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Enantioselective Conjugate Additions of "Difficult" Ketones to Nitrodienynes and Tandem Annulations

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Dedicated to Professor Dieter Enders on the occasion of his 70th birthday.

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Abstract: The first enantioselective conjugate additions of problematic aromatic ketones and acetone to nitrodienynes have been achieved by employing a chiral multifunctional primary amine catalyst recently developed by us. The reactions took place in a 1,4-manner. Furthermore, by utilizing the resulting chiral functionalized 1,3-enynes as a starting point, we have developed unprecedented *p*-toluenesulfonic acid-catalyzed tandem annulations, which allow the efficient and selective construction of various synthetically useful cyclic 1,5-diketones (R = Ar) and dienones (R = Me).

Keywords: acetone; aromatic ketones; conjugate addition; nitrodienynes; tandem annulations

Introduction

Conjugate addition is one of the most important tools for the construction of C–C bonds.[1] In this context, the direct conjugate addition of carbonyl compounds to nitroolefins has received much attention, as the resulting adducts, γ-nitrocarbonyl compounds, are valuable building blocks in organic synthesis.[2] Hence, considerable effort has been devoted to the development of asymmetric catalysts for such processes. In sharp contrast to the high enantioselectivities obtained with cyclic ketones, especially cyclohexanones,[3] aromatic ketones and acetone still remain two of the most problematic substrates for the nitro-Michael addition. To date, only a few catalysts have been reported for the conjugate addition of either aromatic ketones[4] or acetone[5] with enantiomeric excesses of >90%. Moreover, it is noteworthy that there are few catalysts with broad substrate scope that can catalyze the asymmetric conjugate addition of both aromatic ketones and acetone to nitroolefins with high enantioselectivities.[6] Recently, we designed and synthesized a new class of chiral primary amine catalysts bearing multiple hydrogen-bonding donors which efficiently catalyzed the conjugate addition of both aromatic ketones and acetone to nitroolefins with excellent enantioselectivities (up to 99% *ee*).[6a,7] To additionally demonstrate the significance and generality of this class of chiral primary amine catalysts, we became interested in the more "difficult" transformations – regioselective and enantioselective conjugate addition of aromatic ketones to polyconjugated nitrodienynes and the reaction between acetone and nitrodienynes. Such previously unreported processes, if successful, would provide an efficient access to 1,3-enynes, which are important structural motifs found in many natural products and drugs,[8] and are versatile building blocks for organic synthesis.[9]

In recent years, the conjugate addition of polyconjugated substrates has received increasing attention.[10] Recently, we introduced nitrodienynes as a new class of polyconjugated substrates,[11] and reported the enantioselective nickel-catalyzed conjugate addition of 1,3-dicarbonyl compounds to nitrodienynes.[11] Later, we developed the enantioselective conjugate addition of acetaldehyde to nitrodienynes catalyzed by a chiral secondary amine.[12] The obtained 1,3-enynes have been demonstrated to be useful intermediates for the enantioselective synthesis of *Amaryllidaceae* alkaloids such as (+)-α-lycorane and (+)-ly-

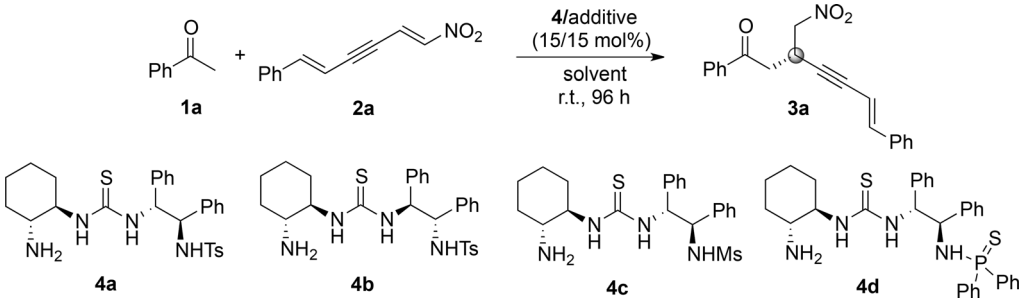
corine.[13] Encouraged by these successes, we decided to significantly expand the scope of the conjugate addition reactions of nitrodienynes by using both aromatic ketones and acetone as more challenging reacting partners.

