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Iterative Coupling of Two Different Enones by Nitromethane Using Bifunctional Thiourea Organocatalysts. Stereocontrolled Assembly of Cyclic and Acyclic Structures

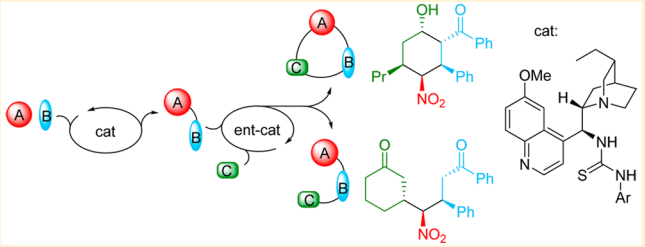
Szilárd Varga,[†] Gergely Jakab,[†] Antal Csámpai,[‡] and Tibor Soós*[,†]

[†]Institute of Organic Chemistry, Research Centre for Natural Sciences, HAS, P.O. Box 286, Budapest, H-1519, Hungary

[‡]Institute of Chemistry, Department of Inorganic Chemistry, L. Eötvös University, Pázmány Péter sétány 1/A, Budapest H-1117, Hungary

Supporting Information

ABSTRACT: An organocatalytic iterative assembly line has been developed in which nitromethane was sequentially coupled with two different enones using a combination of pseudoenantiomeric cinchona-based thiourea catalysts. Application of unsaturated aldehydes and ketones in the second step of the iterative sequence allows the construction of cyclic *syn*-ketols and acyclic compounds with multiple contiguous stereocenters. The combination of the multifunctional substrates and ambident electrophiles rendered some organocatalytic transformations possible that have not yet been realized in bifunctional noncovalent organocatalysis.

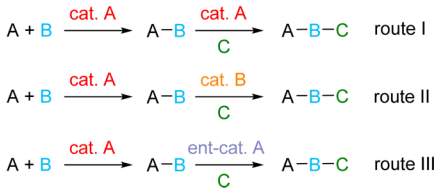


INTRODUCTION

Over the past decade, organocatalysis has risen from an interesting niche application into a mainstream catalytic concept for constructing chiral molecules.[1] Today, the subfield of organocascade reactions[2] is experiencing a dynamic expansion due to their unique capacity to deliver a large variety of complex molecules with multiple stereocenters.[3] While there is a growing interest in the utilization of this appealing synthetic approach in total synthesis,[4] the current focus is still to explore the applicability of organocascade reactions and develop an in-depth understanding of the mechanisms.[5]

Many of the reported organocascade applications have employed only one catalyst (Scheme 1, route I) in multicomponent domino reactions. Nevertheless, in several cases, consecutive reaction steps cannot be promoted by a single organocatalyst;[6] therefore, combination of two organocatalysts in a one-pot reaction is needed to synthesize densely functionalized chiral molecules (Scheme 1, route II).

Scheme 1. Multicomponent Organocatalytic Assemblies of Chiral Molecules



As most of the organocascade reactions proceed through chiral intermediates, the importance and reactivity consequence of double diastereocontrol cannot be neglected. For instance, we have recently found a limiting case for multicomponent reactions in bifunctional thiourea organocatalysis due to the exaggerated form of the double diastereocontrol.[7] Accordingly, the chiral product of the first organocatalytic Michael addition step precluded its own further reactions owing to a special mismatched catalyst–substrate combination. To overcome this mismatch limitation, we used the opposite enantiomer of the first applied organocatalyst to promote subsequent organocatalytic steps. Since the catalytic activity of the enantiomeric catalysts is not orthogonal, it became necessary to conduct these reactions in an iterative manner to gain access to densely functionalized cyclohexanes[2i] in a Michael–(Michael–Henry) sequence (Scheme 1, route III).

Herein, we report the extension of this iterative assembly line using enals or enones in the second step. Interestingly, the unique combination of multifunctional chiral intermediates and ambident electrophiles renders some organocatalytic transformations possible that would be hard to realize using monofunctional substrates and a single thiourea catalyst. Furthermore, the iterative application of enantiomeric bifunctional thioureas allowed the access to not only cyclic, but also acylic products.

