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Highly Enantioselective 1,4-Michael Additions of Nucleophiles to Unsaturated Aryl Ketones with Organocatalysis by Bifunctional Cinchona Alkaloids

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The development of general and efficient asymmetric organocatalytic additions of malononitrile and nitromethane to 1,5-diarylpenta-2,4-dien-1-ones (cinnamylideneacetophenones) catalyzed by cinchona organocatalysts is reported. The reactions afforded excellent enantioselectivities (up to 99 %), high yields (up to 97 %), and exclusive 1,4-addition regioselectivities. The potential of these new enantioselective additions lies in the demonstration that organocatalysts bearing primary amino groups in combination with TFA provide effective catalytic systems for the activation of a broad range of aryl ketones under mild conditions to give compounds with high levels of enantioselectivity and yields.

Introduction

Asymmetric organocatalysis has emerged as a new and powerful methodology for the catalytic production of enantiomerically pure organic compounds and also as one of the most rapidly growing and competitive research areas in synthetic organic chemistry,[1] in particular with respect to 1,4-Michael additions.[2] Organocatalysis has attracted considerable attention in chemistry in recent years because usually it uses nontoxic metal-free catalysts. This approach might become valuable for the preparation of pharmaceutical compounds, in which metal contamination cannot be tolerated.[3]

Small chiral organic molecules can function as catalytically active species; among them, cinchona alkaloids are present in numerous biologically active and therapeutically important molecules. In the last two decades, cinchona alkaloids have also become widely used as catalysts in asymmetric syntheses, to give access to chiral building blocks of high enantiopurity. In particular, the 9-amino-(9-deoxy)-*epi*-cinchona alkaloids **1**[2c,4] and the 9-thiourea-(9-deoxy)-*epi*-cinchona alkaloids **2**[1e,5] (Figure 1) have been extensively used as organocatalysts in 1,4-Michael additions to α,β-unsaturated ketones.

The catalysts **1** and **2** were designed as bifunctional organocatalysts, because both the electrophilic and the nucleophilic components of a reaction can be activated simultaneously (Figure 2). The catalysts **1** form ketiminium ions[4c,4e,4j] and each possesses a Lewis base functionality. The in situ generation of an iminium ion from a chiral aminocatalyst and a carbonyl compound is thought to lower the LUMO energy in the system and is a powerful strategy for asymmetric transformations.[4a] The catalysts **2** synergistically employ Brønsted acid and Lewis base functionalities.[5j] Organic chemists have begun to appreciate the tremendous potential offered by hydrogen bonding as a mechanism for electrophile activation in small molecules.[5f–5h] Hydrogen bonding with an electrophile serves to decrease the electron density in this species, activating it toward nucleophilic attack. This principle is frequently employed by nature's catalysts (enzymes) for the acceleration of a wide range of chemical processes.

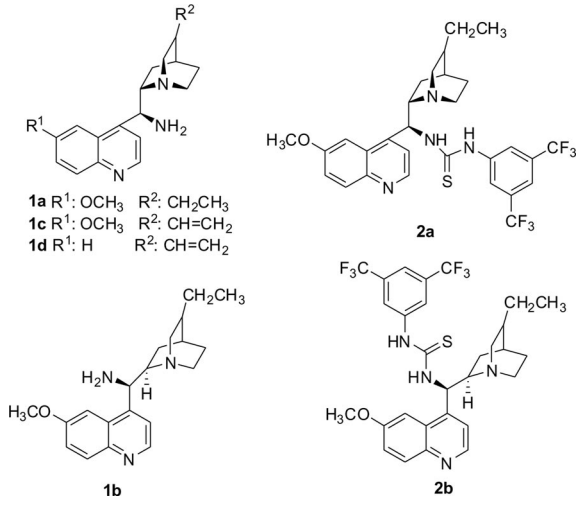

Figure 1. Structures of screened organocatalysts.

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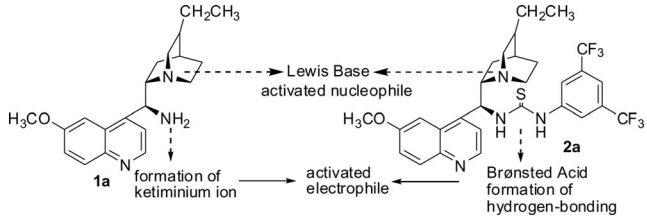


Figure 2. Activation of bifunctional cinchona alkaloids.

Several nucleophilic species capable of undergoing 1,4-Michael additions to α,β-unsaturated ketones with catalysis by cinchona alkaloids have been extensively reported. Such species include *C*-nucleophiles (nitroalkanes,[4n,5b,5k,5m,6] malononitrile,[4i,5e,7] malonates,[5e,8] α,α-dicyanoalkenes,[4a,4k] α-cyanosulfones,[9] 4-hydroxycoumarins,[4b] indoles,[4d,4g,10] cyanoacetates,[5i,11] ketones,[12] and 1-fluorobis(phenylsulfonyl)methane[13]), *N*-nucleophiles,[4j,4m,14] *O*-nucleophiles,[4f,15] and *S*-nucleophiles.[4h,16] Amongst these nucleophiles, malononitrile and nitromethane represent versatile functional compounds that can be chemically transformed into a variety of functional useful compounds.

We have recently developed a new methodology for 1,4-Michael additions of nitromethane to cinnamylideneacetophenones (δ-aryl α,β,γ,δ-unsaturated aryl ketones)[5m] in the presence of the 9-thiourea-9-(deoxy)-*epi*-hydroquinine **2a** with excellent levels of enantioselectivity and isolated yields, as well as exclusive regioselectivities. α,β-Unsaturated aryl ketones are a class of compounds that have been receiving less attention than the corresponding alkyl ketones or aldehydes because the aromatic group can block the interaction of the carbonyl group with the catalyst. In particular, few organocatalytic examples of reactions of α,β-unsaturated aryl ketones catalyzed by the primary amines **1** have been reported.[4g–4i,4n] Only moderate levels of enantioselectivity and yield have been obtained, which is probably due to the fact that the generation of the corresponding iminium cations is unfavorable as a result of steric hindrance caused by the aryl group.

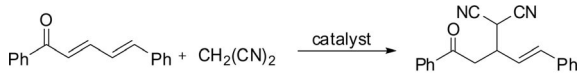
A number of additions of nitromethane to chalcones have been achieved,[5b,5k,6a] but additions of nitromethane to cinnamylideneacetophenones has been reported only rarely.[5k] In this case only one example has been described: for a δ-phenyl α,β,γ,δ-unsaturated *N*-acylpyrrole ketone, with 54% yield and 94% *ee*. Until now, organocatalyzed Michael additions of malononitrile to chalcones[4h,5e] have been less well studied than those of nitromethane, and moderate values of enantioselectivity and yield have been achieved. To the best of our knowledge, no study of organocatalytic additions of malononitrile to cinnamylideneacetophenones has yet appeared.

In this communication we present general and efficient organocatalytic 1,4-Michael additions of malononitrile to different cinnamylideneacetophenones assisted by organocatalysis by compounds of types **1** and **2**. We have also extended the scope of reactions between nitromethane and cinnamylideneacetophenones catalyzed by the organocatalysts **2**.

Results and Discussion

The addition of malononitrile to 1,5-diphenylpenta-2,4-dien-1-one (**3a**) in the presence of catalysts **1a** or **2a** was investigated (Table 1). The initial reaction conditions involved a solution of **3a** (0.1 M) and the catalyst (20 mol-%). Poor enantioselectivities were found when catalyst **1a** and benzoic acid were used (Entries 1 and 2), but the use of a more acidic additive such as TFA increased the *ee* values (Entries 3–9). Variation of the solvent had an influence in the course of the reaction: THF (Entry 3) and CH_2Cl_2 (Entry 4) gave acceptable levels of *ee* and moderate yields, $CHCl_3$ (Entry 5) and toluene (Entry 6) gave better yields but worst levels of *ee*, CH_3CN (Entry 7) gave an acceptable *ee* but a poor yield, and CH_3OH (Entry 8) gave a poor yield and *ee*. The enantioselectivity was increased when the reaction was carried out with exclusion of oxygen (Entry 9). When the reaction was performed in the presence of catalyst **2a** poor enantioselectivities were obtained (Entries 10 and 11).

Table 1. Catalyst and solvent screening for the conjugate addition of malononitrile to **3a**.[a]



3a **4a**

Entry	Catalyst	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	**1a**	THF	$PhCO_2H$	52	27[d]
2[e]	**1a**	CH_2Cl_2	$PhCO_2H$	56	16[d]
3	**1a**	THF	TFA	60	82[d]
4	**1a**	CH_2Cl_2	TFA	49	84[d]
5	**1a**	$CHCl_3$	TFA	85	69[d]
6	**1a**	toluene	TFA	70	74[d]
7	**1a**	CH_3CN	TFA	20	71[d]
8	**1a**	CH_3OH	TFA	19	19[d]
9[f]	**1a**	THF	TFA	51	90[d]
10[f]	**2a**	THF	—[g]	68	35[h]
11[f]	**2a**	CH_2Cl_2	—[g]	78	43[h]

[a] Reactions were carried out with a solution of **3a** (0.1 M, 15 mg, 0.064 mmol), catalyst **1a** or **2a** (20 mol-%, 0.013 mmol), a suitable additive (40 mol-%, 0.026 mmol), and malononitrile (25.3 mg, 0.38 mmol) in solvent (0.64 mL) for 7 d at room temp. [b] Yield of isolated products after chromatography. [c] Determined by chiral HPLC with a Chiralpak IA column. [d] The *S* configuration was assigned to the major enantiomer by chiral HPLC. [e] The reaction was carried out for 2 d. [f] The reaction was carried out under nitrogen. [g] Without additive. [h] The *R* configuration was assigned to the major enantiomer by chiral HPLC. TFA: trifluoroacetic acid.

The 9-amino-(9-deoxy)-*epi*-hydroquinine **1a** in combination with TFA has been shown to provide an effective catalytic system for the activation of the phenyl ketone **3a**. Presumably, the sterically less hindered primary amine group in **1a** reacts more readily with the ketone functionality of **3a** than that in catalyst **2a**, to initiate the iminium catalysis, and the quinuclidine motif of hydroquinine can then bind to malononitrile, through hydrogen-bonding interactions, thereby activating the nucleophilic attack (Figure 3).

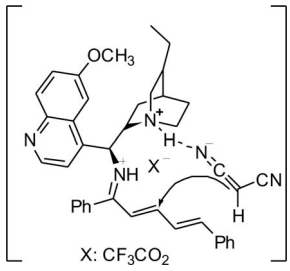


Figure 3. Activation of the α,β,δ,γ-unsaturated phenyl ketone **3a** and malononitrile by the bifunctional catalyst **1a**.

The catalytic system and THF as solvent having been selected, the influence of catalyst loading and molar concentration were investigated (Table 2). In a solution of the substrate **3a** (0.1 M) and catalyst (20 mol-%), increasing the amount of malononitrile produced a decrease in the yield (Entry 2), whereas the yield was significantly increased by increasing the temperature (Entry 3) and adding molecular sieves (Entry 4). In these cases the *ee* values were acceptable. Raising the molar concentration gave better yields (Entries 5–7). Increasing of the catalyst loading, from 30% (Entries 8 and 9) to 40% (Entries 10 and 11) and 50% (Entry 12), was also investigated. Entry 9, in which a 0.3 M solution of **3a** and 30% molar equivalent of catalyst **1a** was used, represents the best reaction conditions, with an excellent yield (96%) and a high level of enantioselectivity (90%). Recrystallization of the obtained compound led to an increase in the *ee* value to 99%. The absolute configuration of (*S*)-**4a** was assigned by chiral HPLC and X-ray analysis. Different 9-amino-(9-deoxy)-*epi*-cinchona alkaloids were also evaluated: i) **1b** gave the opposite enantiomer (*R*)-**4a** in good yield (79%) and *ee* value (90%) (Entry 13), whereas ii) catalysts **1c** (Entry 14) and **1d** (Entry 15) did not improve the previous results.

