyst **3**. We began with the known *tert*-butoxycarbonyl (Boc)-protected (*S*)-2-aminomethylpyrrolidine (**1**),[12] which was treated with ketopinic acid chloride (**2**) (derived from ketopinic acid and $SOCl_2$) in the presence of Et_3N (Scheme 2). $NaBH_4$ reduc-



Scheme 2. Synthesis of pyrrolidinyl–camphor organocatalyst **3**.

tion of the *N*-Boc-protected amide afforded the corresponding C2-*exo*-alcohol (camphor numbering), which was treated with trifluoroacetic acid (TFA) in CH_2Cl_2 to provide the desired organocatalyst **3**. The synthetic route to **3** is quite straightforward and can be scaled up to gram quantities.

We envisaged that organocatalysts **7a–h** could be easily prepared from the known L-proline-derived *N*-Boc-protected tosylate analogues (**4a–c**) and (1*S*)-1-(mercaptomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**5**)[13] (Scheme 3). The common intermediates, ketone sulfides **6a–c**, were ob-

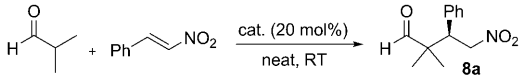


Scheme 3. Synthesis of novel pyrrolidinyl–camphor organocatalysts **7a–h**. Na_2EDTA = disodium ethylenediamine tetraacetate, TBDPS = tert-butyldiphenylsilyl.

tained by the nucleophilic-substitution reaction of *N*-Boc-*O*-tosyl prolinol derivatives (**4a–c**) with **5** in the presence of NaH as a base in 72–88% yield. Subsequently, *N*-Boc-deprotection of **6a–c** with TFA provided the desired organocatalysts **7a–c** in good to high chemical yields (60–94%). The sulfone-linked organocatalyst **7d** was obtained by oxidation of *N*-Boc-protected **6c** with Oxone in the presence of disodium ethylenediamine tetraacetate (Na_2EDTA) followed by cleavage of the Boc group. Reduction of *N*-Boc-protected **6a–c** with $NaBH_4$ afforded the corresponding C2-*exo* alcohols (camphor numbering) as a single diastereomers. This was followed by TFA treatment in CH_2Cl_2 to give the desired organocatalysts **7e–g** with high to excellent overall yields (82–98%). Sulfone organocatalyst **7h** was prepared with an overall yield of 86%, in a three-step reaction sequence from **6c**: oxidation, reduction, and deprotection. The structures of organocatalysts **3** and **7a–h** were fully characterized by IR, ^1H, and ^{13}C NMR spectroscopy, and HRMS techniques. The structure of catalyst **7b** was further confirmed by single-crystal X-ray data analysis (see the Supporting Information).[14]

With success in synthesizing the above organocatalysts, we tested the efficacy of **7a–h** in asymmetric reactions. Isobutyraldehyde and *trans*-β-nitrostyrene were used as model substrates for the Michael reaction under neat conditions in the presence of 20 mol% of **7a–h** at ambient temperature (Table 1). We first evaluated the pyrrolidinyl–camphor derivatives with a C2-ketone functionality (**7a–d**). Despite the high chemical yield obtained, only moderate enantioselectivity was observed when catalyst **7a** was used (Table 1, entry 1). The stereoselectivity was significantly improved by the presence of the *trans*-4-hydroxy group of pyrrolidine cat-

Table 1. Catalyst screening for the asymmetric Michael reaction of isobutyraldehyde with *trans*-β-nitrostyrene.[a]



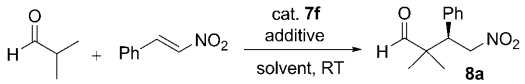
Entry	Catalyst	*t*	Yield [%][b]	*ee* [%][c]
1	**7a**	18 h	92	57
2	**7b**	18 h	91	87
3	**7c**	3 d	47	51
4	**7d**	3 d	25	40
5	**7e**	18 h	91	60
6	**7f**	12 h	93	91
7	**7g**	3 d	84	55
8	**7h**	3 d	32	33

[a] All reactions were carried out with isobutyraldehyde (4 equiv) and *trans*-β-nitrostyrene (1 equiv) in 20 mol% of organocatalyst (**7a–h**) under neat conditions at ambient temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

alyst **7b** (Table 1, entry 2). Interestingly, both the reactivity and stereoselectivity decreased noticeably when the *trans*-4-hydroxy group was protected as its TBDPS ether, with either sulfide- or sulfone-linked catalysts **7c** and **7d** (Table 1, entries 3 and 4). The organocatalysts **7e–h** were explored next. High chemical yield (91%) and moderate enantioselectivity (60% enantiomeric excess (*ee*)) was obtained with catalyst **7e** (Table 1, entry 5). With catalyst **7f** the presence of a hydroxyl group on the pyrrolidine ring restored high enantioselectivity (91% *ee*) (Table 1, entry 6). Both the reactivity and stereoselectivity diminished when the TBDPS-protected organocatalysts **7g** and **7h** were used (Table 1, entries 7 and 8). The data presented above indicates the importance of the presence of the *trans*-4-hydroxy group[6g,9d] (Table 1, entries 2 and 6), which may take part in the activation of substrates through hydrogen bonding and thus improve chemical activity and selectivity in the reaction.[15] The pyrrolidinyl–camphor sulfide **7f**, with an *exo*-hydroxyl group at the C2-carbon atom, emerged to be the most efficient catalyst for the Michael addition.