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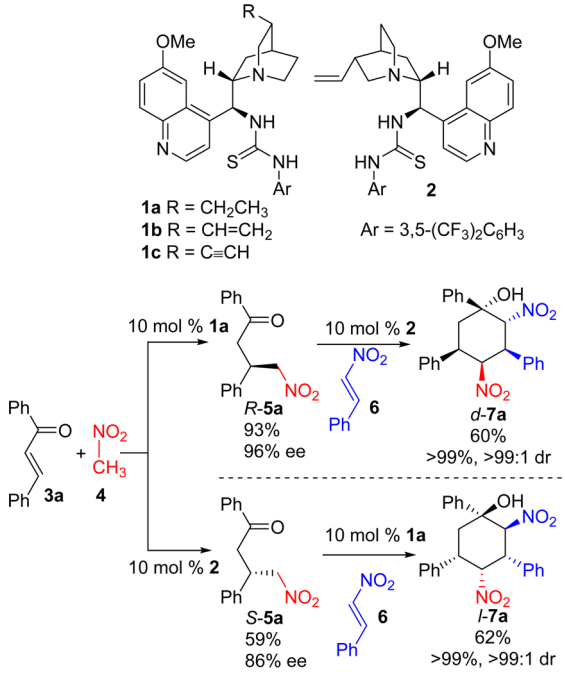
RESULTS AND DISCUSSION

Our group has recently reported an iterative organocatalytic process in which the (*R*)-**5a** or (*S*)-**5a** chiral chalcone–nitromethane Michael adducts were transformed into functionalized cyclohexanes (*d*-**8a** or *l*-**8a**, respectively) in a second step using a variety of nitroalkenes (Scheme 2).[7] The second organocatalytic Michael–Henry cascade afforded a large variety of densely functionalized chiral molecules with high diastereoselectivities.

Scheme 2. Iterative Organocatalytic Michael–(Michael–Henry) Cyclization



Encouraged by the efficiency and selectivity of this iterative process, we were interested in expanding the utility of this approach toward more challenging substrates that are not commonly used in bifunctional thiourea catalysis.[8,9] Therefore, a variety of α,β-unsaturated aldehydes and ketones were probed in the second organocatalytic step. Notwithstanding being less electrophilic, the structural features of these substrates rendered the outcome of the organocatalytic reaction more complex. A plausible Henry adduct **10** (Figure 1, path 1),[10] a Michael adduct **9** (path 2) or its ring-closed aldol derivatives **11**, and **12** (path 3a,b) could be envisioned as possible products.

These synthetic possibilities led us to probe the ability of α,β-unsaturated aldehyde **8a** to participate in an iterative or even in a cascade organocatalytic sequence (Scheme 3). We first examined whether our envisioned reactions could be performed in a single-catalyst, one-pot fashion using the same organocatalyst that afforded the first chiral Michael adduct (Scheme 3, route a). However, similar to our previous results,[7] neither a Henry reaction nor a Michael–aldol organocascade occurred owing to the catalyst–substrate mismatch. However, to our delight, the iterative approach (Scheme 3, route b) that employs the combination of pseudoenantiomeric catalysts **1a** and **2** provided the cyclohexane derivative **13a** with excellent enantio-, diastereo-, and chemoselectivity. Most importantly, the bifunctional organocatalysts were able to induce a Michael addition onto α,β-unsaturated aldehyde **8a** and then promote a

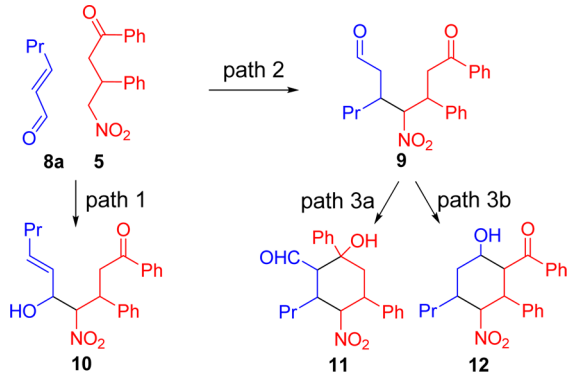
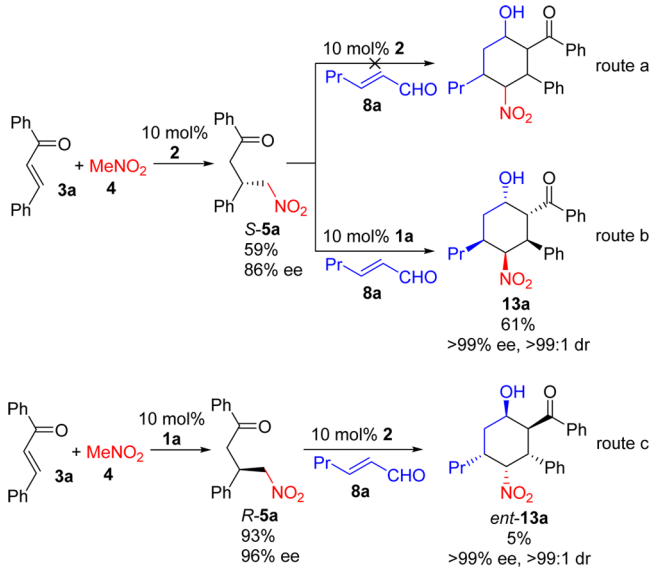