The best protocol for obtaining high levels of enantioselectivity and yield now having been established, the scope of the reaction for the different cinnamylideneacetophenones **3b**–**i** was investigated (Table 3).

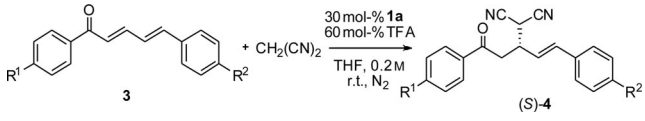
The results show that the synthesis of the new (*S,E*)-2-(1-oxo-1,5-diarylpent-4-en-3-yl)malononitriles **4b**–**i** took place efficiently with good enantioselectivities (80–97%). These compounds were recrystallized with enantioselectivities higher than 98%. The yields, however were influenced by the nature and pattern of the substitution on the starting materials (56–97%; see Table 3). When an electron-withdrawing substitution was present in the *para* position of the δ-aryl group (Entry 1), moderate yield and *ee* values were found, possibly because the charge density decrease in the α,β,γ,δ-unsaturated ketone system and the iminium cation formation might be more unfavorable. When an electron-donating group was present (Entry 2), a high enantioselectivity and a good yield were obtained. The yields and *ee* values were good with a range of different substituents present in the *para* position of the ketone aryl group (Entries 3–8). It is noteworthy that aromatic ketones are a class of substrates not generally suitable for iminium activation, because the aryl groups exert great steric hindrance and cation formation is unfavorable. We would like to emphasize that these asymmetric additions constitute the first example of the use of 9-amino-9-(deoxy)-*epi*-hydroquinine in combi-

Table 2. Optimization of reaction conditions for asymmetric conjugate addition of malononitrile to **3a** in the presence of catalysts **1a**–**d**.[a]

Entry	Catalyst	mol-% Catalyst	mol-% TFA	M	Yield [%][b]	*ee* [%][c]
1	**1a**	20	40	0.1	51	90
2[d]	**1a**	20	40	0.1	31	86
3[e]	**1a**	20	40	0.1	70	84
4[f]	**1a**	20	40	0.1	78	84
5	**1a**	20	40	0.2	84	89
6	**1a**	20	40	0.3	96	81
7[g]	**1a**	20	40	0.3	82	83
8	**1a**	30	60	0.1	70	88
9	**1a**	30	60	0.2	96	90[h,i]
10	**1a**	40	80	0.1	88	89
11[f]	**1a**	40	80	0.1	75	83
12	**1a**	50	100	0.1	80	81
13	**1b**	30	60	0.2	79	90[j]
14	**1c**	40	80	0.1	69	77
15	**1d**	40	80	0.1	61	48

[a] Reactions were carried out with **3a** (15 mg, 0.064 mmol), catalysts **1a**–**d**, TFA, and malononitrile (25.3 mg, 0.38 mmol) in THF for 7 d at room temp. under N_2. [b] Yield of isolated products after chromatography. [c] Determined by chiral HPLC with a Chiralpak IA column. [d] Reaction was carried out with malononitrile (60 mol-%). [e] Reaction was carried at 40 °C. [f] With molecular sieves (4 Å,10 mg). [g] Reaction was carried out with malononitrile (2 mol equiv.). [h] *ee* > 99% after recrystallization. [i] The absolute configuration of (*S*)-**4a** was assigned by chiral HPLC and X-ray analysis. [j] The (*R*)-**4a** configuration was confirmed by chiral HPLC. TFA: trifluoroacetic acid.

Table 3. Scope of enantioselective 1,4-Michael additions of malononitrile to the 1,5-diarylpenta-2,4-dien-1-ones **3b**–**i** catalyzed by **1a**.[a]



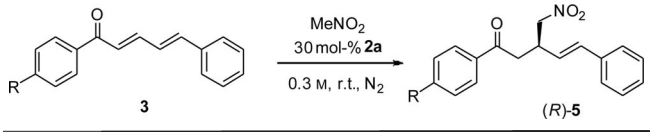
Entry	**3**	R^1	R^2	**4** [%][b]	*ee* [%][c]
1	**3b**	H	NO_2	**4b** (56)	80[d,e]
2	**3c**	H	OCH_3	**4c** (91)	97[d]
3	**3d**	CH_3	H	**4d** (97)	84[d,f]
4	**3e**	OCH_3	H	**4e** (95)	84[d]
5	**3f**	Cl	H	**4f** (87)	90[d,f]
6	**3g**	Br	H	**4g** (93)	94[d,e]
7	**3h**	F	H	**4h** (65)	92[d,f]
8	**3i**	CN	H	**4i** (77)	82[d]

[a] Reactions took place in the presence of **3b**–**i** (0.128 mmol) and catalyst **1a** (30 mol-%, 12.3 mg, 0.038 mmol) dissolved in THF (0.32 mL) under nitrogen. TFA (60 mol-%, 5.8 μL, 0.076 mmol) and malononitrile (50.7 mg, 0.768 mmol) dissolved in THF (0.32 mL) were next added. Reactions conditions: solution of **3b**–**i** (0.2 M) at room temp. for 7 d. [b] Yield of isolated products after chromatography. [c] Determined by chiral HPLC with a Chiralpak IA column. [d] The *S* configuration was confirmed by chiral HPLC. [e] *ee* > 99% after recrystallization. [f] *ee* > 98% after recrystallization.

nation with TFA, and provide an effective catalytic system for the activation of a broad range of cinnamylideneacetophenones under mild conditions.

In our previous study on 1,4-Michael additions of nitromethane to cinnamylideneacetophenones,[5m] the reactions were carried out in neat nitromethane, with solutions of the substrates (0.3 M), and with catalyst **2a** (30 mol-%; see Experimental Section – **2a** was the best catalyst found after the screening of chiral organocatalysts **1**, **2**, and a diarylprolinol silyl ether). The synthesis of the (*R*,*E*)-1,5-diaryl-3-(nitromethyl)-5-pent-4-en-1-ones **5a**–**h** (see Exp. Section) took place with good levels of enantioselectivity (87–99%) and moderate to excellent yields (19–97%). These reactions have now been extended (Table 4) to the synthesis of the new derivatives **5i**–**k** (Entries 1–3) with good levels of enantioselectivity (84–94%) and yields (77–86%). These compounds were recrystallized and their enantioselectivities were increased up to 99%.

Table 4. Enantioselective 1,4-Michael additions of nitromethane to the 1,5-diarylpenta-2,4-dien-1-ones **3g**–**i** organocatalyzed by **2a**.[a]



Entry	**3**	R	**5** [%][b]	*ee* [%][c]
1	**3g**	Br	**5i** (77)	84[d,e]
2	**3h**	F	**5j** (81)	91[d,f]
3	**3i**	CN	**5k** (86)	94[d,f]

[a] Reactions took place with **3g**–**i** (0.128 mmol) and catalyst **2a** (30 mol-%, 22.9 mg, 0.038 mmol) in nitromethane solution (0.3 M, 0.47 mL) under nitrogen for 7 d at room temp. [b] Yield of isolated products after chromatography. [c] Determined by chiral HPLC with a Chiralpak IA column. [d] The *R* configuration was confirmed by chiral HPLC. [e] *ee* >96% after recrystallization. [f] *ee* >99% after recrystallization.

As shown earlier, treatment of 1,5-diphenylpenta-2,4-dien-1-one (**3a**) with nitromethane in the presence of catalyst **2a** gave (*R*,*E*)-1,5-diphenyl-3-(nitromethyl)-5-pent-4-en-1-one [(*R*)-**5a**],[5m] but the corresponding reaction in the presence of the 9-thiourea-(9-deoxy)-*epi*-hydroquinidine **2b** led to the synthesis of the opposite enantiomer (*S*,*E*)-**5a** with good yield (85%) and *ee* (92%). Recrystallization of the obtained compound led to an increase in the *ee* value to 99%. The absolute configuration of (*S*)-**5a** was assigned by chiral HPLC and X-ray analysis.

The crystal structures of compounds (*S*)-**4a**[17] and (*S*)-**5a**[18] (Figure 4) were determined both to be in the chiral orthorhombic $P2_12_12_1$ space group (for details see Supporting Information). Although the absolute configurations of the molecules could not be unequivocally determined solely from the single-crystal X-ray diffraction data (due to the presence only of light atoms in the compounds: i.e., Z < Si), their determination was ensured by taking data from the synthesis and the results of chiral HPLC separation into consideration.

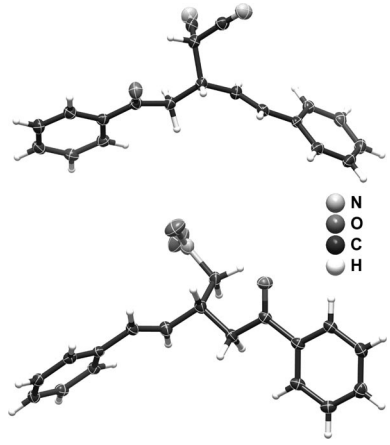


Figure 4. Schematic representation of the molecular units present in compounds (*S*)-**4a** and (*S*)-**5a**. Non-hydrogen atoms are represented as thermal ellipsoids drawn at the 50% probability level and hydrogen atoms as spheres with arbitrary radii.

Conclusions

In summary, we have developed the first general organocatalytic 1,4-Michael additions of malononitrile to different 1,5-diarylpenta-2,4-dien-1-ones in the presence of 9-amino-9-(deoxy)-*epi*-hydroquinine and TFA. Excellent levels of enantioselectivity (up to 99%) and isolated yields (up to 97%) have been achieved for a wide spectrum of substrates and β-addition regioselectivities were obtained exclusively, with no δ-addition being observed. We have also extended the 1,4-Michael additions of nitromethane to 1,5-diarylpenta-2,4-dien-1-ones in the presence of 9-thiourea-9-(deoxy)-*epi*-hydroquinine with good levels of enantioselectivity and isolated yields.

Experimental Section

General Methods: Melting points were determined with a Büchi melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 300 or 500 [300.13 MHz (^{1}H), 75.47 MHz (^{13}C) or 500.13 MHz (^{1}H), 125.77 MHz (^{13}C)] spectrometers with TMS as internal reference. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity [s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet)], coupling constant [Hz], integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Unequivocal ^{1}H assignments were made with aid of 2D COSY (^{1}H/^{1}H), whereas ^{13}C assignments were made on the basis of 2D HSQC (^{1}H/^{13}C) and HMBC (delays for one-bond and long-range C,H couplings were optimized for 145 and 7 Hz, respectively) experiments. High-resolution mass spectra analyses (HRMS-ESI$^+$) were performed with a microTOF (focus) mass spectrometer. Ions were generated with an ApolloII (ESI) source. Ionization was achieved by electrospray, with use of a voltage of 4500 V applied to the needle, and a counter voltage between 100 and 150 V applied to the capillary. High-resolution mass spectra analyses (HRMS-EI, 70 eV) were measured with a VG Autospec M spectrometer. Elemental analyses were obtained with a Carlo Erba 1108 CHNS analyzer. Silica gel (60 F_{254}, Merck) was used for TLC, and the spots were detected with UV light (254 nm). Flash column chromatography

was carried out with silica gel 60 (Merck). Enantiomeric excesses (*ee* values) were measured by chiral HPLC analysis with a Chiralpak IA column (0.46 × 25 cm). UV detection was monitored at 254 nm.