A survey of the reaction media was studied with **7f** as the catalyst. The reactivity was slow when the reaction was carried out in water, but increased when brine was used (Table 2, entries 1 and 2). Surprisingly, the Michael adduct **8a** was obtained after only 12 h in methanol, with excellent chemical yield and high selectivity (Table 2, entry 3). Both chemical yield and enantioselectivity decreased when the reaction was performed in ethanol, and further decreased when isopropyl alcohol was utilized (Table 2, entries 4 and 5). Similar results were observed when polar solvents, such as CH_3CN, DMSO, and THF, were used (Table 2, entries 6–8). The desired product **8a** was obtained with high chemical yield and enantioselectivity in CH_2Cl_2 at ambient temperature (Table 2, entry 9). Slight improvements on this result were observed when the reaction was carried out in nonpolar solvents, such as hexane or toluene, at ambient temperature (Table 2, entries 10 and 11). The stereoselectivity was further improved when the reaction was carried out at 0°C in toluene (Table 2, entry 13). Deviation of the amount of

Table 2. Optimization of the Michael reaction of isobutyraldehyde with *trans*-β-nitrostyrene.[a]



Entry	Catalyst [mol%]	Solvent	Additive [mol%]	*t* [d]	Yield [%][b]	*ee* [%][c]
1	20	H_2O	–	5.0	46	79
2	20	brine	–	1.5	78	88
3	20	MeOH	–	0.5	93	81
4	20	EtOH	–	1.0	84	65
5	20	IPA[d]	–	3.0	<10	n.d.
6	20	CH_3CN	–	3.0	<10	n.d.
7	20	DMSO	–	3.0	<10	n.d.
8	20	THF	–	3.0	<10	n.d.
9	20	CH_2Cl_2	–	1.0	88	88
10	20	hexane	–	1.0	90	89
11	20	toluene	–	1.0	90	93
12[e]	20	toluene	–	2.0	83	93
13[f]	20	toluene	–	3.0	78	96
14[g]	20	toluene	–	1.0	63	92
15[h]	20	toluene	–	1.0	80	94
16[i]	20	toluene	–	1.0	75	93
17	5	toluene	–	3.0	<10	n.d.
18	10	toluene	–	3.0	94	93
19	15	toluene	–	2.0	96	93
20	25	toluene	–	1.0	93	92
21	20	toluene	AcOH	1.0	80	94
22	20	toluene	PhCOOH	1.0	81	94
23	20	toluene	TsOH	3.0	<10	n.d.
24	20	toluene	TFA	3.0	<10	n.d.

[a] Unless otherwise specified, all reactions were carried out with isobutyraldehyde (4 equiv), *trans*-β-nitrostyrene (1 equiv), and **7f** (20 mol%) at ambient temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] IPA = isopropyl alcohol. [e] Reaction was carried out at 0°C–RT. [f] Reaction was carried out at 0°C. [g] 2 equiv of isobutyraldehyde was used. [h] 6 equiv of isobutyraldehyde was used. [i] 10 equiv of isobutyraldehyde was used.

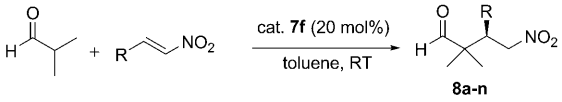
isobutyraldehyde under the same reaction conditions resulted in a decrease in chemical yields but retained enantioselectivity (Table 2, entries 14–16 versus 11).

Catalyst loading and additive effects were also studied. Only a trace amount of product **8a** was isolated when the catalyst loading was reduced to 5 mol% (Table 2, entry 17). Excellent chemical yields, without compromise to the enantioselectivity of the reaction, were obtained using catalyst loadings of 10 and 15 mol% (Table 2, entries 18 and 19) however, extended reaction times were required. An increase in catalyst loading to 25 mol% failed to improve the chemical yield or enantioselectivity (Table 2, entry 20 versus 11). The addition of a catalytic amount of Brønsted acid may promote the formation of the enamine species and subsequently improve reactivity. To test this, various organic acids were used as additives (20 mol%) in the reaction mixture. Comparable enantioselectivity but decreased chemical yields were observed when the reaction was carried out in the presence of acetic acid or benzoic acid (Table 2, entries 21 and 22). Surprisingly, adduct **8a** was obtained in trace amounts when 20 mol% of *p*-toluenesulfonic acid (TsOH) or TFA were used (Table 2, entries 23 and 24). This

may be due to protonation of the amine catalyst by the acid that deactivated the formation of the enamine species.

With the optimal reaction conditions realized, the scope and limitations of this reaction were explored by reaction of isobutyraldehyde with a variety of nitroalkenes (Table 3).

Table 3. Enantioselective Michael reaction of isobutyraldehyde with nitroolefins in the presence of catalyst **7f**.[a]



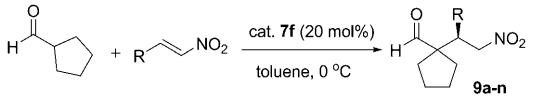
Entry	R=	Product	*t* [d]	Yield [%][b]	*ee* [%][c]
1	C_6H_5	**8a**	1.0	90	93
2	4-MeC_6H_4	**8b**	1.5	92	85
3	2-$MeOC_6H_4$	**8c**	5.0	73	72
4	3-$MeOC_6H_4$	**8d**	1.5	89	90
5	4-$MeOC_6H_4$	**8e**	2.0	88	81
6	3-$CF_3C_6H_4$	**8f**	1.0	89	94
7	2-BrC_6H_4	**8g**	2.0	85	89
8	3-BrC_6H_4	**8h**	2.0	88	93
9	4-BrC_6H_4	**8i**	1.0	90	92
10	3-ClC_6H_4	**8j**	1.0	92	93
11	4-ClC_6H_4	**8k**	1.0	90	93
12	2-thienyl	**8l**	0.5	92	87
13	2-furyl	**8m**	0.5	88	89
14	$PhCH_2CH_2$	**8n**	5.0	43	97

[a] All reactions were carried out with isobutyraldehyde (4 equiv), nitroalkene (1 equiv), and **7f** (20 mol%) at ambient temperature in toluene. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

All reactions were conducted in toluene at ambient temperature with 20 mol% of dihydroxyl sulfide catalyst **7f**. The reaction proceeded smoothly to afford Michael products **8a–k** in high chemical yields (73–92%) and with high enantioselectivity (72–94% *ee*) when aryl-substituted nitroalkenes were used (Table 3, entries 1–11). The reactivity and stereoselectivity were dependent on the aromatic substituent on the nitroalkene. Aromatic nitroalkenes with electron-donating (Table 3, entries 2–5) or -withdrawing (Table 3, entries 6–11) substituents were suitable substrates for the Michael addition. The reaction of heteroaromatic nitroalkenes also proceeded well with isobutyraldehyde to give Michael adducts **8l** and **8m** with high yields and enantioselectivities (Table 3, entries 12 and 13). Michael product **8n**, derived from an aliphatic nitrostyrene, was obtained in only 43% chemical yield, but with excellent enantioselectivity (97% *ee*) (Table 3, entry 14).