Figure 1. Possible outcome of the organocatalyzed reaction of α,β-unsaturated aldehyde **8a** with the Michael adduct **5**.

Scheme 3. Selective Cyclization with Bifunctional Thiourea Organocatalysis



direct intramolecular aldol reaction to selectively furnish the ketocyclohexanol **13a**. Accordingly, the bifunctional thiourea catalyst was not only capable of the activation of the ketone moiety of (*S*)-**5a** but also of inducing the proper alignment of the aldehyde moiety to afford the *syn*-ketol functionality.[11] Using the opposite sequence of organocatalysts **1a** and **2** (Scheme 3, route c) provided the *ent*-**13a** cyclic ketol with the same selectivity but with lower yields (no side reaction was detected) as the applied pseudoenatiomeric catalysts are not enantiomers but diastereomers and the basicities of the quinuclidine nitrogen are also different in the two catalysts.

After the successful demonstration of the Michael–aldol cyclization, we examined the influence of experimental parameters (e.g., solvent, catalyst type and load, reagents' stoichiometry, concentration). The reaction was found to be more rapid and efficient in less polar medium (Table 1, entries 1–4). Nevertheless, the polarity of the solvent did not influence the enantio-, diastereo-, and chemoselectivity of the process. The cyclization reaction failed in MeOH, which might be the result of the combined effect of the solvent polarity and the solvent inhibition of the H-bond catalysis. As compared to toluene, larger amounts of substrates could be dissolved in chloroform; thus, a more concentrated reaction mixture was the reason for the observed higher yield (Table 1, entries 1, 6, and

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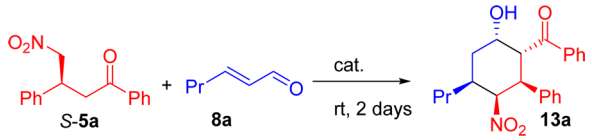
Table 1. Optimization of Reaction Conditions of Michael−Ketol Cyclization



entry[a]	cat.	cat. load (%)	solvent	**8a** (equiv)	vol (mL)	yield (%)	ee[b] (%)	dr[c]
1	**1a**	10	$CHCl_3$	1	1	20	99	>99:1
2	**1a**	10	toluene	1	1	26	>99	>99:1
3	**1a**	10	CH_3CN	1	1	4	>99	>99:1
4	**1a**	10	Et_2O	1	1	5	98	>99:1
5	**1a**	10	MeOH	1	1	0		
6	**1a**	10	$CHCl_3$	1	0.5	40	>99	>99:1
7	**1a**	10	$CHCl_3$	1	0.25	55	>99	>99:1
8	**1a**	10	$CHCl_3$	2	0.25	61	>99	>99:1
9	**1a**	10	$CHCl_3$	5	0.25	15	>99	>99:1
10	**1a**	5	$CHCl_3$	2	0.25	9	>99	>99:1
11	**1a**	1	$CHCl_3$	2	0.25	0		
12	**1b**	10	$CHCl_3$	2	0.25	38	>99	>99:1
13	**1c**	10	$CHCl_3$	2	0.25	6	>99	>99:1

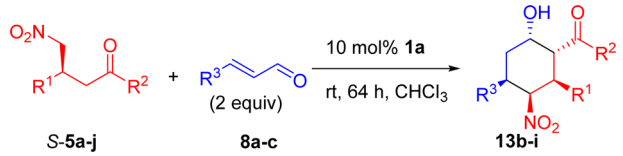
[a]Unless otherwise noted, all reactions were performed with (*S*)-**5a** (0.56 mmol), (*E*)-hex-2-enal (**8a**), and added catalyst in 1.0 mL solvent at room temperature for 2 days. [b]Determined by chiral HPLC analysis. [c]Determined by NMR spectroscopy.