Materials: Hydroquinine, hydroquinidine, quinine, chinchonidine, diisopropyl azidocarboxylate, diphenyl phosphoryl azide, 3,5-bis-(trifluoromethyl)phenyl isothiocyanate, nitromethane, malononitrile, and trifluoroacetic acid (TFA) were purchased from Sigma–Aldrich and used without other purification. The chinchona alkaloids **1a**,[5b] **2a**,[5b] and **2b**[19] and the 1,5-diarylpenta-2,4-dien-1-ones **3a**,[20a] **3b**,[20b] **3c**,[20b] **3d**,[20a] **3e**,[20a] **3f**,[20c] and **3h**[20a] were prepared as described in the literature. THF was distilled from sodium/benzophenone prior to use.

General Procedure for the Preparation of the Primary Amine Catalysts 1b–d: The appropriate hydroquinidine, quinine, or chinchonidine (6.13 mmol) and triphenylphosphane (2.11 g, 7.35 mmol) were dissolved in dry THF (30 mL) and the solution was cooled to 0 °C. Diisopropyl azidocarboxylate (1.52 mL, 7.35 mmol) was added in one portion. A solution of diphenyl phosphoryl azide (1.63 mL, 7.35 mmol) in dry THF (13 mL) was then added dropwise at 0 °C. The mixture was allowed to warm to room temp. After having been stirred for 12 h, the solution was heated at 50 °C for 2 h. Triphenylphosphane (2.29 g, 7.97 mmol) was then added and heating was maintained until the gas evolution had ceased (2 h). The solution was cooled to room temperature, water (0.7 mL) was added, and the solution was stirred for 3 h. Solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2 (30 mL) and diluted hydrochloric acid (10%, 30 mL). The aqueous phase was washed with CH_2Cl_2 (3 × 30 mL). The aqueous phase was then alkalinized with an excess of concd. aqueous ammonia and washed with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 solutions were dried with Na_2SO_4 and concentrated. The concentrated organic phase was purified by column chromatography on silica gel with elution with EtOAc/MeOH/NH_4OH (50:50:1) to afford the title compounds as yellowish viscous oils.

9-Amino-(9-deoxy)-*epi*-hydroquinidine (1b):[21] Yellow oil (1.7 g, 87% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 8.75 (d, ^3J = 4.5 Hz, 1 H, 2′-H), 8.04 (d, ^3J = 9.2 Hz, 1 H, 8′-H), 7.63 (br. s, 1 H, 5′-H), 7.53 (d, ^3J = 4.5 Hz, 1 H, 3′-H), 7.39 (dd, ^3J = 9.2, ^4J = 2.7 Hz, 1 H, 7′-H), 4.70 (d, ^3J = 9.7 Hz, 1 H, 9-H), 3.97 (s, 3 H, CH_3), 3.11–2.94 (m, 4 H, 2-H, 6-H, 8-H), 2.70–2.64 (m, 1 H, 2-H), 1.54–1.34 (m, 6 H, 3-H, 4-H, 5-H, 10-H), 1.13–1.05 (m, 1 H, 7-H), 0.99–0.93 (ddt, ^3J = 13.6, ^3J = 7.4, ^4J = 1.8 Hz 1 H, 7-H), 0.88 (t, ^3J = 7.2 Hz, 3 H, 11-H) ppm. HRMS (ESI$^+$): calcd. for $[C_{20}H_{27}N_3O + H]^+$ 326.2227; found 326.2223.

9-Amino-(9-deoxy)-*epi*-quinine (1c):[22] Yellow oil (1.6 g, 82% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 8.74 (d, ^3J = 4.4 Hz, 1 H, 2′-H), 8.03 (d, ^3J = 9.2 Hz, 1 H, 8′-H), 7.65 (br. s, 1 H, 5′-H), 7.46 (d, ^3J = 4.4 Hz, 1 H, 3′-H), 7.38 (dd, ^3J = 9.2, ^4J = 2.7 Hz, 1 H, 7′-H), 5.80 (ddd, $^3J_{trans}$ = 17.5, $^3J_{cis}$ = 10.3, ^3J = 7.5 Hz, 1 H, 10-H), 5.03–4.95 (m, 2 H, 11-H), 4.60 (d, ^3J = 9.9 Hz, 1 H, 9-H), 3.95 (s, 3 H, CH_3), 3.31–3.16 (m, 2 H, 2-H, 6-H), 3.12–3.04 (m, 1 H, 8-H), 2.84–2.74 (m, 2 H, 2-H, 6-H), 2.27 (br. s 1 H, 3-H), 2.18 (br. s, 2 H, NH_2), 1.63–1.52 (m, 3 H, 4-H, 5-H), 1.46–1.38 (m, 1 H, 7-H), 0.72 (ddt, ^3J = 13.6, ^3J = 7.4, ^4J = 1.8 Hz 1 H, 7-H) ppm. HRMS (ESI$^+$): calcd. for $[C_{20}H_{26}N_3O + H]^+$ 324.2070; found 324.2066.

9-Amino-(9-deoxy)-*epi*-cinchonidine (1d): Yellow oil (1.3 g, 73% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 8.89 (d, ^3J = 4.4 Hz, 1 H, 2′-H), 8.35 (br. s, 1 H, 5′-H), 8.14 (dd, ^3J = 8.3, ^4J = 1.2 Hz, 1 H, 8′-H), 7.70 (td, ^3J = 8.3, ^4J = 1.2 Hz, 1 H, 6′-H), 7.58 (td, ^3J = 8.3, ^4J = 1.2 Hz, 1 H, 7′-H), 7.53 (d, ^3J = 4.4 Hz, 1 H, 3′-H), 5.78 (ddd, $^3J_{trans}$ = 17.4, $^3J_{cis}$ = 10.3, ^3J = 7.3 Hz, 1 H, 10-H), 5.02–4.94 (m, 2 H, 11-H), 4.70 (d, ^3J = 9.6 Hz, 1 H, 9-H), 3.29–3.14 (m, 2 H, 2-H, 6-H), 3.11–3.02 (m, 1 H, 8-H), 2.84–2.73 (m, 2 H, 2-H, 6-H), 2.28 (br. s, 3 H, 3-H, NH_2), 1.60–1.50 (m, 3 H, 4-H, 5-H), 1.44–1.37 (m, 1 H, 7-H), 0.72 (ddd, ^3J = 13.5, ^3J = 9.0, ^3J = 7.5 Hz, 1 H, 7-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 150.0 (C-2′), 148.4 (C-4′), 148.2 (C-4a′), 141.4 (C-10), 130.0 (C-8′), 128.6 (C-6′), 127.5 (C-8a′), 126.1 (C-7′), 123.0 (C-5′), 119.3 (C-3′), 114.0 (C-11), 61.6 (C-9), 55.9 (C-2), 40.6 (C-6), 39.4 (C-8, C-3), 27.7 (C-5), 27.2 (C-4), 25.7 (C-7) ppm. HRMS (ESI$^+$): calcd. for $[C_{19}H_{24}N_3 + H]^+$ 294.1963; found 294.1961.

General Procedure for the Synthesis of 3g and 3i: An aqueous solution of sodium hydroxide (60%, 25 mL) was slowly added to a methanolic solution (30 mL) of the appropriate acetophenone (5.0 mmol). After the solution had been cooled to room temp., cinnamaldehyde (792 mg, 6.0 mmol) was added. The mixture was stirred at room temperature for 20 h and was then poured into water (100 mL), ice (100 g), and conc. hydrochloric acid (pH adjusted to ca. 2). The obtained solid was removed by filtration, dissolved in chloroform (50 mL), and washed with an aqueous solution of sodium hydrogen carbonate (5%, 30 mL). The organic layer was collected and dried with anhydrous sodium sulfate, and the solution was concentrated to dryness. The residue was purified by silica gel column chromatography with dichloromethane as eluent. Finally, the isolated compounds were recrystallized from ethanol.

(*E*,*E*)-1-(4-Bromophenyl)-5-phenylpenta-2,4-dien-1-one (3g):[20c] Yellow solid (1.39 g, 89% yield); m.p. 141–143 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 7.85 (AA′BB′, $^3J_{AB}$ = 8.4, $^4J_{AA'}$ = 2.4, $^5J_{AB'}$ = 1.7 Hz, 2 H, 2′,6′-H), 7.66–7.56 (m, 3 H, 3-H, 3′,5-H), 7.51 (dd, ^3J = 8.2, ^4J = 1.7 Hz, 2 H, 2′′,6′′-H), 7.42–7.33 (m, 3 H, 3′′,5′′-H, 4′′-H), 7.05 (d, $^3J_{trans}$ = 14.5 Hz, 1 H, 2-H), 7.04–7.03 (m, 2 H, 4-H, 5-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 189.3 (C-1), 145.4 (C-3), 142.5 (C-4), 137.0 (C-1′), 136.0 (C-1′′), 131.9 (5′, C-3′), 129.9 (C-2′,6′), 129.4 (C-4′′), 128.9 (C-3′′,5′′), 127.7 (C-4′), 127.4 (C-2′′,6′′), 126.8 (C-5), 124.8 (C-2) ppm. HRMS (EI$^+$): calcd. for $[C_{17}H_{13}BrO + H]^+$ 313.0222; found 313.0215. $C_{17}H_{13}BrO$ calcd. C 65.19, H 4.18; found C 64.84, H 3.86.

4-[(*E*,*E*)-5-Phenylpenta-2,4-dienoyl]benzonitrile (3i):[20c,23] Yellow solid (0.96 g, 74% yield); m.p. 138–140 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 8.04 (AA′BB′, $^3J_{AB}$ = 8.5, $^4J_{AA'}$ = 1.7, $^5J_{AB'}$ = 1.5 Hz, 2 H, 2′,6′-H), 7.79 (AA′BB′, $^3J_{BA}$ = 8.5, $^4J_{BB'}$ = 1.7, $^5J_{BA'}$ = 1.5 Hz, 2 H, 3′,5′-H), 7.63 (ddd, $^3J_{trans}$ = 14.8, ^3J = 8.6, ^4J = 1.9 Hz, 3-H), 7.50–7.53 (m, 2 H, 2′′,6′′-H), 7.42–7.35 (m, 3 H, 4′′-H, 3′′,5′′-H), 7.06–6.99 (m, 3 H, 2-H, 4-H, 5-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 189.0 (C-1), 146.5 (C-3), 143.4 (C-4), 141.5 (C-1′), 135.8 (C-1′′), 132.4 (C-3′,5′), 129.6 (C-4′′), 128.9 (C-3′′,5′′), 128.7 (C-2′,6′), 127.4 (C-2′′,6′′), 126.5 (C-5), 124.3 (C-2), 118 (CN), 115.8 (C-4′) ppm. HRMS (ESI$^+$): calcd. for $[C_{18}H_{13}NO + H]^+$ 260.1070; found 260.1068. $C_{18}H_{13}NO$ calcd. C 83.37, H 5.05, N 4.40; found C 83.17, H 5.04, N 5.42.