Encouraged by these results, cyclopentanecarboxaldehyde was treated with *trans*-β-nitrostyrene. Michael adduct **9a** was afforded with only a 79% enantioselectivity. The reaction conditions were further optimized to improve the reactivity and selectivity. After several studies, we found that the reaction proceeded smoothly at 0°C in toluene and the desired Michael product **9a** was obtained with high yield (88%) and enantioselectivity (94% *ee*) (Table 4, entry 1). The generality of the Michael reaction of cyclopentanecarboxaldehyde with various nitroalkenes catalyzed by **7f** was

Table 4. Enantioselective Michael reaction of cyclopentanecarboxaldehyde with nitroolefins in the presence of catalyst **7f**.[a]



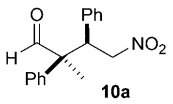
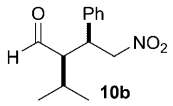
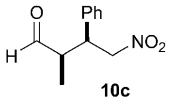
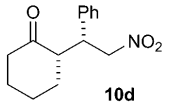
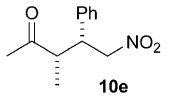
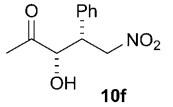
Entry	R=	Product	*t* [d]	Yield [%][b]	*ee* [%][c]
1	C_6H_5	**9a**	1.0	88	94
2	4-MeC_6H_4	**9b**	1.0	96	93
3	2-$MeOC_6H_4$	**9c**	5.0	68	69
4	3-$MeOC_6H_4$	**9d**	1.0	80	79
5	4-$MeOC_6H_4$	**9e**	2.0	85	75
6	3-$CF_3C_6H_4$	**9f**	1.0	92	95
7	2-BrC_6H_4	**9g**	5.0	88	92
8	3-BrC_6H_4	**9h**	2.0	86	93
9	4-BrC_6H_4	**9i**	1.5	90	91
10	3-ClC_6H_4	**9j**	1.0	90	95
11	4-ClC_6H_4	**9k**	1.0	95	95
12	2-thienyl	**9l**	1.0	91	88
13	2-furyl	**9m**	1.0	92	92
14	$PhCH_2CH_2$	**9n**	5.0	54	99

[a] All reactions were carried out with cyclopentanecarboxaldehyde (4 equiv), nitroolefin (1 equiv), and **7f** (20 mol%) at 0°C in toluene. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

explored. It is notable that this reaction tolerated a range of functional groups. The reaction proceeded smoothly with a wide range of aromatic nitroalkenes and gave good chemical yields and high to excellent levels of enantioselectivity (Table 4, entries 1–11). The methoxy-substituted aromatic nitroalkenes afforded only moderate results (Table 4, entries 3–5). To our satisfaction, heteroaromatic nitroalkenes reacted well with cyclopentanecarboxaldehyde under the optimal reaction conditions to give **9l** and **9m** with high enantioselectivities (Table 4, entries 12 and 13). The alkyl-substituted nitroalkene (4-nitrobut-3-enyl)benzene is also a suitable Michael acceptor for this catalytic system and gave the desired Michael product **9n** in moderate yield (54%) and excellent enantioselectivity (99% *ee*) (Table 4, entry 14).

After successfully developing an asymmetric transformation for symmetric α,α-disubstituted aldehydes, the scope of the system was expanded to incorporate various aldehydes and ketones. The use of unsymmetrical α,α-disubstituted aldehydes as nucleophiles remained a challenging task.[7d] Toward this end, the reaction of 2-phenylpropionaldehyde with *trans*-β-nitrostyrene was carried out in the presence of organocatalysts **7f** and **7g** (Table 5). The desired Michael adduct **10a** was obtained in good chemical yield and with high diastereoselectivity (93:7), but with only 12 and 50% enantioselectivity, respectively (Table 5, entry 1). Isovaleraldehyde and propionaldehyde were also employed as donors and provided the desired Michael adducts **10b** and **10c** with high yields, but low to moderate stereoselectivities (Table 5, entries 2 and 3). To further examine the generality of this asymmetric transformation, the organocatalytic asymmetric Michael addition of ketones to *trans*-β-nitrostyrene was investigated in the presence of catalyst **3** or **7f**. Cyclohexanone reacted to give the desired product **10d** in high chemi-

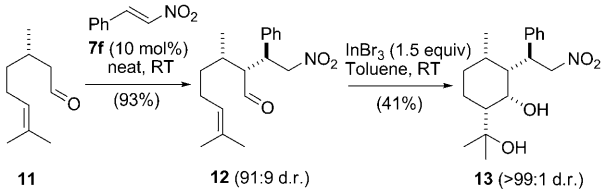
Table 5. Diastereo- and enantioselective Michael addition of aldehydes and ketones to *trans*-β-nitrostyrene.[a]

Entry	Product	Catalyst [20 mol%]	*t*	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	 **10a**	**7f**[e]	4 d	92	93:7	12
		7g[e]	7 d	45	93:7	50
2	 **10b**	**7f**[e]	2 d	86	91:9	72
3	 **10c**	**3**[f]	1 h	93	65:35	26
4	 **10d**	**3**[f]	1 d	95	89:11	73
		7f[f]	1 d	87	98:2	87
5	 **10e**	**3**[f]	2 d	45	99:1	63
		7f[f]	4 d	52	99:1	52
6	 **10f**	**3**[f]	12 h	76	70:30	56
		7f[f]	12 h	76	50:50	25

[a] All reactions were carried out using aldehyde/ketone (4 equiv), *trans*-β-nitrostyrene (1 equiv), and organocatalyst **3**, **7f**, or **7g** (20 mol%). [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy and HPLC analysis. [d] Determined by chiral HPLC analysis. [e] Reaction was carried out in MeOH (with **7f**) and toluene (with **7g**) at ambient temperature. [f] Reaction was carried out with $PhCO_2H$ (20 mol%) at ambient temperature under neat conditions.

cal yield and stereoselectivity, catalyzed by **3** or **7f** in the presence of benzoic acid under neat reaction conditions (Table 5, entry 4). 2-Butanone also worked well with catalysts **3** and **7f** and gave Michael adduct **10e** with excellent diastereomeric ratio (d.r.) and moderate chemical yields (Table 5, entry 5). The use of 2-hydroxy acetone furnished the corresponding adduct **10f** in a reasonable chemical yield (76%) with low to moderate stereoselectivity (Table 5, entry 6).