7). Next, the molar ratio of substrates were changed, and it was found that the optimal conversion was at a 2 molar excess of reagent **8a** (Table 1, entries 7−9). Using the most basic catalyst **1a**, one can decrease the catalyst load only to 5 mol % because the conversions were markedly lowered at reduced catalyst load (Table 1, entries 10 and 11). Probing catalyst systems **1a−c**, no difference between their selectivity was observed, although the least basic catalyst **1c** afforded **13a** with the lowest conversion (Table 1, entries 12 and 13).

Having established an optimal reaction condition, we began to explore the substrate scope (Table 2). The aromatic Michael adducts (*S*)-**5a−g** were able to react with not only aromatic **8c** (Table 2, entry 11) but also aliphatic unsaturated aldehydes **8a,b** (Table 2, entries 1−6, 10). This organocatalytic process also tolerated the presence of different para substituents at the phenyl ring of Michael adducts (*S*)-**5a−g**. However, no transformation was observed with Michael adducts (*S*)-**5h−j** having no aromatic substituents next to their nitroalkane group (Table 2, entries 7−9). As a general observation, no other adduct was observed in these reactions besides the cyclic ketols.

Next, a representative selection of α,β-unsaturated oxo compounds **8d,e** and **14a−d** was tested (Scheme 4). First, the α-substituted methacrolein **8d** was employed in the cyclization process, which afforded a diastereomeric mixture of **13m−m″**. Detailed NMR structural investigation revealed the exclusive syn selectivity of the final ketol-formation step. Accordingly, the organocatalyst **1a** was able to override any steric or stereochemical bias of the newly formed stereocenters (the methyl or nitro groups). As a limitation, the α,β-disubstituted aldehyde (**8e**) and β-substituted acyclic ketone (**14a**) failed to react with the Michael adduct (*S*)-**5a**, which was due to their attenuated reactivity. Nevertheless, methyl vinyl ketone **14b** underwent a smooth organocatalytic Michael reaction to yield a mixture of diastereomers of **13p**. To determine the feasibility of using β-substituted ketones in this organocatalytic transformation, more reactive cyclic ketones (**14c,d**) were considered for investigation. We found that both cyclopentenone and cyclohexenone afforded Michael adducts (**13q,r**) with excellent diastereoselectivity, and no further

Table 2. Investigation of the Substrate Scope of the Organocatalyzed Michael−Aldol Cyclization



entry[a]	R^1, R^2, R^3	**5**	**13**	yield[b] (%)	ee[c] (%)	dr[d]
1	*p*-MeO-C_6H_4, Ph, Pr	**5b**	**13b**	34	>99	96:4
2	*p*-Cl-C_6H_4, Ph, Pr	**5c**	**13c**	42	98	97:3
3	*p*-Me-C_6H_4, Ph, Pr	**5d**	**13d**	48	>99	95:5
4	Ph, *p*-MeO-C_6H_4, Pr	**5e**	**13e**	41	99	94:6
5	Ph, *p*-Cl-C_6H_4, Pr	**5f**	**13f**	41	98	94:6
6	Ph, *p*-Me-C_6H_4, Pr	**5g**	**13g**	51	>99	89:11
7	Cy, Ph, Pr	**5h**	**13h**	0		
8	$C_6H_5CH_2CH_2$, Ph, Pr	**5i**	**13i**	0		
9	C_6H_5CHCH, Ph, Pr	**5j**	**13j**	0		
10	Ph, Ph, Et	**5a**	**13k**	65	>99	94:6
11	Ph, Ph, Ph	**5a**	**13l**	27	>99	> 99:1

[a]The reactions were performed with 0.56 mmol of Michael adduct (*S*)-**5a−j**, 1.12 mmol of α,β-unsaturated aldehydes **8a−c**, and 0.056 mmol of catalyst **1a** in 0.25 mL of chloroform at room temperature for 64 h. [b]Combined yields of diastereomers. [c]Determined by chiral HPLC analysis. [d]Determined by NMR spectroscopy.

reaction, e.g., ring formation, occurred. The observed stereochemistry of the newly formed C−C bond was in accordance with the stereochemical model; i.e., the external chiral induction capacity of bifunctional organocatalyst **1a** was able to override the influence of the configuration of the Michael adduct (*S*)-**5a**. This unique organocatalytic example of the substrate (first Michael adduct) and subsequent catalyst control (second Michael step) enabled us to realize controlled iterative Michael additions to afford molecules with an acyclic vicinal stereotriad. We note in passing that the applied organocatalysts