General Procedure for Enantioselective Addition of Malononitrile to Cinnamylideneacetophenones 3a–i

Synthesis of 4a–i: The 1,5-diarylpenta-2,4-dien-1-ones **3a–i** (0.128 mmol) and the amino catalysts **1a** or **1b** (12.3 mg, 0.038 mmol) were dissolved in THF (0.32 mL) under nitrogen. Next, TFA (5.8 μL, 0.076 mmol) and malononitrile (50.7 mg, 0.768 mmmol) in THF (0.32 mL, 0.2 M) were added. The mixture was stirred for 7 d at room temp. The resulting solution was concentrated to dryness, taken up in CH_2Cl_2, and purified by column chromatography with elution with hexane/AcOEt (9:1). Finally the

residues were crystallized from hexane/iPr$_2$O to give the desire compounds **4a**–**i**.

(*S*,*E*)-2-(1-Oxo-1,5-diphenylpent-4-en-3-yl)malononitrile [(*S*)-4a]:[23] This compound was produced with use of catalyst **1a**. White solid (36.9 mg, 96% yield); m.p. 80–82 °C (hexane/iPr$_2$O). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 7.97 (d, ^3J = 7.3 Hz, 2 H, 2′,6′-H), 7.64 (t, ^3J = 7.3 Hz, 1 H, 4′-H), 7.51 (t, ^3J = 7.3 Hz, 2 H, 3′,5′-H), 7.42 (dt, ^3J = 7.9, ^4J = 1.5 Hz, 2 H, 2′′,6′′-H), 7.38–7.30 (m, 3 H, 3′′,5′′-H, 4′′-H), 6.42 (d, $^3J_{trans}$ = 15.7 Hz, 1 H, 5-H), 6.24 (dd, $^3J_{trans}$ = 15.7, ^3J = 8.8 Hz, 1 H, 4-H), 4.59 (d, ^3J = 4.7 Hz, 1 H, 1′′′-H), 3.61–3.52 (m, 1 H, 3-H), 3.47–3.44 (m, 2 H, 2-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 196.7 (C-1), 136.3 (C-5), 135.7 (C-1′), 135.3 (C-1′′), 134.2 (C-4′), 128.9 (C-3′,5′), 128.7 (C-3′′,5′′), 128.6 (C-4′′), 128.1 (C-2′,6′), 126.8 (C-2′′,6′′), 123.2 (C-4), 112.0 (CN), 111.5 (CN), 40.0 (C-3), 39.6 (C-2), 27.5 (C-1′′′) ppm. MS (EI$^+$): m/z (%) = 300.13 (0.51) [M]$^{+\cdot}$, 234.11 (6.08) [M – 66]$^+$, 180.07 (11.79) [M – 120]$^+$, 153.06 (12.99) [M – 146]$^+$, 115.06 (13.32) [M – 185]$^+$, 105.06 (100) [M – 195]$^+$, 77.04 (31.89) [M – 223]$^+$. HRMS (ESI$^+$): calcd. for [$C_{20}H_{16}N_2O$ + H] 300.1263; found 300.1257. $C_{20}H_{16}N_2O$ calcd. C 79.98, H 5.37, N 9.33; found C 79.91, H 5.39, N 9.11. HPLC (2-propanol/hexane 10:90, flow rate 0.7 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4a** 21.16 min, retention time of (*R*)-**4a** 29.69 min (*ee* = 90%), after recrystallization (*ee* > 99%).

(*R*,*E*)-2-(1-Oxo-1,5-diphenylpent-4-en-3-yl)malononitrile [(*R*)-4a]: This compound was produced with use of catalyst **1b**. White solid (30.4 mg, 79% yield). HPLC (2-propanol/hexane 10:90, flow rate 0.7 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4a** 21.27 min, retention time of (*R*)-**4a** 28.92 min (*ee* = 90%).

(*S*,*E*)-2-[5-(4-Nitrophenyl)-1-oxo-1-phenylpent-4-en-3-yl]malononitrile [(*S*)-4b]:[23] This compound was produced with use of catalyst **1a**. Yellow solid (24.7 mg, 56% yield); m.p. 154–156 °C (hexane/iPr$_2$O). ^{1}H NMR (500.13 MHz, $CDCl_3$, 20 °C): δ = 8.21 (AA′BB′, $^3J_{AB}$ = 8.8, $^4J_{BB'}$ = 2.3, $^5J_{A'B}$ = 1.9 Hz, 2 H, 3′′,5′′-H), 7.98 (d, ^3J = 7.8 Hz, 2 H, 2′,6′-H), 7.65 (t, ^3J = 7.8 Hz, 1 H, 4′-H), 7.57 (AA′BB′, $^3J_{AB}$ = 8.8, $^4J_{AA'}$ = 2.3, $^5J_{AB'}$ = 1.9 Hz, 2 H, 2′′,6′′-H), 7.52 (t, ^3J = 7.8 Hz, 2 H, 3′,5′-H), 6.88 (d, $^3J_{trans}$ = 15.8 Hz, 1 H, 5-H), 6.42 (dd, $^3J_{trans}$ = 15.8, ^3J = 9.1 Hz, 1 H, 4-H), 4.61 (d, ^3J = 4.9 Hz, 1 H, 1′′′-H), 3.65–3.60 (m, 1 H, 3-H), 3.50 (ABX, $^2J_{AB}$ = 18.3, $^3J_{AX}$ = 5.0 Hz, 1 H, 2-H), 3.47 (ABX, $^2J_{AB}$ = 18.3, $^3J_{BX}$ = 7.8 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 196.3 (C-1), 147.6 (C-4′′), 141.5 (C-1′′), 135.6 (C-1′), 134.4 (C-4′), 134.3 (C-5), 129.0 (C-3′,5′), 128.1 (C-2′,6′), 128.0 (C-4), 127.5 (C-2′′,6′′), 124.1 (C-3′′,5′′), 111.7 (CN), 112.3 (CN), 40.0 (C-3), 39.3 (C-2), 27.3 (C-1′′′) ppm. HRMS (ESI$^+$): calcd. for [$C_{20}H_{15}N_3O_3$ + Na]$^+$ 368.1006; found 368.1005. $C_{20}H_{15}N_3O_3$ calcd. C 69.56, H 4.38, N 12.17; found C 69.26, H 3.99, N 11.81. HPLC (2-propanol/hexane 20:80, flow rate 1.5 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4b** 17.72 min, retention time of (*R*)-**4b** 22.88 min (*ee* = 80%) after recrystallization (*ee* > 99%).

(*S*,*E*)-2-[5-(4-Methoxyphenyl)-1-oxo-1-phenylpent-4-en-3-yl]malononitrile [(*S*)-4c]:[23] This compound was produced with use of catalyst **1a**. Yellow oil (38.4 mg, 91% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 7.97 (dt, ^3J = 7.2, ^4J = 1.8 Hz, 2 H, 2′,6′-H), 7.63 (tt, ^3J = 7.2, ^4J = 1.8 Hz, 1 H, 4′-H), 7.50 (td, ^3J = 7.2, ^4J = 1.8 Hz, 2 H, 3′,5′-H), 7.34 (AA′BB′, $^3J_{AB}$ = 8.8, $^4J_{AA'}$ = 2.8, $^5J_{AB'}$ = 2.0 Hz, 2 H, 2′′,6′′-H), 6.87 (AA′BB′, $^3J_{AB}$ = 8.8, $^4J_{BB'}$ = 2.8, $^5J_{A'B}$ = 2.0 Hz, 2 H, 3′′,5′′-H), 6.72 (d, $^3J_{trans}$ = 15.7 Hz, 1 H, 5-H), 6.08 (dd, $^3J_{trans}$ = 15.7, ^3J = 8.8 Hz, 1 H, 4-H), 4.55 (d, ^3J = 4.7 Hz, 1 H, 1′′′-H), 3.82 (s, 3 H, OCH_3), 3.57–3.48 (m, 1 H, 3-H), 3.47 (ABX, $^2J_{AB}$ = 18.5, $^3J_{AX}$ = 4.7 Hz, 1 H, 2-H), 3.40 (ABX, $^2J_{AB}$ = 18.5, $^3J_{BX}$ = 8.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 196.8 (C-1), 160.0 (C-4′′), 135.8 (C-1′), 135.7 (C-5), 134.1 (C-4′), 128.9 (C-3′,5′), 128.1 (C-2′′,6′′), 128.0 (C-2′,6′, C-1′′), 120.9 (C-4), 114.1 (C-3′′,5′′), 112.0 (CN), 111.6 (CN), 55.3 (OCH_3), 40.1 (C-3), 39.8 (C-2), 27.7 (C-1′′′) ppm. HRMS (ESI)$^+$: calcd. for [$C_{21}H_{18}N_2O_2$ + H]$^+$ 331.1441; found 331.1439. HPLC (2-propanol/hexane 10:90, flow rate 0.70 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4c** 45.94 min, retention time of (*R*)-**4c** 50.83 min (*ee* = 97%).

(*S*,*E*)-2-[1-(4-Methylphenyl)-1-oxo-5-phenylpent-4-en-3-yl]malononitrile [(*S*)-4d]:[23] This compound was produced with use of catalyst **1a**. Yellow solid (38.1 mg, 97% yield); m.p. 78–79 °C (hexane/iPr$_2$O). ^{1}H NMR (500.13 MHz, $CDCl_3$, 20 °C): δ = 7.86 (d, ^3J = 8.2 Hz, 2 H, 2′,6′-H), 7.41 (dt, ^3J = 7.1, ^4J = 1.8 Hz, 2 H, 2′′,6′′-H), 7.36–7.33 (m, 2 H, 3′′,5′′-H), 7.31–7.28 (m, 3 H, 3′,5′-H, 4′′-H), 6.78 (d, $^3J_{trans}$ = 15.7 Hz, 1 H, 5-H), 6.23 (dd, $^3J_{trans}$ = 15.7, ^3J = 9.0 Hz, 1 H, 4-H), 4.59 (d, ^3J = 4.7 Hz, 1 H, 1′′′-H), 3.57–3.51 (m, 1 H, 3-H), 3.44 (ABX, $^2J_{AB}$ = 18.3, $^3J_{AX}$ = 5.0 Hz, 1 H, 2-H), 3.40 (ABX, $^2J_{AB}$ = 18.3, $^3J_{BX}$ = 8.1 Hz, 1 H, 2-H), 2.43 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 196.3 (C-1), 145.2 (C-4′), 136.2 (C-5), 135.3 (C-1′′), 133.3 (C-1′), 129.6 (C-3′,5′), 128.7 (C-3′′,5′′), 128.6 (C-4′′), 128.2 (C-2′,6′), 126.8 (C-2′′,6′′), 123.3 (C-4), 112.0 (CN), 111.5 (CN), 40.0 (C-3), 39.4 (C-2), 27.5 (C-1′′′), 21.7 (CH_3) ppm. HRMS (ESI)$^+$: calcd. for [$C_{21}H_{18}N_2O$ + H]$^+$ 315.1492; found 315.1490. HPLC (2-propanol/hexane 10:90, flow rate 0.8 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4d** 19.79 min, retention time of (*R*)-**4d** 32.38 min (*ee* = 84%), after recrystallization (*ee* > 98%).