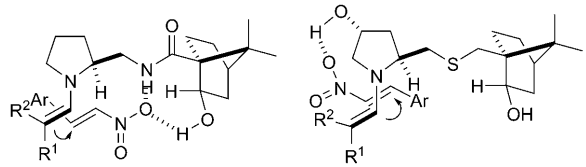
Citronellal is an important building block in organic synthesis for the synthesis of various pheromones and other natural products.[16] The base-catalyzed conjugate addition of citronellal to methyl vinyl ketone has been developed.[17] More recently, Alexakis and co-workers[18] employed citronellal as a donor for reaction with vinyl bis(sulfone) with excellent enantioselectivity. We selected citronellal as a donor partner for *trans*-β-nitrostyrene to demonstrate the synthetic utility of catalysts **3** and **7f**. The reaction of (*S*)-citronellal (**11**) with *trans*-β-nitrostyrene in the presence of organocatalyst **3** or **7f** afforded the desired adduct **12**. After extensive studies (see the Supporting Information), the optimum reaction conditions were realized (Scheme 4). To our delight, the reaction of **11** with *trans*-β-nitrostyrene proceeded smoothly under neat reaction conditions in the presence of



Scheme 4. Michael reaction of **11** with *trans*-β-nitrostyrene, followed by cyclization.

7f (10 mol%). The desired Michael product **12** was obtained with high chemical yield (93%) and diastereoselectivity (91:9). Adduct **12** was treated with $InBr_3$ in toluene to induce Prins-type cyclization. The desired tetrasubstituted-cyclohexane derivative **13** was obtained in 41% yield with excellent diastereoselectivity. The structures of **12** and **13** were fully characterized by IR, ^{1}H and ^{13}C NMR spectroscopies, and HRMS techniques. The structure and stereochemistry of **13** was further confirmed by single-crystal X-ray data analysis.[14]

The pyrrolidinyl–camphor-based catalysts **3** and **7f** could serve as bifunctional organocatalysts and share similar stereochemical bias. Although more studies are required to elucidate the reaction mechanism, the stereochemical outcome can be explained on the basis of the experimental results as follows: As proposed in Scheme 5, the pyrrolidine



Scheme 5. Proposed transition-state models for the asymmetric Michael reaction catalyzed by **3** (left) and **7f** (right).

reacts with a carbonyl compound to form an enamine intermediate. The organocatalyst **3** formed hydrogen bonds between the camphor C2-hydroxy and/or amide groups and the nitro functionality of the acceptor substrate. On the other hand, the nitro group was activated by the 4-hydroxy functionality in organocatalyst **7f** to organize a favorable transition model.[6g,9d] The neighboring rigid, bicyclic camphor scaffold serves as an efficient stereocontrol element. It is believed that the β-nitrostyrene approaches from the less-hindered bottom face in a favorable electrostatic interaction. The nucleophilic enamine attacks the nitroolefin from the *Si* face to generate the major product.

Conclusion

We have presented an efficient and convenient synthesis of a series of novel organocatalysts, **3** and **7a–h**, which contain a rigid pyrrolidinyl–camphor scaffold. The most promising

catalyst for the Michael addition (**7f**) emerged from the combination of the installation of a *trans*-4-hydroxy group on the pyrrolidine ring, a C2-hydroxyl group on the camphor scaffold, and a sulfide link. We have demonstrated the practical applications of organocatalyst **7f** for Michael reaction of symmetrical α,α-disubstituted aldehydes with a wide range of β-nitroalkenes. The products containing an all-carbon quaternary center were obtained with high to excellent levels of chemical yield and enantioselectivity under the optimized conditions. This method provides an alternative route for the efficient synthesis of versatile γ-nitro aldehydes. Moreover, both **3** and **7f** were found to be effective catalysts for reaction of various aldehydes and ketones with β-nitrostyrene to give the corresponding Michael adducts with moderate to high stereoselectivities. The synthetic application of **7f** was demonstrated by the reaction of **11** with *trans*-β-nitrostyrene to give tetrasubstituted-cyclohexane derivative **13** with high stereoselectivity.

Experimental Section

General remarks: All reagents were used as purchased from commercial suppliers without additional purification. IR spectra were recorded on a Perkin–Elmer 500 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) referenced to an internal TMS standard or $CHCl_3$ (77.0 ppm). Optical rotations were measured on a JASCO P-1010 polarimeter. HRMS were recorded on JEOL SX-102A instrument. The X-ray diffraction measurements were carried out at 298 K on a KAPPA APEX II CCD area-detector system equipped with a graphite monochromator and a $Mo_{K\alpha}$ fine-focus sealed tube ($\lambda = 0.71073$ Å). Routine monitoring of reactions was performed by using silica gel, glass-backed TLC plates (Merck Kieselgel 60 F_{254}) and visualized by UV light (254 nm). Flash column chromatography was performed on silica gel (230–400 mesh) with the indicated eluents. Air- or moisture-sensitive reactions were performed under inert atmospheric conditions.

Catalyst 3: A solution of **2** (1.5 g, 7.5 mmol) in CH_2Cl_2 (10 mL) was added slowly to a stirred solution of **1** (1.5 g, 7.5 mmol) and Et_3N (1.25 mL, 9 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred for 5 h at ambient temperature and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), washed with a saturated aqueous solution of NH_4Cl, an aqueous saturated solution of $NaHCO_3$, and brine. The mixture was extracted with CH_2Cl_2 (2×20 mL); the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate 2:1) to give the desired amide as a yellow viscous liquid (2.56 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.73$ (br s, 1H), 4.00–3.66 (m, 1H), 3.58–3.14 (m, 4H), 2.50–2.32 (m, 2H), 2.15–1.96 (m, 2H), 1.93–1.74 (m, 3H), 1.72–1.61 (m, 2H), 1.60–1.49 (m, 1H), 1.48–1.29 (m, 10H), 1.15 (s, 3H), 0.92 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 215.7$, 169.2, 155.1, 79.3, 65.0, 56.5, 49.7, 46.7, 43.6, 43.1, 42.4, 28.8, 28.3, 27.9, 27.4, 23.5, 20.6, 20.4 ppm; HRMS (FAB^+): *m/z*: calcd for $C_{20}H_{33}N_2O_4$: 365.2440 $[M]^+$; found: 365.2439.