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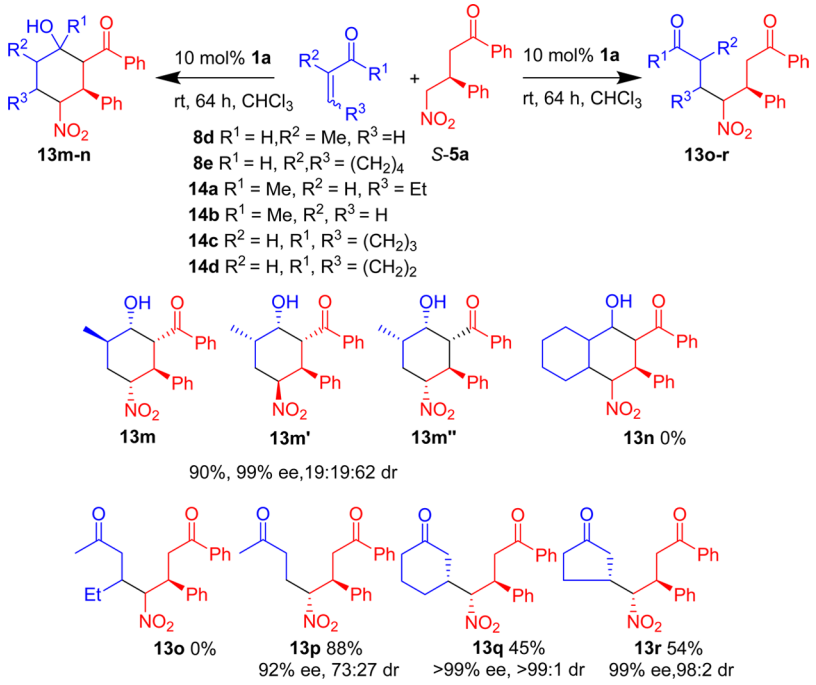
Scheme 4. Representative Substrate Screening for Iterative Organocatalytic Sequences Involving the Michael Adduct 5a



1 or **2** are not able to promote the addition of nitromethane or nitroethane to cyclohexenone **14c**.

CONCLUSION

In summary, we have developed a bifunctional-thiourea-based iterative organocatalytic synthetic approach that utilizes α,β-enals or enones in the second step. Accordingly, in this iterative sequence, the nitromethane was sequentially coupled with two different enones in a well-orchestrated manner. Our results not only reinforce the importance of the double diastereocontrol in noncovalent bifunctional organocatalysis but also demonstrate that by using appropriate multifunctional intermediate one can render many organocatalytic transformations possible that have not yet been realized with less functionalized substrates. An illustrative set of examples was presented, including the activation of aldehydes and the highly selective intramolecular *syn*-ketol and iterative Michael–Michael sequences via this approach. Although not single operational, the merit of this iterative method lies in its efficiency to construct stereochemically dense and synthetically demanding architectures with an exquisite level of both enantio- and diastereoselectivities. Investigations aimed at generalizing the above concept are underway.

EXPERIMENTAL SECTION

General Experimental Procedures. NMR spectra were acquired at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, DMSO-d_6; 2.50 ppm, $CDCl_3$, 77.0 ppm for ^{13}C NMR). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad-band-decoupled mode. Only the NMR shifts (^{1}H, ^{13}C) of the major diastereomer are reported due to the difficulty to assign the minor component. The determination of the structure and relative configuration of products were performed on 500 MHz NMR spectrometer. Chemical shifts are referenced to residual solvent signals.

Mass spectra were recorded on a Q-TOF mass spectrometer operated in electrospray negative-ionization mode. The Cl^- ion adduct or deprotonated molecular ion has been measured. Melting points are uncorrected. IR spectra are reported in wavenumbers (cm^{-1}). The enantiomeric excess (ee) of the products was determined by chiral stationary phase. The chiral HPLC retention time of the minor component was determined in the following manner. Using catalysts **1** and **2** in the reverse order in the organo-iterative procedure, one can obtain the expected cyclohexane with inverted absolute stereochemistry. Therefore, we carried out those experiments on 20 mg scales in every case, with isolated cyclohexane products using preparative-layer chromatography, and they were used as a standard for the determination of the retention time of the minor enantiomer (or generating a mixture with the other enantiomer).