(*S*,*E*)-2-[1-(4-Methoxyphenyl)-1-oxo-5-phenylpent-4-en-3-yl]malononitrile [(*S*)-4e]:[23] This compound was produced with use of catalyst **1a**. Yellow oil (40.2 mg, 95% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 7.95 (AA′BB′, $^3J_{AB}$ = 8.9, $^4J_{AA'}$ = 2.9, $^5J_{AB'}$ = 2.0 Hz, 2 H, 2′,6′-H), 7.43–7.29 (m, 5 H, 4′′-H, 2′′,6′′-H, 3′′,5′′-H), 6.96 (AA′BB′, $^3J_{AB}$ = 8.9, $^4J_{BB'}$ = 2.9, $^5J_{A'B}$ = 2.0 Hz, 2 H, 3′,5′-H), 6.78 (d, $^3J_{trans}$ = 15.7 Hz, 1 H, 5-H), 6.23 (dd, $^3J_{trans}$ = 15.7, ^3J = 8.9 Hz, 1 H, 4-H), 4.61 (d, ^3J = 4.8 Hz, 1 H, 1′′′-H), 3.89 (s, 3 H, OCH_3), 3.58–3.49 (m, 1 H, 3-H), 3.42 (ABX, $^2J_{AB}$ = 18.3, $^3J_{BX}$ = 5.1 Hz, 1 H, 2-H), 3.36 (ABX, $^2J_{AB}$ = 18.3, $^3J_{AX}$ = 7.8 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 195.1 (C-1), 164.3 (C-4′), 136.2 (C-5), 135.4 (C-1′′), 130.4 (C-2′,6′), 128.8 (C-1′), 128.7 (C-3′′,5′′), 128.6 (C-4′′), 126.8 (C-2′′,6′′), 123.4 (C-4), 114.0 (C-3′,5′), 112.1 (CN), 111.6 (CN), 55.6 (OCH_3), 40.1 (C-3), 39.2 (C-2), 27.5 (C-1′′′) ppm. HRMS (ESI)$^+$: calcd. for [$C_{21}H_{18}N_2O_2$ + H]$^+$ 331.1441; found 331.1439. HPLC (2-propanol/hexane 10:90, flow rate 1.2 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4e** 21.70 min, retention time of (*R*)-**4e** 37.62 min (*ee* = 84%).

(*S*,*E*)-2-[1-(4-Chlorophenyl)-1-oxo-5-phenylpent-4-en-3-yl]malononitrile [(*S*)-4f]:[23] This compound was produced with use of catalyst **1a**. Yellow solid (37.2 mg, 87% yield); m.p. 75–77 °C (hexane/iPr$_2$O). ^{1}H NMR (500.13 MHz, $CDCl_3$, 20 °C): δ = 7.91 (AA′BB′, $^3J_{AB}$ = 8.7, $^4J_{AA'}$ = 2.4, $^5J_{AB'}$ = 1.9 Hz, 2 H, 2′,6′-H), 7.48 (AA′BB′, $^3J_{AB}$ = 8.7, $^4J_{BB'}$ = 2.4, $^5J_{A'B}$ = 1.9 Hz, 2 H, 3′,5′-H), 7.41 (dt, ^3J = 7.3, ^4J = 2.0 Hz, 2 H, 2′′,6′′-H), 7.37–7.33 (m, 2 H, 3′′,5′′-H), 7.30 (tt, ^3J = 7.3, ^4J = 2.0 Hz, 1 H, 4′′-H), 6.79 (d, $^3J_{trans}$ = 15.7 Hz, 1 H, 5-H), 6.21 (dd, $^3J_{trans}$ = 15.7, ^3J = 9.1 Hz, 1 H, 4-H), 4.55 (d, ^3J = 4.8 Hz, 1 H, 1′′′-H), 3.58–3.53 (m, 1 H, 3-H), 3.45 (ABX, $^2J_{AB}$ = 18.7, $^3J_{AX}$ = 5.2 Hz, 1 H, 2-H), 3.40 (ABX, $^2J_{AB}$ = 18.7, $^3J_{BX}$ = 8.2 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 195.5 (C-1), 140.8 (C-4′), 136.5 (C-5), 135.2 (C-1′′), 134.0 (C-1′), 129.5 (C-2′,6′), 129.3 (C-3′,5′), 128.7 (C-3′′,5′′, C-4′′), 126.8 (C-2′′,6′′), 123.0 (C-4), 111.8 (CN),

111.4 (CN), 39.9 (C-3), 39.6 (C-2), 27.5 (C-1‴) ppm. HRMS (ESI)$^+$: calcd. for $[C_{20}H_{15}ClN_2O + H]^+$ 335.0946; found 335.0944. HPLC (2-propanol/hexane 10:90, flow rate 0.8 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4f** 23.53 min, retention time of (*R*)-**4f** 35.14 min (*ee* = 90%), after recrystallization (*ee* > 98%).

(*S*,*E*)-2-[1-(4-Bromophenyl)-1-oxo-5-phenylpent-4-en-3-yl]malononitrile [(*S*)-4g]:[23] This compound was produced with use of catalyst **1a**. Yellow solid (45.1 mg, 93% yield); m.p. 98.6–100.3 °C (hexane/*i*Pr$_2$O). ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): δ = 7.83 (AA′BB′, $^3J_{AB}$ = 8.6, $^4J_{AA'}$ = 2.3, $^5J_{AB'}$ = 1.9 Hz, 2 H, 2′,6′-H), 7.65 (AA′BB′, $^3J_{AB}$ = 8.6, $^4J_{BB'}$ = 2.3, $^5J_{A'B}$ = 1.9 Hz, 2 H, 3′,5′-H), 7.43–7.30 (m, 5 H, 2″,6″-H, 4″-H, 3″,5″-H), 6.79 (d, $^3J_{trans}$ = 15.7 Hz, 1 H, 5-H), 6.21 (dd, $^3J_{trans}$ = 15.7, ^3J = 9.0 Hz, 1 H, 4-H), 4.54 (d, ^3J = 4.8 Hz, 1 H, 1‴-H), 3.57–3.47 (m, 1 H, 3-H), 3.43–3.39 (m, 2 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 195.7 (C-1), 136.4 (C-5), 135.2 (C-1″), 134.4 (C-1′), 132.2 (C-3′,5′), 129.5 (C-2′,6′), 128.7 (C-3″,5″, C-4″), 126.8 (C-2″,6″), 123.0 (C-4), 111.9 (CN), 111.5 (CN), 108.8 (C-4′), 39.8 (C-3), 39.6 (C-2), 27.5 (C-1‴) ppm. HRMS (ESI)$^+$: calcd. for $[C_{20}H_{15}BrNO_2 + H]^+$ 379.0440; found 379.0444. HPLC (2-propanol/hexane 10:90, flow rate 0.9 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4g** 24.63 min, retention time of (*R*)-**4g** 32.48 min (*ee* = 94%), after recrystallization (*ee* > 99%).

(*S*,*E*)-2-[1-(4-Fluorophenyl)-1-oxo-5-phenylpent-4-en-3-yl]malononitrile [(*S*)-4h]:[23] This compound was produced with use of catalyst **1a**. Yellow solid (26.5 mg, 65% yield); m.p. 74–75 °C (hexane/*i*Pr$_2$O). ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): δ = 8.01 (dd, ^3J = 8.9, ^4J = 5.3 Hz, 2 H, 2′,6′-H), 7.44–7.31 (m, 5 H, 2″,6″-H, 3′,5′-H, 4″-H), 7.18 (t, ^3J = 8.6 Hz, 2 H, 3″,5″-H), 6.79 (d, $^3J_{trans}$ = 15.7 Hz, 1 H, 5-H), 6.22 (dd, $^3J_{trans}$ = 15.7, ^3J = 9.0 Hz, 1 H, 4-H), 4.56 (d, ^3J = 4.8 Hz, 1 H, 1‴-H), 3.62–3.56 (m, 1 H, 3-H), 3.44–3.36 (m, 2 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 195.1 (C-1), 166.3 (d, ^1J = 256.9 Hz, C-4′), 136.3 (C-5), 135.2 (C-1″), 132.2 (d, ^4J = 3.2 Hz, C-1′), 130.8 (d, ^3J = 9.6 Hz, C-2′,6′), 128.7 (C-3″,5″, C-4″), 126.8 (C-2″,6″), 123.1 (C-4), 116.1 (d, ^2J = 22.0 Hz, C-3′,5′), 111.9 (CN), 111.5 (CN), 39.9 (C-3), 39.5 (C-2), 27.5 (C-1‴) ppm. HRMS: calcd. for $[C_{20}H_{15}FN_2O + H]^+$ 319.1241; found 319.1244. HPLC (2-propanol/hexane 10:90, flow rate 0.8 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4h** 20.12 min, retention time of (*R*)-**4h** 28.07 min (*ee* = 92%), after recrystallization (*ee* > 98%).

(*S*,*E*)-2-[1-(4-Cyanophenyl)-1-oxo-5-phenylpent-4-en-3-yl]malononitrile [(*S*)-4i]:[23] This compound was produced with use of catalyst **1a**. Yellow oil (35.9 mg, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.06 (AA′BB′, $^3J_{AB}$ = 8.7, $^4J_{AA'}$ = 1.9, $^5J_{AB'}$ = 1.5 Hz, 2 H, 2′,6′-H), 7.82 (AA′BB′, $^3J_{AB}$ = 8.7, $^4J_{BB'}$ = 1.9, $^5J_{A'B}$ = 1.5 Hz, 2 H, 3′,5′-H), 7.43–7.26 (m, 5 H, 2″,6″-H, 3″,5″-H, 4′-H), 6.80 (d, $^3J_{trans}$ = 15.7 Hz, 1 H, 5-H), 6.20 (dd, $^3J_{trans}$ = 15.7, ^3J = 8.9 Hz, 1 H, 4-H), 4.49 (d, ^3J = 4.8 Hz, 1 H, 1‴-H), 3.61–3.54 (m, 1 H, 3-H), 3.49–3.39 (m, 2 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 195.3 (C-1), 138.5 (C-1′), 136.7 (C-5), 135.0 (C-1″), 132.7 (C-3′,5′), 128.8 (C-4″), 128.7 (C-3″,5″), 128.5 (C-2′,6′), 126.8 (C-3″,5″), 122.6 (C-4), 117.5 (CN), 117.3 (C-4′) 111.7 (CN), 111.3 (CN), 40.1 (C-3), 39.8 (C-2), 27.6 (C-1‴) ppm. HPLC (2-propanol/hexane 10:90, flow rate 2.0 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**4i** 22.17 min, retention time of (*R*)-**4i** 31.76 min (*ee* = 82%).