The amide (2.56 g, 7.1 mmol) was dissolved in 10:1 CH_2Cl_2/MeOH (20 mL) and $NaBH_4$ (2.6 g, 71 mmol) was added portionwise (3 portions) at room temperature. After stirring for 2 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl, washed with brine, and the mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude *exo*-alcohol was purified by flash chromatography (hexane/ethyl acetate 1:1) to give the desired *exo*-alcohol as a yellow solid (2.49 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.93–7.80 (br s, 1H), 5.90–5.79 (br s, 1H), 4.13–4.06 (m, 1H), 4.06–3.95 (m, 1H), 3.47–3.26 (m, 3H), 3.26–3.12 (m, 1H), 2.16–1.95 (m, 2H), 1.95–1.79 (m, 4H), 1.79–1.55 (m, 3H), 1.46 (s, 9H), 1.26 (s, 3H), 1.20–1.05 (m, 2H), 1.04 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.7$, 156.8, 80.1, 79.2, 56.5, 55.9, 49.8, 47.1, 46.3, 45.6, 41.1, 29.7, 29.6, 28.5, 27.4, 23.9, 21.7, 21.0 ppm.

The *exo* alcohol (2.49 g, 6.8 mmol) was dissolved in CH_2Cl_2 (10 mL) and TFA (1.0 mL) was added at room temperature. After stirring for 1 h, the reaction was diluted with CH_2Cl_2, washed with 2 N NaOH, and the mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give **3** as a pale-yellow solid (1.68 g, 93%). M.p. 140–142 °C; $[\alpha]_D^{25} = +16.49$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.81$ (s, 1H), 4.02 (dd, $J = 7.8$, 3.5 Hz, 1H), 3.68 (br s, 2H), 3.57–3.46 (m, 1H), 3.38–3.25 (m, 1H), 3.17–2.98 (m, 1H), 2.91 (t, $J =$ 6.8 Hz, 2H), 2.19–1.98 (m, 1H), 1.97–1.88 (m, 2H), 1.86–1.60 (m, 5H), 1.49–1.32 (m, 1H), 1.32–1.19 (m, 4H), 1.16–1.04 (m, 1H), 1.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.8$, 77.9, 58.1, 58.0, 49.0, 46.2, 45.9, 43.0, 41.0, 30.2, 29.0, 27.0, 25.5, 21.6, 21.0 ppm; IR (neat): $\tilde{\nu} = 3271$, 2953, 2725, 1634, 1557 cm^{-1}; HRMS (FAB^+): *m/z*: calcd for $C_{15}H_{27}N_2O_2$: 267.2703 $[M+H]^+$; found: 267.2706; crystal data for **3** at 296(2) K; $C_{15}H_{26}N_2O_2$; M_r 266.38; monoclinic; *P2l*; $a = 8.0727(3)$ Å, $b = 9.2759(4)$ Å, $c = 10.3149(4)$ Å; $\alpha = 90.00$, $\beta = 96.558(2)$, $\gamma = 90.00$; $V = 767.34(5)$ Å^3; $F_{000} = 292$; $\lambda(Mo_{K\alpha}) = 0.71073$ Å; $Z = 2$; $\rho = 1.153$ mg m^{-3}; $\mu = 0.076$ mm^{-1}; 1389 reflections; 1 restraints; 173 parameters; $R = 0.0766$; $Rw = 0.2475$ for all data.

Catalyst 7a: Compound **5** (2.48 g, 13.5 mmol) was added to a stirred suspension of NaH (2.40 g, 56.3 mmol) in anhydrous THF (140 mL) under a nitrogen atmosphere. The reaction mixture was added dropwise to a solution of **4a** (4.00 g, 11.3 mmol) in anhydrous THF (40 mL) at ambient temperature. After stirring for 2 h, the reaction was quenched with H_2O at 0 °C and extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate 2:1) to afford **6a** as a colorless viscous liquid (77%). $[\alpha]_D^{33} = -17.6$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.99$–3.90 (m, 1H), 3.37–3.34 (m, 2H), 2.95–2.82 (m, 2H), 2.56–2.52 (m, 2H), 2.36 (d, $J = 18.3$ Hz, 1H), 2.10–2.01 (m, 3H), 2.00–1.91 (m, 2H), 1.86 (d, $J =$ 18.3 Hz, 3H), 1.48 (s, 9H), 1.48–1.45 (m, 1H), 1.40–1.38 (m, 1H), 1.05 (s, 3H), 0.91 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 216.9$, 154.1, 79.3, 60.7, 56.7, 47.6, 46.4, 43.3, 42.9, 38.1, 30.0, 29.7, 28.4, 26.7, 26.6, 23.5, 22.6, 20.1 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3469$, 2878, 2649, 1742, 1668, 1384 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{20}H_{33}NO_3S$: 367.2181; found: 367.2180.

Compound **6a** (1.00 g, 2.72 mmol) in CH_2Cl_2 (20 mL) was treated with TFA (4.04 mL, 54.4 mmol) at ambient temperature. After stirring for 1 h, the reaction mixture was quenched with H_2O and the resulting solution was adjusted to pH 9–10 with aqueous solution of $NaHCO_3$ (1.0 M). The reaction mixture was then extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to yield **7a** as a pale-yellow viscous liquid (0.67 g, 92%). $[\alpha]_D^{33} = +27.1$ ($c =$ 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.24$–3.20 (m, 1H), 2.98–2.93 (m, 2H), 2.87–2.80 (m, 2H), 2.78–2.74 (m, 2H), 2.29 (dt, $J = 6.7$, 3.6 Hz, 1H), 2.02–1.83 (m, 4H), 1.82–1.70 (m, 3H), 1.45–1.31 (m, 3H), 0.98 (s, 3H), 0.83 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 217.2$, 60.8, 57.8, 47.5, 45.8, 43.2, 42.9, 40.1, 30.7, 29.4, 29.3, 26.6, 26.5, 24.8, 20.0, 19.9 ppm; IR (CH_2Cl_2): $\tilde{\nu} = 3460$, 2955, 2881, 1739, 1683, 1538, 1416 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{15}H_{25}NO_2S$: 267.1657; found: 267.1665.