As part of our interest in developing new catalytic asymmetric reactions involving conjugated alkynes,[14] herein we report the first enantioselective conjugate addition of problematic aromatic ketones and acetone to polyconjugated nitrodienynes catalyzed by a chiral multifunctional primary amine catalyst recently developed by us. These processes provide novel and useful 1,3-enynes bearing a γ-nitro ketone motif in good yields with high enantioselectivities. Furthermore, by utilizing the resulting chiral 1,3-enynes as a new starting point, we have developed unprecedented Brønsted acid-catalyzed tandem annulations, which allow the efficient and selective construction of various synthetically useful cyclic 1,5-diketones (R = Ar) and dienones (R = Me).

Results and Discussion

Initially, the model reaction between aromatic ketone **1a** and nitrodienyne **2a** was explored in the presence of our chiral primary amine catalysts in DCM at room temperature. To our delight, these newly developed primary amine catalysts prompted the model reaction (Table 1). Among these catalysts, **4a** provided the best results (75% yield and 97% *ee*) (entry 1). Its diastereoisomer **4b** afforded 54% yield and 91% *ee* (entry 2).The presence of acid additives was crucial for the reaction to occur. Without an acid additive, the reaction became sluggish (entry 7). Among the acid additives examined, 4-$MeOC_6H_4CO_2H$ was found to be the best. Solvents had varied effects on the yield but little influence on the enantioselectivity (entries 9–14). DCM was found to be the optimal solvent. When the reaction took place at an elevated temperature (40 °C), the product **3a** was obtained in 53% yield and 93% *ee* (entry 8). Thus, under the optimized reaction conditions, 1,4-addition product **3a** with a propargylic stereocenter was obtained in 75% yield with 97% *ee*. Notably, either the 1,6- or 1,8-addition product was not detected in any case.

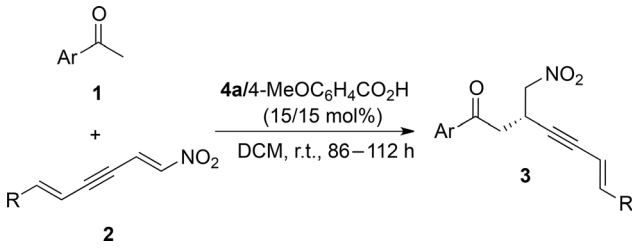
Table 1. Optimization of the reaction conditions for the enantioselective conjugate addition of **1a** to **2a**.[a]



Entry	**4**	Additive	Solvent	Yield [%][b]	*ee* [%][c]
1	**4a**	4-$MeOC_6H_4CO_2H$	DCM	**75**	**97**
2	**4b**	4-$MeOC_6H_4CO_2H$	DCM	54	91
3	**4c**	4-$MeOC_6H_4CO_2H$	DCM	56	96
4	**4d**	4-$MeOC_6H_4CO_2H$	DCM	60	96
5	**4a**	4-$NO_2C_6H_4CO_2H$	DCM	60	95
6	**4a**	$PhCO_2H$	DCM	50	92
7	**4a**	–	DCM	trace	ND
8[d]	**4a**	4-$MeOC_6H_4CO_2H$	DCM	53	93
9	**4a**	4-$MeOC_6H_4CO_2H$	$CHCl_3$	68	96
10	**4a**	4-$MeOC_6H_4CO_2H$	DCE	62	96
11	**4a**	4-$MeOC_6H_4CO_2H$	toluene	58	95
12	**4a**	4-$MeOC_6H_4CO_2H$	*m*-xylene	60	96
13	**4a**	4-$MeOC_6H_4CO_2H$	ether	55	91
14	**4a**	4-$MeOC_6H_4CO_2H$	EtOAc	42	92

[a] *Reaction conditions:* **1a** (0.3 mmol), **2a** (0.1 mmol), **4** (0.015 mmol), additive (0.015 mmol), and solvent (0.3 mL) at room temperature.
[b] Yield of isolated product.
[c] Determined by HPLC on a chiral stationary phase.
[d] At 40 °C.