General Procedure for Enantioselective Addition of Nitromethane to Cinnamylideneacetophenones 3a–k – Synthesis of 5a–k: The 1,5-diarylpenta-2,4-dien-1-ones **3a**–**k** (0.128 mmol) and the thiourea catalysts **2a** or **2b** (22.9 mg, 0.038 mmol) were dissolved in nitromethane (0.47 mL, 0.3 M) under nitrogen. The mixture was stirred for 7 d at room temp. The resulting solution was concentrated and purified by column chromatography with elution with hexane/AcOEt (9:1). Finally the residues were crystallized from hexane/AcOEt to afford the desire compounds **5a**–**k**. Compounds (*R*)-**5a** and (*R*)-**5f** have been described previously.[5m]

(*S*,*E*)-3-(Nitromethyl)-1,5-diphenylpent-4-en-1-one [(*S*)-5a]: This compound was produced with use of catalyst **2b**. White solid (32.2 mg, 85% yield); m.p. 105–107 °C (hexane/AcOEt). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 7.96 (d, ^3J = 7.5 Hz, 2 H, 2′,6′-H), 7.60 (t, ^3J = 7.5 Hz, 1 H, 4′-H), 7.48 (t, ^3J = 7.5 Hz, 2 H, 3′,5′-H), 7.34–7.21 (m, 5 H, 2″,6″-H, 3″,5″-H, 4″-H), 6.58 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, 5-H), 6.17 (dd, $^3J_{trans}$ = 15.9, ^3J = 8.6 Hz, 1 H, 4-H), 4.72 (ABX, $^2J_{AB}$ = 12.2, $^3J_{AX}$ = 5.9 Hz, 1‴-H), 4.62 (ABX, $^2J_{AB}$ = 12.2, $^3J_{BX}$ = 7.4 Hz, 1 H, 1‴-H), 3.81–3.70 (m, 1 H, 3-H), 3.30 (d, ^3J = 6.5 Hz, 2 H, 2-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 197.0 (C-1), 136.5 (C-1′), 136.2 (C-1″), 133.6 (C-4′), 133.4 (C-5), 128.8 (C-3′,5′), 128.6 (C-3″,5″), 128.1 (C-2′,6′), 128.0 (C-4″), 126.5 (C-4), 126.4 (C-2″,6″), 78.8 (C-1‴), 40.3 (C-2), 37.3 (C-3) ppm. HRMS (ESI$^+$): calcd. for $[C_{18}H_{17}NO_3 + H]^+$ 296.1281; found 296.1279. $C_{18}H_{17}NO_3$ calcd. C 73.20, H 5.80, N 4.74; found C 73.17, H 5.82, N 4.79. HPLC (2-propanol/hexane 10:90, flow rate 0.7 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5a** 18.21 min, retention time of (*R*)-**5a** 20.63 min (*ee* = 92%), after recrystallization (*ee* > 99%).

(*R*,*E*)-3-(Nitromethyl)-1,5-diphenylpent-4-en-1-one [(*R*)-5a]:[5m] This compound was produced with use of catalyst **2a**. HPLC (2-propanol/hexane 10:90, flow rate 0.7 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5a** 18.31 min, retention time of (*R*)-**5a** 20.70 min (*ee* = 92%), after recrystallization (*ee* > 99%).

(*R*,*E*)-3-(Nitromethyl)-5-(4-nitrophenyl)-1-phenylpent-4-en-1-one [(*R*)-5b]: This compound was produced with use of catalyst **2a**. Yellow solid (28.7 mg, 66% yield); m.p. 121–123 °C (hexane/AcOEt). ^{1}H NMR (500.13 MHz, $CDCl_3$, 20 °C): δ = 8.16 (AA′BB′, $^3J_{AB}$ = 8.8, $^4J_{BB'}$ = 2.4, $^5J_{AB'}$ = 1.9 Hz, 2 H, 3″,5″-H), 7.96 (dt, ^3J = 8.0, ^4J = 1.3 Hz, 2 H, 2′,6′-H), 7.61 (tt, ^3J = 8.0, ^4J = 1.3 Hz, 1 H, 4′-H), 7.50 (td, ^3J = 8.0, ^4J = 1.3 Hz, 2 H, 3′,5′-H), 7.47 (AA′BB′, $^3J_{AB}$ = 8.8, $^4J_{AA'}$ = 2.4, $^5J_{AB'}$ = 1.9 Hz, 2 H, 2″,6″-H), 6.66 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, 5-H), 6.38 (dd, $^3J_{trans}$ = 15.9, ^3J = 8.5 Hz, 1 H, 4-H), 4.77 (ABX, $^2J_{AB}$ = 12.3, $^3J_{AX}$ = 5.6 Hz, 1 H, 1‴-H), 4.66 (ABX, $^2J_{AB}$ = 12.3, $^3J_{BX}$ = 7.6 Hz, 1 H, 1‴-H), 3.84–3.74 (m, 1 H, 3-H), 3.34 (d, ^3J = 6.4 Hz, 2 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 196.6 (C-1), 147.2 (C-4″), 142.5 (C-1″), 136.2 (C-1′), 133.8 (C-4′), 131.6 (C-5), 131.5 (C-4), 128.8 (C-3′,5′), 128.0 (C-2′,6′), 127.0 (C-2″,6″), 124.0 (C-3″,5″), 78.4 (C-1‴), 40.0 (C-2), 37.3 (C-3) ppm. HRMS (ESI$^+$): calcd. for $[C_{18}H_{16}N_2O_5 + Na]^+$ 363.0951; found 363.0950. $C_{18}H_{16}N_2O_5$ calcd. C 63.52, H 4.74, N 8.23; found C 63.47, H 4.63, N 8.00. HPLC (2-propanol/hexane 20:80, flow rate 1.5 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5b** 19.46 min, retention time of (*R*)-**5b** 25.45 min (*ee* = 88%), after recrystallization (*ee* > 99%).

(*R*,*E*)-5-(4-Methoxyphenyl)-3-(nitromethyl)-1-phenylpent-4-en-1-one [(*R*)-5c]: This compound was produced with use of catalyst **2a**. Brown solid (37.9 mg, 91% yield); m.p. 74–75 °C (hexane/AcOEt). ^{1}H NMR (500.13 MHz, $CDCl_3$, 20 °C): δ = 7.95 (dt, ^3J = 7.3, ^4J = 1.6 Hz, 2 H, 2′,6′-H), 7.60 (tt, ^3J = 7.3, ^4J = 1.6 Hz, 1 H, 4′-H), 7.48 (td, ^3J = 7.3, ^4J = 1.6 Hz, 2 H, 3′,5′-H), 7.26 (AA′BB′, $^3J_{AB}$ = 8.7, $^4J_{AA'}$ = 2.9, $^5J_{AB'}$ = 2.0 Hz, 2 H, 2″,6″-H), 6.83 (AA′BB′, $^3J_{AB}$ = 8.7, $^4J_{BB'}$ = 2.9, $^5J_{A'B}$ = 2.0 Hz, 2 H, 3″,5″-H), 6.51 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, 5-H), 6.01 (dd, $^3J_{trans}$ = 15.9, ^3J = 8.6 Hz, 1 H, 4-H), 4.71 (ABX, $^2J_{AB}$ = 12.1, $^3J_{AX}$ = 5.9 Hz, 1 H, 1‴-H), 4.59 (ABX, $^2J_{AB}$ = 12.1, $^3J_{BX}$ = 7.4 Hz, 1 H, 1‴-H), 3.79 (s, 3 H, OCH_3), 3.77–3.66 (m, 1 H, 3-H), 3.28 (d, ^3J = 6.5 Hz, 2 H, 2-

H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 197.2 (C-1), 159.5 (C-4′′), 136.5 (C-1′), 133.6 (C-4′), 132.9 (C-5), 128.9 (C-1′′), 128.7 (C-3′,5′), 128.0 (C-2′,6′), 127.6 (C-2′′,6′′), 124.2 (C-4), 114.0 (C-3′′,5′′), 78.9 (C-1′′′), 55.3 (O*C*H$_3$), 40.4 (C-2), 37.4 (C-3) ppm. HRMS (ESI$^+$): calcd. for [$C_{19}H_{19}NO_4$ + H]$^+$ 326.1387; found 326.1385. $C_{19}H_{19}NO_4$ calcd. C 70.14, H 5.89, N 4.31; found C 70.43, H 5.80, N 3.98. HPLC (2-propanol/hexane 10:90, flow rate 1.2 mL min^{-1}, λ = 254 nm), retention time of (*R*)-**5c** 20.54 min (*ee* > 99%).

(*R*,*E*)-1-(4-Methylphenyl)-3-(nitromethyl)-5-phenylpent-4-en-1-one [(*R*)-5d]: This compound was produced with use of catalyst **2a**. White solid (32.9 mg, 83% yield); m.p. 140–141 °C (hexane/AcOEt). ^{1}H NMR (500.13 MHz, $CDCl_3$, 20 °C): δ = 7.85 (d, ^3J = 8.2 Hz, 2 H, 2′,6′-H), 7.34–7.22 (m, 7 H, 2′′,6′′-H, 3′,5′-H, 3′′,5′′-H, 4′-H), 6.57 (d, $^3J_{trans}$ = 15.8 Hz, 1 H, 5-H), 6.17 (dd, $^3J_{trans}$ = 15.8, ^3J = 8.6 Hz, 1 H, 4-H), 4.72 (ABX, $^2J_{AB}$ = 12.1, $^3J_{AX}$ = 5.7 Hz, 1 H, 1′′′-H), 4.61 (ABX, $^2J_{AB}$ = 12.1, $^3J_{BX}$ = 7.5 Hz, 1 H, 1′′′-H), 3.78–3.71 (m, 1 H, 3-H), 3.27 (d, ^3J = 6.7 Hz, 2 H, 2-H), 2.42 (s, 3 H, C*H*$_3$) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 196.6 (C-1), 144.5 (C-4′), 136.2 (C-1′′), 134.0 (C-1′), 133.3 (C-5), 129.4 (C-3′,5′), 128.6 (C-3′′,5′′), 128.2 (C-2′,6′), 128.0 (C-4′′), 126.6 (C-4), 126.4 (C-2′′,6′′), 78.8 (C-1′′′), 40.2 (C-2), 37.4 (C-3), 21.7 (*C*H$_3$) ppm. HRMS (ESI$^+$): calcd. for [$C_{19}H_{19}NO_3$ + H]$^+$ 310.1438; found 310.1436. $C_{19}H_{19}NO_3$ calcd. C 73.77, H 6.19, N 4.53; found C 73.81, H 6.20, N 4.50. HPLC (2-propanol/hexane 10:90, flow rate 0.7 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5d** 19.32 min, retention time of (*R*)-**5d** 24.30 min (*ee* = 90%), after recrystallization (*ee* > 99%).

(*R*,*E*)-1-(4-Methoxyphenyl)-3-(nitromethyl)-5-phenylpent-4-en-1-one [(*R*)-5e]: This compound was produced with use of catalyst **2a**. Brown solid (33.7 mg, 81% yield); m.p. 101–103 °C (hexane/AcOEt). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 7.94 (AA′BB′, $^3J_{AB}$ = 7.9, $^4J_{AA'}$ = 2.9, $^5J_{AB'}$ = 2.0 Hz, 2 H, 2′,6′-H), 7.35–7.23 (m, 5 H, 4′′-H, 2′′,6′′-H, 3′′,5′′-H), 6.96 (AA′BB′, $^3J_{AB}$ = 7.9, $^4J_{BB'}$ = 2.9, $^5J_{AB'}$ = 2.0 Hz, 2 H, 3′,5′-H), 6.57 (d, $^3J_{trans}$ = 15.8 Hz, 1 H, 5-H), 6.17 (dd, $^3J_{trans}$ = 15.8, ^3J = 8.5 Hz, 1 H, 4-H), 4.72 (ABX, $^2J_{AB}$ = 12.1, $^3J_{AX}$ = 5.9 Hz, 1 H, 1′′′-H), 4.60 (ABX, $^2J_{AB}$ = 12.1, $^3J_{BX}$ = 7.4 Hz, 1 H, 1′′′-H), 3.88 (s, 3 H, OC*H*$_3$), 3.81–3.68 (m, 1 H, 3-H), 3.24 (d, ^3J = 6.6 Hz, 2 H, 2-H) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$, 20 °C): δ = 195.5 (C-1), 163.8 (C-4′), 136.2 (C-1′′), 133.3 (C-5), 130.4 (C-2′,6′), 129.5 (C-1′), 128.5 (C-3′′,5′′), 127.9 (C-4′′), 126.7 (C-4), 126.4 (C-2′′,6′′), 113.9 (C-3′,5′), 78.9 (C-1′′′), 55.5 (O*C*H$_3$), 39.9 (C-2), 37.5 (C-3) ppm. HRMS (ESI$^+$): calcd. for [$C_{19}H_{19}NO_4$ + H]$^+$ 326.1387; found 326.1386. $C_{19}H_{19}NO_4$ calcd. C 70.14, H 5.89, N 4.31; found C 70.44, H 6.16, N 3.99. HPLC (2-propanol/hexane 10:90, flow rate 1.2 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5e** 21.55 min, retention time of (*R*)-**5e** 28.04 min (*ee* = 92%), after recrystallization (*ee* > 99%).