Catalyst 7b: Following the procedure described above for **6a**, compound **4b** was used for the synthesis of **6b**, which was isolated as a colorless viscous liquid (88%). $[\alpha]_D^{33} = -18.0$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.45$–4.41 (m, 1H), 4.19–4.11 (m, 1H), 3.61–3.43 (m, 2H), 2.92 (d, $J = 12.8$ Hz, 1H), 2.87 (d, $J = 12.8$ Hz, 1H), 2.72–2.67 (m, 1H), 2.57 (d, $J = 12.0$ Hz, 1H), 2.36 (dq, $J = 4.7$, 2.6 Hz, 1H), 2.15–2.02 (m, 3H), 2.01–1.95 (m, 3H), 1.86 (d, $J = 18.3$ Hz, 1H), 1.84–1.51 (m, 1H), 1.39 (s, 9H), 1.04 (s, 3H), 0.90 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 216.9, 154.3, 79.5, 68.4, 60.5, 55.4, 54.6, 47.4, 43.1, 42.7, 38.7, 37.7, 29.7, 28.1, 26.4, 26.3, 19.9, 19.8 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3424, 3055, 2959, 2878, 1742, 1668, 1407 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{20}H_{33}NO_4S$: 383.2130; found: 383.2138.

Following the procedure described above for **7a**, compound **6b** (1.00 g, 2.61 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (3.87 mL, 52.2 mmol) to afford **7b** as a yellow solid (0.44 g, 60%). M.p. 96–98 °C; $[\alpha]_D^{33}$ = +34.3 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.40 (t, *J* = 5.1 Hz, 1H), 3.61–3.54 (m, 1H), 3.40 (s, 2H), 3.11 (dd, *J* = 11.6, 4.7 Hz, 1H), 2.87 (d, *J* = 11.7 Hz, 1H), 2.82 (d, *J* = 13.0 Hz, 1H), 2.70–2.60 (m, 2H), 2.57 (d, *J* = 13.0 Hz, 1H), 2.39 (dq, *J* = 4.3, 2.6 Hz, 1H), 2.09–1.93 (m, 4H), 1.86 (d, *J* = 18.3 Hz, 1H), 1.67–1.60 (m, 1H), 1.55–1.49 (m, 1H), 1.41–1.35 (m, 1H), 1.05 (s, 3H), 0.90 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.4, 71.9, 60.8, 56.1, 54.6, 47.6, 43.2, 42.9, 41.1, 40.3, 29.4, 26.6 (2C), 20.0, 19.9 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3424, 2959, 2886, 1738, 1650, 1414 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{15}H_{25}NO_2S$: 283.1606; found: 283.1608; crystal data for **7b** at 273(2) K: $C_{15}H_{25}NO_2S$; M_r 283.42; orthorhombic; *P2l2l2l*; *a* = 9.0657(2) Å; *b* = 10.6218(2) Å, *c* = 31.5723(7) Å; *V* = 3040.23(11) Å^3; *Z* = 8; ρ = 1.238 mg m^{-3}; μ = 0.212 mm^{-1}; 19384 reflections; 0 restraints; 343 parameters; *R* = 0.0939; *Rw* = 0.1509 for all data.

Catalyst 7c: Following the procedure described above for **7a**, compound **4c** was used for synthesis of **6c**, which was isolated as a colorless viscous liquid (72%). $[\alpha]_D^{33}$ = −5.5 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 4H), 7.43–7.40 (m, 3H), 7.39–7.36 (m, 3H), 4.38–4.34 (m, 1H), 4.17 (s, 1H), 3.51 (d, *J* = 10.6 Hz, 1H), 3.22 (dd, *J* = 11.3, 4.2 Hz, 1H), 2.83 (d, *J* = 12.6 Hz, 2H), 2.66 (s, 1H), 2.52 (d, *J* = 12.6 Hz, 1H), 2.34 (dq, *J* = 4.7, 2.2 Hz, 1H), 2.15–2.07 (m, 1H), 2.05–2.00 (m, 1H), 1.99–1.94 (m, 1H), 1.93–1.87 (m, 1H), 1.86–1.72 (m, 3H), 1.47 (s, 9H), 1.45–1.43 (m, 1H), 1.04 (s, 9H), 1.00 (s, 3H), 0.87 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.2, 154.2, 135.2 (2C), 133.3 (3C), 129.4 (2C), 127.4 (4C), 79.2, 70.9, 60.4, 55.7, 55.2, 47.3, 43.1, 42.7, 39.7, 38.7, 29.8, 28.2 (2C), 26.5 (6C), 26.3, 19.9, 18.7 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3077, 2959, 2856, 1746, 1694, 1591, 1392 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{36}H_{51}NO_4SSi$: 621.3308; found: 621.3315.

Following the procedure described above for the synthesis of **7a**, TFA (0.36 mL, 4.83 mmol) was added to **6c** (1.0 g, 1.61 mmol) in CH_2Cl_2 (10 mL) to give **7c** as a colorless viscous liquid (0.79 g, 94%). $[\alpha]_D^{33}$ = +3.9 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.61 (m, 4H), 7.43–7.40 (m, 3H), 7.39–7.36 (m, 3H), 5.35 (br s, 1H; NH), 4.48–4.46 (m, 1H), 3.93–3.85 (m, 1H), 3.22 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.07 (d, *J* = 12.0 Hz, 1H), 2.86 (d, *J* = 13.2 Hz, 1H), 2.81–2.77 (m, 2H), 2.57 (d, *J* = 13.2 Hz, 1H), 2.36 (dq, *J* = 4.6, 2.1 Hz, 1H), 2.06–1.96 (m, 4H), 1.86 (d, *J* = 18.4 Hz, 1H), 1.65–1.57 (m, 1H), 1.54–1.49 (m, 1H), 1.38–1.34 (m, 1H), 1.06 (s, 9H), 1.02 (s, 3H), 0.90 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.5, 135.5 (4C), 133.5 (2C), 129.71 (2C), 127.7 (4C), 73.2, 61.0, 57.4, 54.5, 47.7, 43.5, 43.0, 40.8, 38.4, 29.4, 26.9 (2C), 26.8 (3C), 20.1, 20.0, 18.9 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3478, 3070, 2967, 2856, 1742, 1683, 1591, 1429 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{31}H_{43}NO_2SSi$: 521.2784; found: 521.2782.