Table 2. Enantioselective conjugate addition of aromatic ketones to nitrodienynes.[a]



Entry	Ar	R	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	**3a**, 75	97
2	Ph	4-Me-C_6H_4	**3b**, 76	97
3	Ph	3-Me-C_6H_4	**3c**, 70	94
4	Ph	4-MeO-C_6H_4	**3d**, 72	95
5	Ph	1,3-benzodioxole	**3e**, 79	96
6	Ph	4-Cl-C_6H_4	**3f**, 82	96
7	Ph	2-thienyl	**3g**, 64	83
8	Ph	Me	**3h**, 73	91
9	4-Me-C_6H_4	Ph	**3i**, 64	96
10	4-MeO-C_6H_4	Ph	**3j**, 69	97
11	4-NO_2-C_6H_4	Ph	**3k**, 70	96
12	3-NO_2-C_6H_4	Ph	**3l**, 72	96
13	4-CF_3-C_6H_4	Ph	**3m**, 69	97
14	4-Br-C_6H_4	Ph	**3n**, 78	98

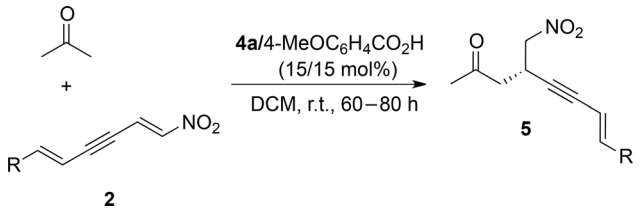
[a] *Reaction conditions:* **1** (0.3 mmol), **2** (0.1 mmol), **4a** (0.015 mmol), 4-$MeOC_6H_4CO_2H$ (0.015 mmol), and DCM (0.3 mL) at room temperature.
[b] Yield of isolated product.
[c] Determined by HPLC on a chiral stationary phase.

Under the optimized reaction conditions, the scope of the conjugate addition reaction of aromatic ketones to nitrodienynes was examined (Table 2). The reaction has a broad substrate scope with respect to both aromatic ketones and nitrodienynes. Various aromatic- and heteroaromatic-substituted nitrodienynes underwent smoothly the conjugate addition reaction with aromatic ketones (entries 1–7). Notably, an alkyl-substituted nitrodienyne was also a suitable substrate for the conjugate reaction (entry 8). With regard to aromatic ketones, it appears that the position and the electronic property of the substituent on the aromatic ring are well tolerated by the conjugate addition reaction (entries 9–14).

The present catalyst systems were also suitable for the enantioselective conjugate addition of acetone to nitrodienynes (Table 3). Various functionalized 1,3-enynes **5** were obtained in good yields with high enantioselectivities.

The 1,4-adducts obtained through the present protocols are versatile building blocks because they contain three functional groups: an enyne, a ketone, and a nitro group. For example, Pd/C-catalyzed chemoselective hydrogenation of 1,3-enyne **3h** gave saturated

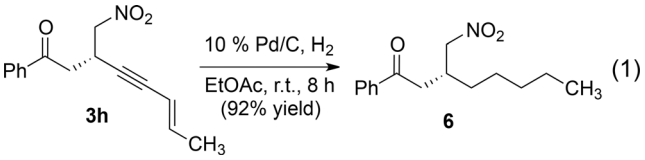
Table 3. Enantioselective conjugate addition of acetone to nitrodienynes.[a]



Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph	**5a**, 90	91
2	4-Me-C_6H_4	**5b**, 88	90
3	3-Me-C_6H_4	**5c**, 83	82
4	4-MeO-C_6H_4	**5d**, 88	90
5	1,3-benzodioxole	**5e**, 86	93
6	4-Cl-C_6H_4	**5f**, 85	87
7	2-thienyl	**5g**, 81	91
8	Me	**5h**, 84	80