(*R*,*E*)-1-(4-Chlorophenyl)-3-(nitromethyl)-5-phenylpent-4-en-1-one [(*R*)-5f]:[5m] HPLC (2-propanol/hexane 10:90, flow rate 0.7 mL min^{-1}, λ = 254 nm), retention times minor 24.31 min, retention times major 28.95 min (*ee* = 94%), after recrystallization (*ee* > 99%).

(*R*,*E*)-1-(2-Hydroxyphenyl)-3-(nitromethyl)-5-phenylpent-4-en-1-one [(*R*)-5g]: This compound was produced with use of catalyst **2a**. Colorless oil (13.2 mg, 33%). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 12.0 (s, 1 H, O*H*), 7.74 (dd, ^3J = 8.2, ^4J = 1.6 Hz, 1 H, 6′-H), 7.50 (td, ^3J = 8.2, ^4J = 1.6 Hz, 1 H, 4′-H), 7.35–7.27 (m, 5 H, 2′′,6′′-H, 4′′-H, 3′′,5′′-H), 7.00 (d, ^3J = 8.2 Hz, 1 H, 3′-H), 6.93 (t, ^3J = 8.2 Hz, 1 H, 5′-H), 6.59 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, 5-H), 6.14 (dd, $^3J_{trans}$ = 15.9, ^3J = 8.5 Hz, 1 H, 4-H), 4.70 (ABX, $^2J_{AB}$ = 12.2, $^3J_{AX}$ = 6.0 Hz, 1 H, 1′′′-H), 4.61 (ABX, $^2J_{AB}$ = 12.2, $^3J_{BX}$ = 7.2 Hz, 1 H, 1′′′-H), 3.80–3.73 (m, 1 H, 3-H), 3.33 (d, ^3J = 6.6 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 202.9 (C-1), 162.6 (C-2′), 136.9 (C-4′), 136.0 (C-1′′), 133.8 (C-5), 129.6 (C-6′), 128.6 (C-3′′,5′′), 128.1 (C-4′′), 127.4 (C-1′), 126.4 (C-2′′,6′′), 126.0 (C-4), 119.2 (C-5′), 118.8 (C-3′), 78.8 (C-1′′′), 40.0 (C-2), 37.1 (C-3) ppm. HRMS (ESI$^+$): calcd. for [$C_{18}H_{17}NO_4$ + Na]$^+$ 334.1050; found 334.1049. HPLC (2-propanol/hexane 3:97, flow rate 0.9 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5g** 28.49 min, retention time of (*R*)-**5g** 31.50 min (*ee* = 90%).

(*R*,*E*)-1-(2-Aminophenyl)-3-(nitromethyl)-5-phenylpent-4-en-1-one [(*R*)-5h]: This compound was produced with use of catalyst **2a**. Colorless oil (7.5 mg, 19%). ^{1}H NMR (300.13 MHz, $CDCl_3$, 20 °C): δ = 7.70 (dd, ^3J = 8.5, ^3J = 1.4 Hz 1 H, 6′-H), 7.34–7.23 (m, 6 H, 4′-H, 2′′,6′′-H, 4′′-H, 3′′,5′′-H), 6.67–6.64 (m, 2 H, 3′-H, 5′-H), 6.57 (d, $^3J_{trans}$ = 15.8 Hz, 1 H, 5-H), 6.28 (br. s, 2 H, N*H*$_2$), 6.17 (dd, $^3J_{trans}$ = 15.8, ^3J = 8.6 Hz, 1 H, 4-H), 4.71 (ABX, $^2J_{AB}$ = 12.1, $^3J_{AX}$ = 5.6 Hz, 1 H, 1′′′-H), 4.57 (ABX, $^2J_{AB}$ = 12.1, $^3J_{BX}$ = 7.9 Hz, 1 H, 1′′′-H), 3.78–3.71 (m, 1 H, 3-H), 3.27 (ABX, $^2J_{AB}$ = 17.1, $^3J_{AX}$ = 6.0 Hz, 1 H, 2-H), 3.23 (ABX, $^2J_{AB}$ = 17.1, $^3J_{BX}$ = 7.1 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$, 20 °C): δ = 195.6 (C-1), 152.5 (C-2′), 138.0 (C-1′′), 134.8 (C-4′), 133.2 (C-5), 130.7 (C-6′), 128.6 (C-3′′,5′′), 127.9 (C-4′′), 126.9 (C-4), 126.4 (C-2′′,6′′), 118.4 (C-1′), 117.5 (C-5′), 116.0 (C-3′), 79.0 (C-1′′′), 40.8 (C-2), 37.6 (C-3) ppm. HRMS (ESI$^+$): calcd. for [$C_{18}H_{18}N_2O_3$ + H]$^+$ 311.1390; found 311.1389. HPLC (2-propanol/hexane 20:80, flow rate 1.5 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5h** 14.86 min, retention time of (*R*)-**5h** 18.19 min (*ee* = 87%).

(*R*,*E*)-1-(4-Bromophenyl)-3-(nitromethyl)-5-phenylpent-4-en-1-one [(*R*)-5i]: This compound was produced with use of catalyst **2a**. Yellow solid (36.8 mg, 77% yield); m.p. 147–148 °C (hexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.82 (AA′BB′, $^3J_{AB}$ = 8.6, $^4J_{AA'}$ = 2.4, $^5J_{AB'}$ = 1.9 Hz, 2 H, 2′,6′-H), 7.63 (AA′BB′, $^3J_{BA}$ = 8.6, $^4J_{BB'}$ = 2.4, $^5J_{BA'}$ = 1.9 Hz, 2 H, 3′,5′-H), 7.35–7.24 (m, 5 H, 4′′-H, 2′′,6′′-H, 3′′,5′′-H), 6.58 (d, $^3J_{trans}$ = 15.8 Hz, 1 H, 5-H), 6.15 (dd, $^3J_{trans}$ = 15.8, ^3J = 8.6 Hz, 1 H, 4-H), 4.70 (ABX, $^2J_{AB}$ = 12.1, $^3J_{AX}$ = 4.1 Hz, 1 H, 1′′′-H), 4.61 (ABX, $^2J_{AB}$ = 12.1, $^3J_{BX}$ = 7.1 Hz, 1 H, 1′′′-H), 3.79–3.68 (m, 1 H, 3-H), 3.30 (ABX, $^2J_{AB}$ = 17.7, $^3J_{AX}$ = 6.5 Hz, 1 H, 2-H), 3.22 (ABX, $^2J_{AB}$ = 17.7, $^3J_{BX}$ = 6.3 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 196.0 (C-1), 136.0 (C-1′′), 135.1 (C-1′), 133.6 (C-5), 132.1 (C-3′,5′), 128.9 (C-4′), 129.5 (C-2′,6′), 128.6 (C-3′′,5′′), 128.1 (C-4′′), 126.4 (C-2′′,6′′), 126.2 (C-4), 78.7 (C-1′′′), 40.3 (C-2), 37.2 (C-3) ppm. HRMS: calcd. for [$C_{18}H_{16}NO_3$ + H]$^+$ 374.0386; found 374.0387. $C_{18}H_{16}NO_3$ calcd. C 57.77, H 4.31, N 3.74; found C 57.51, H 4.27, N 3.76. HPLC (2-propanol/hexane 10:90, flow rate 0.9 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5i** 24.64 min, retention time of (*R*)-**5i** 29.38 min (*ee* = 84%), after recrystallization (*ee* > 96%).

(*R*,*E*)-1-(4-Fluorophenyl)-3-(nitromethyl)-5-phenylpent-4-en-1-one [(*R*)-5j]: This compound was produced with use of catalyst **2a**. Yellow solid (32.4 mg, 81% yield); m.p. 80–82 °C (hexane/AcOEt). ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): δ = 7.99 (dd, ^3J = 9.0, ^4J = 5.4 Hz, 2 H, 2′,6′-H), 7.35–7.24 (m, 5 H, 3′,5′-H, 2′′,6′′-H, 4′′-H), 7.15 (t, ^3J = 8.6 Hz, 2 H, 3′′,5′′-H), 6.58 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, 5-H), 6.16 (dd, $^3J_{trans}$ = 15.9, ^3J = 8.6 Hz, 1 H, 4-H), 4.71 (ABX, $^2J_{AB}$ = 12.1, $^3J_{AX}$ = 6.0 Hz, 1 H, 1′′′-H), 4.62 (ABX, $^2J_{AB}$ = 12.1, $^3J_{BX}$ = 7.2 Hz, 1 H, 1′′′-H), 3.80–3.68 (m, 1 H, 3-H), 3.30 (ABX, $^2J_{AB}$ = 17.8, $^3J_{AX}$ = 6.6 Hz, 1 H, 2-H), 3.24 (ABX, $^2J_{AB}$ = 17.8, $^3J_{BX}$ = 6.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 195.4 (C-1), 166.0 (d, ^1J = 255.8 Hz, C-4′), 136.1 (C-1′′), 133.5 (C-5), 132.9 (d, ^4J = 3.0 Hz, C-1′), 130.72 (d, ^3J = 9.4 Hz, C-2′,6′), 128.6 (C-3′′,5′′), 128.0 (C-4′′), 126.4 (C-2′′,6′′),

126.3 (C-4), 115.9 (d, ^2J = 22.0 Hz, C-3′,5′), 78.7 (C-1′′′), 40.2 (C-2), 37.3 (C-3) ppm. HRMS: calcd. for $[C_{18}H_{16}FNO_3 + H]^+$ 314.1187; found 314.1186. $C_{18}H_{16}FNO_3$ calcd. C 69.00, H 5.15, N 4.47; found C 68.98, H 5.15, N 4.51. HPLC (2-propanol/hexane 10:90, flow rate 0.9 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5j** 20.34 min, retention time of (*R*)-**5j** 23.61 min (*ee* = 91%), after recrystallization (*ee* > 99%).