Catalyst 7d: *N*-Boc-protected compound **6c** was dissolved in a mixture of CH_3CN (90 mL), aqueous Na_2EDTA (4×10^{-4} M, 60 mL), and acetone (30 mL) at ambient temperature. Oxone (3.00 g, 4.82 mmol) and $NaHCO_3$ (1.23 g, 14.46 mmol) were added portionwise and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate 4:1) to give the *N*-Boc-protected ketone sulfone (1.47 g, 93%). The obtained sulfone was dissolved in CH_2Cl_2 (20 mL) and was treated with TFA (0.50 mL, 6.75 mmol) at ambient temperature and stirred for 1 h. The mixture was quenched with H_2O (10 mL) and the resulting solution was adjusted to pH 9–10 with an aqueous solution of $NaHCO_3$ (1.0 M). The mixture was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic layer were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to give **7d** as a viscous liquid (1.18 g, 95%). $[\alpha]_D^{33}$ = +10.1 (*c* = 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.61 (m, 4H), 7.44–7.41 (m, 3H), 7.40–7.35 (m, 3H), 4.25–4.18 (m, 1H), 3.70 (d, *J* = 15.0 Hz, 1H), 3.37–3.32 (m, 2H), 3.10–3.01 (m, 2H), 2.82 (d, *J* = 15.0 Hz, 1H), 2.45–2.34 (m, 3H), 2.13–2.04 (m, 3H), 1.93 (d, *J* = 18.5 Hz, 1H), 1.85–1.78 (m, 1H), 1.64–1.57 (m, 1H), 1.49–1.43 (m, 1H), 1.06 (s, 12H), 0.88 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.5, 135.6 (4C), 133.6 (2C), 129.8 (2C), 127.7 (2C), 72.5, 59.8, 58.8, 55.1, 51.9, 51.4, 48.7, 42.6, 42.5, 41.3, 27.1, 26.8 (3C), 24.9, 19.7, 19.6, 19.0 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3365, 3063, 2930, 2886, 1746, 1683, 1587, 1429 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{31}H_{43}NO_4SSi$: 553.2682; found: 553.2689.

Catalyst 7e: $NaBH_4$ (1.55 g, 40.8 mmol) was added to a stirred solution of **6a** (1.50 g, 4.08 mmol) in CH_2Cl_2/MeOH (1:1, 20 mL) at ambient temperature. After stirring for 2 h, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The obtained crude *exo*-alcohol (1.37 g, 3.71 mmol) in CH_2Cl_2 (20 mL) was treated with TFA (5.51 mL, 74.2 mmol) at ambient temperature for 1 h. The mixture was quenched with H_2O and the resulting solution was adjusted to pH 9–10 with an aqueous solution of $NaHCO_3$ (1.0 M). The mixture was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed under reduced pressure to afford **7e** as a pale-yellow solid (0.98 g, 98%). M.p. 97–99 °C; $[\alpha]_D^{25}$ = +4.8 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.97 (q, *J* = 3.8 Hz, 1H), 3.54 (s, 2H), 3.31–3.23 (m, 1H), 2.99–2.95 (m, 2H), 2.87–2.67 (m, 3H), 2.42 (dd, *J* = 13.4, 9.7 Hz, 1H), 1.99–1.64 (m, 7H), 1.51–1.38 (m, 2H), 1.25–1.17 (m, 2H), 1.05 (s, 3H), 0.81 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.9, 59.9, 52.7, 47.4, 46.0, 45.3, 40.2, 39.2, 34.2, 31.5, 30.7, 27.1, 25.5, 20.6, 20.0 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3364, 2938, 2875, 1680, 1527, 1414 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{15}H_{27}NO_2S$: 269.1813; found: 269.1802.

Catalyst 7f: Following the procedure described above for **7e**, $NaBH_4$ reduction of **6b** in CH_2Cl_2/MeOH and subsequent treatment with TFA in CH_2Cl_2 provided **7f** as a viscous liquid (82%). $[\alpha]_D^{33}$ = −2.5 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.42 (s, 1H), 3.96 (s, 1H), 3.56 (s, 4H), 2.98–2.86 (m, 2H), 2.85–2.65 (m, 3H), 2.38 (t, *J* = 11.6 Hz, 1H), 1.99–1.94 (m, 1H), 1.72–1.65 (m, 4H), 1.61–1.55 (m, 1H), 1.50–1.45 (m, 1H), 1.32–1.16 (m, 2H), 1.04 (s, 3H), 0.81 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.7, 72.1, 57.8, 54.2, 52.5, 47.3, 45.2, 41.2, 39.9, 39.3, 33.8, 30.7, 27.0, 20.6, 19.9 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3392, 2903, 1646, 1428 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{15}H_{27}NO_2S$: 285.1762; found: 285.1768.

Catalyst 7g: Following the procedure described above for **7e**, $NaBH_4$ reduction of **6c** in CH_2Cl_2/MeOH and subsequent treatment with TFA in CH_2Cl_2 provided **7g** as a viscous liquid (84%). $[\alpha]_D^{33}$ = +5.6 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.60 (m, 4H), 7.44–7.39 (m, 3H), 7.38–7.32 (m, 3H), 4.44–4.38 (m, 1H), 4.21 (s, 2H), 3.99 (q, *J* = 3.9 Hz, 1H), 3.63–3.58 (m, 1H), 2.94 (d, *J* = 12.2 Hz, 1H), 2.87–2.77 (m, 3H), 2.66 (d, *J* = 12.2 Hz, 1H), 2.33 (dd, *J* = 13.6, 9.9 Hz, 1H), 1.96 (q, *J* = 6.8 Hz, 1H), 1.79–1.64 (m, 4H), 1.49–1.38 (m, 2H), 1.22–1.16 (m, 1H), 1.05 (s, 9H), 1.03 (s, 3H), 0.79 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.4 (4C), 133.5 (2C), 129.6 (2C), 127.5 (4C), 75.5, 73.7, 58.5, 54.2, 53.2, 52.5, 47.2, 45.2, 41.2, 39.2, 33.9, 30.5, 26.9, 26.7 (3C), 20.5, 19.8, 18.8 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3373, 3077, 2959, 1679, 1591, 1469 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{31}H_{45}NO_2SSi$: 523.2940; found: 523.2950.