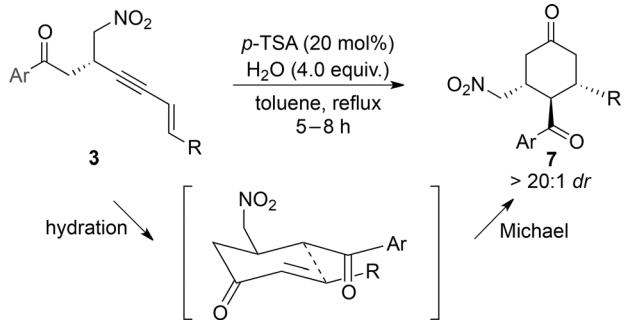
[a] *Reaction conditions:* acetone (1.0 mmol), **2** (0.1 mmol), **4a** (0.015 mmol), 4-$MeOC_6H_4CO_2H$ (0.015 mmol), and DCM (0.3 mL) at room temperature.
[b] Yield of isolated product.
[c] Determined by HPLC on a chiral stationary phase.

γ-nitro ketone **6** in 92% yield [Eq. (1)], thus demonstrating an efficient route to products equivalent to the direct conjugate addition of aromatic ketones to alkyl-substituted nitroolefins *via* two effective atom-economic catalytic addition processes.[15] The (*S*) configuration was established by comparison of the optical rotation of **6** with the previously reported value of this compound.[16]



To further demonstrate the utility of our Michael adducts, tandem annulations were then investigated. Treatment of 1,4-adducts **3** of aromatic ketones with H_2O in the presence of *p*-toluenesulfonic acid (*p*-TSA) (20 mol%) in toluene at 110 °C produced 1,5-diketones **7** bearing three contiguous stereocenters in good yields with excellent diastereoselectivities (> 20:1) without loss of enantioselectivities (Table 4).[17] 1,5-Diketones exhibit various bioactivities including antitumor and antidiabetic.[18] They are also useful intermediates for the preparation of heterocyclic compounds such as substituted pyridines and quinolines.[19] Thus, the development of a new and efficient method to prepare 1,5-diketones is of great value. The present catalytic tandem reaction, which involved regioselective hydration of 1,3-enynes (*in situ* genera-

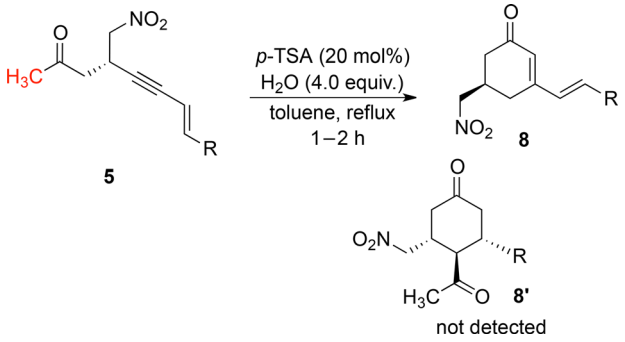
Table 4. Tandem hydration/intramolecular Michael cyclization: synthesis of 1,5-diketones.[a]



Entry	Ar	R	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	**7a**, 88	97
2	Ph	4-Me-C_6H_4	**7b**, 86	96
3	Ph	3-Me-C_6H_4	**7c**, 85	95
4	Ph	4-MeO-C_6H_4	**7d**, 85	96
5	Ph	1,3-benzodioxole	**7e**, 81	95
6	Ph	4-Cl-C_6H_4	**7f**, 92	94
7	Ph	Me	**7g**, 80	93
8	4-Me-C_6H_4	Ph	**7h**, 91	98
9	4-MeO-C_6H_4	Ph	**7i**, 90	96
10	4-NO_2-C_6H_4	Ph	**7j**, 88	96
11	3-NO_2-C_6H_4	Ph	**7k**, 93	96
12	4-CF_3-C_6H_4	Ph	**7l**, 92	97
13	4-Br-C_6H_4	Ph	**7m**, 91	88

[a] The reaction was performed with **3** (0.1 mmol), *p*-TSA (0.02 mmol) and H_2O (4.0 equiv.) in toluene (0.5 mL) under reflux for 5–8 h.
[b] Yield of isolated product.
[c] Determined by HPLC on a chiral stationary phase.