General Procedure for Synthesis of Cyclohexane Derivatives in the Michael–Aldol or Michael Reactions. A 4 mL vial equipped with a magnetic stirring bar was charged with nitromethane chalcone adduct (0.56 mmol (*S*)-**5a–j**), α,β-unsaturated oxo compound (1.1 mmol **8a–e**, **14a–d**), and chloroform (0.25 mL). Then catalyst (30 mg, 0.05 mmol, 10 mol % **1a**) was added. Stirring was maintained at room temperature for 64 h. The solvent was evaporated from the crude reaction mixture and purified by flash chromatography using a hexane/acetone eluent system.

*((1R,2S,3S,4S,6S)-6-Hydroxy-3-nitro-2-phenyl-4-propylcyclohexyl)phenylmethanone (**13a**):* yield 61% (126 mg); white crystal; mp = 143 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.94 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.15–7.09 (m, 5H), 5.12 (dd, J = 2.1, 12.3 Hz, 1H), 4.99 (t, J = 4.2 Hz, 1H), 4.42 (d, J = 2.4 Hz, 1H), 4.03 (dd, J = 4.2, 12.3 Hz, 1H), 2.65–2.55 (m, 1H), 2.18 (td, J = 2.4, 14.4 Hz, 1H), 2.00 (dt, J = 3.9, 14.1 Hz, 1H), 1.50–1.24 (m, 4H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 30 °C) δ = 202.3, 137.4, 136.2, 134.0, 128.91, 128.87, 128.3, 127.8, 127.4, 92.5, 66.4, 45.4, 41.7, 34.2, 33.1, 32.2, 19.8, 14.0; IR (KBr) 3447, 2958, 2931, 1685, 1544, 1447, 1375, 1272, 702 cm^{-1}; HR-MS ESI exact mass calcd for $C_{22}H_{25}NO_4Cl$ $[M + Cl]^-$ 402.1472, found 402.1481; $[\alpha]^{25}_D$ = −78 (c = 0.01 in chloroform, >99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak OD column, 20% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times major 5.5 min, minor 6.4 min.

*((1R,2S,3S,4S,6S)-6-Hydroxy-2-(4-methoxyphenyl)-3-nitro-4-propylcyclohexyl)phenylmethanone (**13b**):* yield 34% (77 mg); white

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crystal; mp = 73 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.94 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 6,67 (d, J = 8.7 Hz, 2H) 5.07 (dd, J = 2.1, 12.3 Hz, 1H), 4.96 (t, J = 4.2 Hz, 1H), 4.40 (br s, 1H), 3.97 (dd, J = 4.2, 12.3 Hz, 1H), 3.67 (s, 3H), 2.71 (br s, 1H), 2.60−2.53 (m, 1H), 2.17 (br t, J = 14.1 Hz, 1H), 1.98 (dt, J = 3.6, 14.4 Hz, 1H), 1.47−1.23 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 30 °C) δ = 202.6, 158.9 136.3, 133.9, 129.4, 128.9, 128.5, 128.3, 114.2, 92.7, 66.4, 55.0, 45.6, 40.8, 34.3, 33.0, 32.1, 19.8, 14.0; IR (KBr) 3483, 2957, 2929, 1672, 1613, 1544, 1514, 1447, 1375, 1343, 1251, 1180, 1034, 700 cm^{-1}; HR-MS ESI exact mass calcd for $C_{23}H_{26}NO_5$ [M − H]$^-$ 396.1811, found 396.1820; $[\alpha]^{25}_D$ = −76 (c = 0.01 in chloroform, >99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak OD column, 10% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times major 10.2 min, minor 14.7 min.