Catalyst 7h: Following the procedure described above for the synthesis of **7d**, treatment of **6c** with Oxone, $NaBH_4$ in CH_2Cl_2/MeOH, then TFA in CH_2Cl_2 afforded **7h** as a colorless viscous liquid (86%). $[\alpha]_D^{33}$ = −12.1 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (t, *J* = 6.0 Hz, 4H), 7.46–7.40 (m, 3H), 7.39–7.32 (m, 3H), 4.15–4.10 (m, 2H), 3.66 (d, *J* = 13.6 Hz, 1H), 3.51 (s, 2H), 3.31–3.22 (m, 1H), 3.07–2.87 (m, 4H), 2.07–2.03 (m, 1H), 1.87–1.78 (m, 2H), 1.77–1.65 (m, 3H),1.57–1.46 (m, 2H), 1.06 (s, 12H), 0.82 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5 (4C), 133.6 (2C), 129.7 (2C), 127.6 (4C), 75.9, 73.3, 60.6, 55.1, 53.8, 51.6, 50.1, 48.9, 44.0, 41.5, 39.1, 30.3, 27.4, 26.8 (3C), 20.4, 19.8, 18.9 ppm; IR (CH_2Cl_2): $\tilde{\nu}$ = 3491, 3077, 2952, 2856, 1653, 1591, 1473, 1307 cm^{-1}; HRMS (EI): *m/z*: calcd for $C_{31}H_{45}NO_4SSi$: 555.2839; found: 555.2830.

Typical procedure for the asymmetric Michael reaction catalyzed by 7f: Isobutyraldehyde (0.073 mL, 0.804 mmol), *trans*-β-nitrostyrene (30 mg, 0.201 mmol), organocatalyst **7f** (11.5 mg, 0.040 mmol), and toluene (0.5 mL) were added to a round-bottomed flask. The reaction mixture was stirred at ambient temperature. After the nitroalkene was consumed, detected by TLC analysis, the reaction was quenched with brine and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane/ethyl acetate 6:1) to provide **8a** as a colorless liquid (90%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.53$ (s, 1H), 7.36–7.19 (m, 5H), 4.85 (dd, $J=13.0$, 11.3 Hz, 1H), 4.69 (dd, $J=13.0$, 4.2 Hz, 1H), 3.78 (dd, $J=11.3$, 4.2 Hz, 1H), 1.14 (s, 3H), 1.01 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=204.2$, 135.4, 129.1, 128.7, 128.1, 76.3, 48.5, 48.2, 21.7, 18.9 ppm; HPLC: Chiralcel OD-H (hexane/*i*PrOH: 80/20, flow rate: 0.8 mL/min, $\lambda=254$ nm); retention time: 16.9 min (major), 24.4 min (minor).

Compound 12: (*S*)-Citronellal (**11**; 0.073 mL, 0.8 mmol), *trans*-β-nitrostyrene (30 mg, 0.2 mmol), and organocatalyst **7f** (5.7 mg, 0.02 mmol) were added to a round-bottomed flask. The reaction mixture was stirred at ambient temperature. After the *trans*-β-nitrostyrene was consumed, determined by TLC analysis, the reaction was quenched with H_2O and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane/ethyl acetate 8:1) to provide **12** as a pale-yellow liquid (93%). $[\alpha]_D^{18}=-40.2$ ($c=1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=9.89$ (d, $J=1.7$ Hz, 1H), 7.35–7.26 (m, 3H), 7.16 (d, $J=7.2$ Hz, 2H), 4.93 (t, $J=6.5$ Hz, 1H), 4.67 (dd, $J=12.4$, 4.3 Hz, 1H), 4.52 (dd, $J=12.3$, 10.1 Hz, 1H), 3.92 (td, $J=10.7$, 4.3 Hz, 1H), 2.87 (d, $J=11.2$ Hz, 1H), 2.03–1.90 (m, 2H), 1.62 (s, 3H), 1.52 (s, 3H), 1.50–1.45 (m, 2H), 1.41–1.31 (m, 1H), 0.85 ppm (d, $J=6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=204.2$, 136.8, 132.2, 128.9, 127.9, 123.2, 79.2, 56.3, 41.6, 35.4, 32.1, 25.4, 17.6, 14.7 ppm; IR (CH_2Cl_2): $\tilde{\nu}=2921$, 1716, 1557, 1455, 1378, 1205, 1089 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{25}NO_3$+Na$^+$: 326.1732 [*M*+Na$^+$]; found 326.1740; HPLC: Chiralcel AD-H (hexane/*i*PrOH 95:5, flow rate: 0.5 mL min^{-1}, $\lambda=254$ nm); retention time: 13.61 min (major), 14.61 min (minor).

Compound 13: $InBr_3$ (70 mg, 0.19 mmol) was added to a stirred solution of **12** (40 mg, 0.13 mmol) in toluene (0.5 mL) at ambient temperature. After 24 h, the reaction was quenched with H_2O and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane/ethyl acetate 4:1) to afford **13** as a white solid (17 mg, 41%). M.p. 155–157°C; $[\alpha]_D^{18}=-29.2$ ($c=1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.33$–7.29 (m, 2H), 7.24–7.22 (m, 3H), 5.00 (dd, $J=11.6$, 4.8 Hz, 1H), 4.63 (t, $J=11.2$ Hz, 1H), 4.41 (s, 1H), 3.96 (br s, 1H), 3.84 (td, $J=11.0$, 4.8 Hz, 1H) 1.80–1.75 (m, 2H), 1.64–1.61 (m, 1H), 1.55–1.51 (m, 1H), 1.43–1.41 (m, 2H), 1.41 (s, 3H), 1.31 (s, 3H), 1.26–1.22 (m, 2H), 1.06 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=139.0$, 128.7, 128.1, 127.4, 80.1, 74.3, 68.0, 49.6, 46.9, 43.5, 33.4, 29.6, 28.4, 27.7, 15.1 ppm; IR (CH_2Cl_2): $\tilde{\nu}=3402$, 2958, 1640, 1548, 1448, 1376, 1200, 115 0 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{27}NO_4$+Na: 344.1838 [*M*+Na$^+$]; found: 344.1840; crystal data for **13** at 200(2) K; $C_{18}H_{27}NO_4$; M_r 321.41; orthorhombic; *P212121*; $a=9.6849$ (7) Å, $b=18.6629$ (11) Å, $c=29.4837$ (19) Å; $\alpha=90$, $\beta=90$, $\gamma=90$; $V=5329.1$ (6) Å^3; $F_{000}=2088$; $\lambda=0.71073$ Å; $Z=12$, $\rho=1.202$ mg m^{-3}; $\mu=0.084$ mm^{-1}; 28950 reflections; 0 restraints; 622 parameters; $R=0.0844$; $Rw=0.1265$ for all data.

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