Table 5. Tandem hydration/intramolecular aldol cyclization: synthesis of dienones.[a]



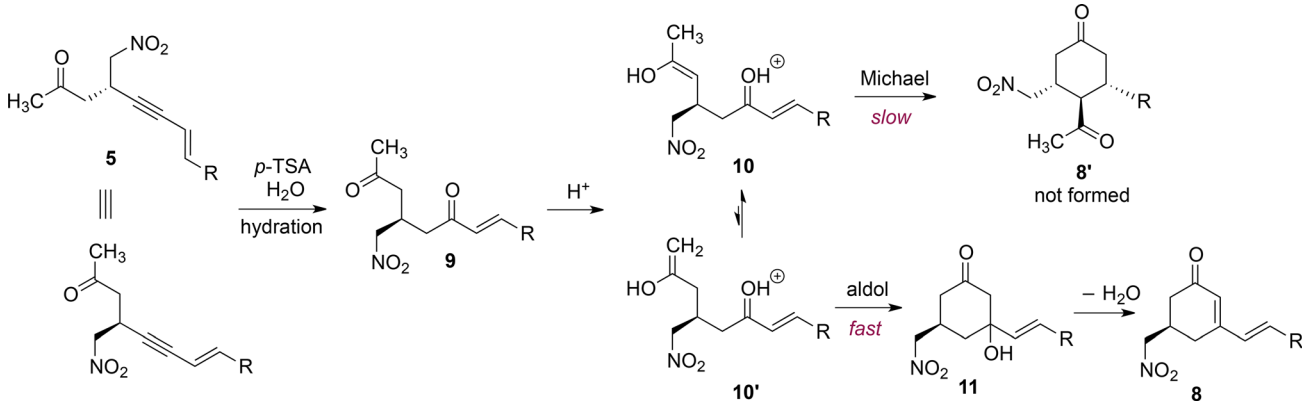
Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph	**8a**, 92	94
2	4-Me-C_6H_4	**8b**, 95	88
3	3-Me-C_6H_4	**8c**, 90	85
4	4-MeO-C_6H_4	**8d**, 96	89
5	1,3-benzodioxole	**8e**, 93	92
6	4-Cl-C_6H_4	**8f**, 96	89
7	2-thienyl	**8g**, 90	94

[a] The reaction was performed with **5** (0.1 mmol), *p*-TSA (0.02 mmol) and H_2O (4.0 equiv.) in toluene (0.5 mL) under reflux for 1–2 h.
[b] Yield of isolated product.
[c] Determined by HPLC on a chiral stationary phase.

tion of enones) followed by intramolecular Michael cyclization, provides a new and attractive alternative for the preparation of these synthetically useful compounds.

Interestingly, when the 1,4-adducts **5** of acetone were subjected to the same reaction conditions, a distinct annulation reaction took place, providing synthetically useful enantioenriched cyclic dienones **8** rather than 1,5-diketones **8′** (Table 5). It is noteworthy that due to the vinylogous reactivity, cyclic dienones have been demonstrated as a useful class of compounds, for example, in enantioselective transition metal-catalyzed and organocatalyzed reactions.[20]

The exclusive formation of **8** suggested that this tandem annulation reaction proceeded through hydration of 1,3-enynes followed by intramolecular aldol cyclization instead of Michael cyclization. A possible reaction mechanism is proposed in Scheme 1. The *p*-TSA was proposed to play multiple roles in the tandem reactions: (i) catalyzing the regioselective hy-



Scheme 1. Proposed reaction mechanism for the tandem reaction of **5**.

dration of alkynes to *in situ* generate α,β-unsaturated enones; (ii) promoting the subsequent either Michael or aldol cyclization. The formation of dienones **8** rather than 1,5-diketones **8′** suggested that the intramolecular aldol cyclization of **10′** is faster than the corresponding Michael cyclization of **10**.