(*R*,*E*)-1-(4-Cyanophenyl)-3-(nitromethyl)-5-phenylpent-4-en-1-one [(*R*)-5k]: This compound was produced with use of catalyst **2a**. Yellow solid (35.2 mg, 86% yield); m.p. 95–96 °C (hexane/AcOEt). ^{1}H NMR (300.13 MHz, $CDCl_3$, 25 °C): δ = 8.04 (dd, ^3J = 8.7, ^4J = 1.7 Hz, 2 H, 2′,6′-H), 7.79 (dd, ^3J = 8.7, ^4J = 1.7 Hz, 2 H, 3′,5′-H), 7.34–7.24 (m, 5 H, 2′′,6′′-H, 3′′,5′′-H, 4′′-H), 6.59 (d, $^3J_{trans}$ = 15.9 Hz, 1 H, 5-H), 6.14 (dd, $^3J_{trans}$ = 15.9, ^3J = 8.6 Hz, 1 H, 4-H), 4.70 (ABX, $^2J_{AB}$ = 12.2, $^3J_{AX}$ = 6.3 Hz, 1 H, 1′′′-H), 4.63 (ABX, $^2J_{AB}$ = 12.2, $^3J_{BX}$ = 6.8 Hz, 1 H, 1′′′-H), 3.78–3.71 (m, 1 H, 3-H), 3.36 (ABX, $^2J_{AB}$ = 17.5, $^3J_{AX}$ = 6.7 Hz, 1 H, 2-H), 3.28 (ABX, $^2J_{AB}$ = 17.5, $^3J_{BX}$ = 6.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 195.8 (C-1), 139.2 (C-1′), 135.9 (C-1′′), 133.9 (C-5), 132.6 (C-3′,5′), 128.6 (C-3′′,5′′), 128.4 (C-2′,6′), 128.2 (C-4′′), 125.8 (C-2′′,6′′), 125.5 (C-4), 117.7 (CN), 116.8 (C-4′), 78.5 (C-1′′′), 40.6 (C-2), 37.1 (C-3) ppm. HRMS: calcd. for $[C_{19}H_{16}N_2O_3 + H]^+$ 321.1234; found 321.1236. $C_{19}H_{16}N_2O_3$ calcd. C 71.24, H 5.03, N 8.74; found C 70.94, H 5.02, N 8.75. HPLC (2-propanol/hexane 10:90, flow rate 2.0 mL min^{-1}, λ = 254 nm), retention time of (*S*)-**5k** 19.69 min, retention time of (*R*)-**5k** 29.38 min (*ee* = 94%), after recrystallization (*ee* > 99%).

CCDC-739751 [for (*S*)-**4a**] and CCDC-739750 [for (*S*)-**5a**] 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.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra, chiral HPLC analysis and X-ray data.

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[1] a) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771–806; b) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; c) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; d) G. Guillena, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492; e) D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299–365; f) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065–2092; g) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; h) K. Maruoka, *Org. Process Res. Dev.* **2008**, *12*, 679–697; i) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171.

[2] a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; b) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656–5682; c) L.-W. Xu, J. Luoa, Y. Lu, *Chem. Commun.* **2009**, 1807–1821.

[3] M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discov. Today* **2007**, *12*, 8–27.

[4] a) J. W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y. C. Chen, Y. Wu, J. Zhu, J. G. Deng, *Angew. Chem. Int. Ed.* **2007**, *46*, 389–392; b) J. W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J. G. Deng, Y. C. Chen, *Org. Lett.* **2007**, *9*, 413–415; c) W. Chen, W. Du, Y. Z. Duan, Y. Wu, S. Y. Yang, Y. C. Chen, *Angew. Chem. Int. Ed.* **2007**, *46*, 7667–7670; d) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L. S. Ding, Y. C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816–821; e) A. Erkkila, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470; f) A. Carlone, G. Bartoli, M. Bosco, F. Pesciaioli, P. Ricci, L. Sambri, P. Melchiorre, *Eur. J. Org. Chem.* **2007**, 5492–5495; g) G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403–1405; h) X. F. Li, L. F. Cun, C. X. Lian, L. Zhong, Y. C. Chen, J. Liao, J. Zhu, J. G. Deng, *Org. Biomol. Chem.* **2008**, *6*, 349–353; i) P. Ricci, A. Carlone, G. Bartoli, M. Bosco, L. Sambri, P. Melchiorre, *Adv. Synth. Catal.* **2008**, *350*, 49–53; j) X. J. Lu, L. Deng, *Angew. Chem. Int. Ed.* **2008**, *47*, 7710–7713; k) C. Ying-Chun, *Synlett* **2008**, 1919–1930; l) G. Bartoli, P. Melchiorre, *Synlett* **2008**, 1759–1772; m) S. Gogoi, C. G. Zhao, D. R. Ding, *Org. Lett.* **2009**, *11*, 2249–2252; n) L. T. Dong, R. J. Lu, Q. S. Du, J. M. Zhang, S. P. Liu, Y. N. Xuan, M. Yan, *Tetrahedron* **2009**, *65*, 4124–4129.

[5] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) B. Vakulya, S. Varga, A. Csampai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969; c) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; d) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; e) J. Wang, H. Li, L. S. Zu, W. Jiang, H. X. Xie, W. H. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652–12653; f) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; g) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; h) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; i) C. L. Gu, L. Liu, Y. Sui, J. L. Zhao, D. Wang, Y. J. Chen, *Tetrahedron: Asymmetry* **2007**, *18*, 455–463; j) S. J. Connon, *Chem. Commun.* **2008**, 2499–2510; k) B. Vakulya, S. Varga, T. Soós, *J. Org. Chem.* **2008**, *73*, 3475–3480; l) L. Hai-Hua, W. Xu-Fan, Y. Chang-Jiang, Z. Jian-Ming, W. Hong, X. Wen-Jing, *Chem. Commun.* **2009**, 4251–4253; m) C. G. Oliva, A. M. S. Silva, F. A. A. Paz, J. A. S. Cavaleiro, *Synlett* **2010**, in press.

[6] a) E. J. Corey, F. Y. Zhang, *Org. Lett.* **2000**, *2*, 4257–4259; b) D. Y. Kim, S. C. Huh, *Tetrahedron* **2001**, *57*, 8933–8938; c) S. Hanessian, S. Govindan, J. S. Warrier, *Chirality* **2005**, *17*, 540–543; d) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933–971; e) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346–5348; f) T. Ooi, S. Takada, S. Fujioka, K. Maruoka, *Org. Lett.* **2005**, *7*, 5143–5146; g) C. E. T. Mitchell, S. E. Brenner, J. García-Fortanet, S. V. Ley, *Org. Biomol. Chem.* **2006**, *4*, 2039–2049; h) S. Hanessian, Z. H. Shao, J. S. Warrier, *Org. Lett.* **2006**, *8*, 4787–4790; i) P. F. Li, Y. C. Wang, X. M. Liang, J. X. Ye, *Chem. Commun.* **2008**, 3302–3304; j) K. Mei, M. Jin, S. L. Zhang, P. Li, W. J. Liu, X. B. Chen, F. Xue, W. H. Duan, W. Wang, *Org. Lett.* **2009**, *11*, 2864–2867.

[7] a) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 4032–4035; b) T. Inokuma, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2006**, *128*, 9413–9419.

[8] a) N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 661–665; b) K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66–68; c) P. F. Li, S. G. Wen, F. Yu, Q. X. Liu, W. J. Li, Y. C. Wang, X. M. Liang, J. X. Ye, *Org. Lett.* **2009**, *11*, 753–756.

[9] M. B. Cid, J. Lopez-Cantarero, S. Duce, J. L. G. Ruano, *J. Org. Chem.* **2009**, *74*, 431–434.

[10] D. P. Li, Y. C. Guo, Y. Ding, W. J. Xiao, *Chem. Commun.* **2006**, 799–801.

[11] T. Y. Liu, R. Li, Q. Chai, J. Long, B. J. Li, Y. Wu, L. S. Ding, Y. C. Chen, *Chem. Eur. J.* **2007**, *13*, 319–327.
[12] a) F. Y. Zhang, E. J. Corey, *Org. Lett.* **2000**, *2*, 1097–1100; b) J. Wang, H. Li, L. S. Zu, W. Wang, *Adv. Synth. Catal.* **2006**, *348*, 425–428.
[13] T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem. Int. Ed.* **2008**, *47*, 8051–8054.
[14] a) T. E. Horstmann, D. J. Guerin, S. J. Miller, *Angew. Chem. Int. Ed.* **2000**, *39*, 3635–3638; b) D. Pettersen, F. Plana, L. Bernardi, F. Fini, M. Fochi, V. Sgarzani, A. Ricci, *Tetrahedron Lett.* **2007**, *48*, 7805–7808; c) D. Perdicchia, K. A. Jørgensen, *J. Org. Chem.* **2007**, *72*, 3565–3568.
[15] a) S. Jew, J. H. Lee, B. S. Jeong, M. S. Yoo, M. J. Kim, Y. J. Lee, J. Lee, S. H. Choi, K. Lee, M. S. Lah, H. Park, *Angew. Chem. Int. Ed.* **2005**, *44*, 1383–1385; b) D. R. Li, A. Murugan, J. R. Falck, *J. Am. Chem. Soc.* **2008**, *130*, 46–48.
[16] a) P. McDaid, Y. G. Chen, L. Deng, *Angew. Chem. Int. Ed.* **2001**, *41*, 338–340; b) B. J. Li, L. Jiang, M. Liu, Y. C. Chen, L. S. Ding, Y. Wu, *Synlett* **2005**, 603–606; c) Y. Liu, B. F. Sun, B. M. Wang, M. Wakem, L. Deng, *J. Am. Chem. Soc.* **2009**, *131*, 418–419.
[17] Further details on the single-crystal X-ray diffraction studies are given as Supporting Information. This compound crystallize as colorless prisms, in the orthorhombic $P2_12_12_1$ space group with $Z = 4$. Crystal data for (*S*)-**4a**: $C_{20}H_{16}N_2O$, $M = 300.35$, $T = 150(2)$ K, $a = 5.65340(10)$ Å, $b = 13.6153(4)$ Å, $c = 20.6207(6)$ Å, $V = 1587.23(7)$ Å^3, μ(Mo-K_α) = 0.079 mm^{-1}, $D_c = 1.257$ g cm^{-3}, crystal size: $0.26 \times 0.08 \times 0.08$ mm^3. Of a total of 19017 reflections collected, 2439 were independent ($R_{int} = 0.0242$). Final $R1 = 0.0345$ [$I > 2\sigma(I)$] and $wR2 = 0.0851$ (all data). Data completeness to $\theta = 29.12°$, 98.8%. CCDC-739751.
[18] Further details on the single-crystal X-ray diffraction studies are given as Supporting Information. This compound crystallizes as colorless prisms, in the orthorhombic $P2_12_12_1$ space group with $Z = 4$. Crystal data for (*S*)-**5a**: $C_{18}H_{17}NO_3$, $M = 295.33$, $T = 180(2)$ K, $a = 5.6100(2)$ Å, $b = 11.9959(3)$ Å, $c = 23.0786(7)$ Å, $V = 1553.12(8)$ Å^3, μ(Mo-K_α) = 0.086 mm^{-1}, $D_c = 1.263$ g cm^{-3}, crystal size: $0.26 \times 0.19 \times 0.16$ mm^3. Of a total of 31462 reflections collected, 3376 were independent ($R_{int} = 0.0274$). Final $R_1 = 0.0525$ [$I > 2\sigma(I)$] and $wR_2 = 0.1433$ (all data). Data completeness to $\theta = 33.15°$, 99.6%. CCDC-739750.
[19] S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370.
[20] a) D. C. G. A. Pinto, A. M. S. Silva, A. Levai, J. A. S. Cavaleiro, J. Elguero, T. Patonay, *J. Eur. J. Org. Chem.* **2000**, 2593; b) C. M. M. Santos, A. M. S. Silva, J. A. S. Cavaleiro, A. Levai, T. Patonay, *Eur. J. Org. Chem.* **2007**, 2877; c) D. I. S. P. Resende, C. G. Oliva, A. M. S. Silva, F. A. A. Paz, J. A. S. Cavaleiro, *Synlett* **2010**, 115–118.
[21] U. Sundermeier, C. Dobler, G. M. Mehltretter, W. Baumann, M. Beller, *Chirality* **2003**, *15*, 127–134.
[22] H. Brunner, J. Bugler, B. Nuber, *Tetrahedron: Asymmetry* **1995**, *6*, 1699–1702.
[23] The numbering of the cinnamylideneacetophenone moiety has been kept for easier comprehension of the NMR spectroscopic data.

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