Conclusions

In summary, we have developed two more "difficult" conjugate addition reactions – the conjugate addition of aryl ketones to our newly designed polyconjugated nitrodienynes and the reaction between acetone and nitrodienynes. These two transformations were efficiently catalyzed by a common chiral primary amine organocatalyst recently developed by us. The reactions took place in 1,4-manner. The processes provided new and synthetically useful 1,3-enynes bearing a γ-nitro ketone motif in good yields with high enantioselectivities. Furthermore, by utilizing the resulting chiral functionalized 1,3-enynes as a unique starting point, we have developed unprecedented *p*-TSA-catalyzed tandem annulations, which provided a new, rapid and selective method to various synthetically valuable 1,5-diketones (R = Ar) and dienones (R = Me), respectively.

Experimental Section

General Methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrophotometer. Chemical shifts (δ) are expressed in ppm, and *J* values are given in Hz. The enantiomeric excess was determined by HPLC using Chiralpak AD-H, Chiralcel OD-H and Chiralcel OJ-H columns with *n*-hexane and 2-propanol as eluents. High resolution mass spectrometry (HR-MS) was recorded on a VG Auto Spec-3000 spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (230–400 mesh).

General Procedure for the Enantioselective Conjugate Addition of Aromatic Ketones to Nitrodienynes

To a solution of aromatic ketone **1** (0.3 mmol) and nitrodienyne **2** (0.1 mmol) in DCM (0.3 mL) was added catalyst **4a** (15 mol%) and 4-MeOC$_6$H$_4$CO$_2$H (15 mol%). The resulting solution was stirred at room temperature until the reaction was complete (monitored by TLC). The crude product was purified by flash silica gel chromatography (petroleum ether/ethyl acetate as eluents).

Characterization of a representative compound – (*S*,*E*)-3-(nitromethyl)-1,7-diphenylhept-6-en-4-yn-1-one (3a): yield: 23.9 mg (75%); yellow oil; $[\alpha]_D^{20}$: + 50.4 (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.6 Hz, 2H), 7.57–7.53 (m, 1H), 7.46–7.42 (m, 2H), 7.29–7.27 (m, 3H), 7.23–7.21 (m, 2H), 6.82 (d, *J* = 16.4 Hz, 1H), 6.01 (d, *J* = 16.0 Hz, 1H), 4.66 (dd, *J* = 12.4 Hz, *J* = 5.6 Hz, 1H), 4.56 (dd, *J* = 12.0 Hz, *J* = 6.8 Hz, 1H), 3.99 (t, *J* = 6.4 Hz, 1H), 3.38 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.2, 142.2, 136.1, 136.0, 133.8, 128.8, 128.8, 128.7, 128.2, 126.3, 107.2, 87.9, 83.4, 77.5, 40.4, 27.0; HR-MS: *m/z* = 342.1100, calcd. for $C_{20}H_{17}NO_3Na$ $[M+Na]^+$: 342.1102; HPLC (Chiralcel AD-H, 2-propanol/*n*-hexane = 30/70, flow rate 0.95 mL min^{-1}, λ = 254 nm): t_{major} = 12.9 min, t_{minor} = 14.9 min.

General Procedure for the Enantioselective Conjugate Addition of Acetone to Nitrodienynes

To a solution of acetone (1.0 mmol) and nitrodienyne **2** (0.1 mmol) in DCM (0.3 mL) was added catalyst **4a** (15 mol%) and 4-MeOC$_6$H$_4$CO$_2$H (15 mol%). The resulting solution was stirred at room temperature until the reaction was complete (monitored by TLC). The crude product was purified by flash silica gel chromatography (petroleum ether/ethyl acetate as eluents).

Characterization of a representative compound – (*S*,*E*)-4-(nitromethyl)-8-phenyloct-7-en-5-yn-2-one (5a): yield: 23.1 mg (90%); yellow oil; $[\alpha]_D^{20}$: +118.5 (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.19 (m, 5H), 6.83 (d, *J* = 16.4 Hz, 1H), 6.00 (d, *J* = 16.4, 1H), 4.56–4.50 (m, 1H), 4.49–4.44 (m, 1H), 3.78–3.72 (m, 1H), 2.80 (d, *J* = 7.2 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.7, 142.2, 135.9, 128.8, 128.7, 128.6, 126.3, 107.1, 87.6, 83.3, 77.3, 44.9, 30.2, 26.7; HR-MS: *m/z* = 280.0944, calcd. for $C_{15}H_{15}NO_3Na$ $[M+Na]^+$: 280.0948; HPLC (Chiralcel AD-H, 2-propanol/*n*-hexane = 30/70, flow rate 0.9 mL min^{-1}, λ = 254 nm): t_{major} = 10.7 min, t_{minor} = 11.7 min.

General Procedure for the Tandem Hydration/Michael Cyclization

To a solution of **3** (0.1 mmol) in toluene (0.5 mL) was added *p*-TSA (20 mol%) and H_2O (4.0 equiv.). The resulting solution was stirred under reflux until the reaction was complete (monitored by TLC). The crude product was purified by flash silica gel chromatography (petroleum ether/ethyl acetate as eluents).

Characterization of a representative compound – (3*S*,4*S*,5*R*)-4-benzoyl-3-(nitromethyl)-5-phenylcyclohexanone (7a): yield: 29.6 mg (88%); colourless oil; $[\alpha]_D^{20}$: −2.4 (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.13–7.11 (m, 3H), 6.82–6.80 (m, 2H), 4.53 (dd, *J* = 12.0 Hz, *J* = 4.8 Hz, 1H), 4.42 (dd, *J* = 12.0 Hz, *J* = 5.6 Hz, 1H), 4.13–4.10 (m, 1H), 3.74–3.70 (m, 1H), 3.16–3.10 (m, 2H), 2.98–2.92 (m, 1H), 2.76–2.71 (m, 1H), 2.47–2.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 199.9, 138.8, 136.6, 133.7, 129.0, 128.5, 128.2, 127.9, 127.7, 77.8, 47.6, 44.2, 42.4, 41.9, 34.0; HR-MS: *m/z* = 336.1241, calcd. for $C_{20}H_{18}NO_4$ $[M-H]^+$: 336.1240; HPLC (Chiralcel AD-H, 2-propanol/*n*-hexane = 20/80, flow rate 0.9 mL min^{-1}, λ = 254 nm): t_{minor} = 10.0 min, t_{major} = 12.6 min.

General Procedure for the Tandem Hydration/Aldol Cyclization

To a solution of **5** (0.1 mmol) in toluene (0.5 mL) was added *p*-TSA (20 mol%) and H_2O (4.0 equiv.). The resulting solution was stirred under reflux until the reaction was complete (monitored by TLC). The crude product was purified by flash silica gel chromatography (petroleum ether/ethyl acetate as eluents).

Characterization of a representative compound – (*R*,*E*)-5-(nitromethyl)-3-styrylcyclohex-2-enone (8a): yield: 28.0 mg (93%); yellow solid; $[\alpha]_D^{20}$: −34.0 (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.43 (m, 2H), 7.34–7.30 (m, 3H), 6.99–6.92 (m, 1H), 6.88–6.82 (m, 1H), 6.09–6.08 (m, 1H), 4.46–4.42 (m, 2H), 2.98 (m, 1H), 2.87–2.82 (m, 1H), 2.60–2.55 (m, 1H), 2.42–2.34 (m, 1H), 2.31–2.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.4, 154.3, 136.2, 135.6, 129.5, 129.0, 128.3, 127.7, 127.4, 79.3, 40.5, 33.4, 28.4; HR-MS: *m/z* = 257.1049, calcd. for $C_{15}H_{15}NO_3$ $[M]^+$: 257.1052; HPLC (Chiralcel OD-H, 2-propanol/*n*-hexane = 25/75, flow rate 0.9 mL min^{-1}, λ = 254 nm): t_{minor} = 34.526 min, t_{major} = 40.329 min.

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