*((1R,2S,3S,4S,6S)-2-(4-Chlorophenyl)-6-hydroxy-3-nitro-4-propylcyclohexyl)phenylmethanone (**13c**):* yield 42% (95 mg); white crystal; mp = 144 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.94 (d, J = 7.2 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.18−7.03 (m, 4H), 5.06 (dd, J = 2.1, 12.3 Hz, 1H), 4.96 (t, J = 4.2 Hz, 1H), 4.44 (br s, 1H), 4.02 (dd, J = 4.2, 12.3 Hz, 1H), 2.59−2.52 (m, 2H), 2.17 (t, J = 13.5 Hz, 1H), 1.99 (dt, J = 3.9, 14.1 Hz, 1H), 1.47−1.24 (m, 4H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 30 °C) δ = 201.8, 136.1, 136.0, 134.1, 133.7, 129.1, 129.0, 128.8, 128.3, 92.3, 66.3, 45.6, 40.9, 34.2, 33.0, 32.2, 19.8, 14.0 ppm; IR (KBr) 3435, 2955, 2928, 1686, 1545, 1492, 1374, 1013, 698 cm^{-1}; HR-MS ESI exact mass calcd for $C_{22}H_{23}NO_4Cl$ [M − H]$^-$ 400.1316, found 400.1316; $[\alpha]^{25}_D$ = −76 (c = 0.01 in chloroform, >99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak OD column, 10% ethanol in hexane, 1.0 mL/min, λ = 211 nm, retention times major 8.8 min, minor 11.4 min.

*((1R,2S,3S,4S,6S)-6-Hydroxy-3-nitro-4-propyl-2-p-tolylcyclohexyl)phenylmethanone (l-**13d**):* yield 48% (103 mg); white crystal; mp = 154 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.95 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.01−6.93 (m, 4H), 5.10 (dd, J = 1.8, 12.3 Hz, 1H), 4.97 (t, J = 4.2 Hz, 1H), 4.41 (br s, 1H), 3.99 (dd, J = 4.5, 12.3 Hz, 1H), 2.63−2.55 (m, 2H), 2.19 (s, 3H), 1.98 (dt, J = 3.9, 14.1 Hz, 1H), 1.50−1.21 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 30 °C) δ = 202.4, 137.4, 136.2, 134.4, 133.9, 126.6, 128.9, 128.4, 127.3, 92.7, 66.4, 45.5, 41.2, 34.3, 33.0, 32.2, 20.9, 19.8, 14.0; IR (KBr) 3449, 2957, 2929, 1681, 1546, 1449, 1375, 700 cm^{-1}; HR-MS ESI exact mass calcd for $C_{23}H_{27}NO_4Cl$ [M + Cl]$^-$ 416.1629, found 416.1629; $[\alpha]^{25}_D$ = −78 (c = 0.01 in chloroform, >99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak OD column, 10% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times major 8.9 min, minor 11.3 min.

*((1R,2S,3S,4S,6S)-6-Hydroxy-3-nitro-2-phenyl-4-propylcyclohexyl)(4′-methoxyphenyl)methanone (**13e**):* yield 41% (91 mg); white crystal; mp = 172 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.95 (d, J = 9.0 Hz, 2H), 7.16−7.09 (m, 5H), 6.93 (d, J = 8.7 Hz, 2H), 5.06 (dd, J = 1.8, 12.3 Hz, 1H), 4.98 (t, J = 4.2 Hz, 1H), 4.38 (br s, 1H), 4.02 (dd, J = 4.2, 12.3 Hz, 1H), 3,87 (s, 3H), 2.86 (br s, 1H), 2.61−2.56(m, 1H), 2.16(td, J = 1.8, 13.8 Hz, 1H), 1.99 (dt, J = 3.9, 13.8 Hz, 1H), 1.47−1.24 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 30 °C) δ = 200.8, 164.3, 137.5, 130.8, 129.2, 128.8, 127.7, 127.5, 114.1, 92.6, 66.5, 55.5, 44.7, 41.6, 34.3, 33.1, 32.1, 19.8, 14.0; IR (KBr) 3483, 2959, 2927, 1676, 1600, 1547, 1257, 1169, 700 cm^{-1}; HR-MS ESI exact mass calcd for $C_{23}H_{27}NO_5Cl$ [M + Cl]$^-$ 432.1578, found 432.1592; $[\alpha]^{25}_D$ = −140 (c = 0.01 in chloroform, 99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak IA column, 30% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times minor 10.6 min, major 24.0 min.

*((1R,2S,3S,4S,6S)-6-Hydroxy-3-nitro-2-phenyl-4-propylcyclohexyl)(4′-chlorophenyl)methanone (**13f**):* yield 41% (93 mg); white crystal; mp = 186 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.87 (d, J = 8.7 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.17−7.07 (m, 5H), 5.05 (dd, J = 1.8, 12.3 Hz, 1H), 4.98 (t, J = 4.5 Hz, 1H), 4.41 (d, J = 2.1 Hz, 1H), 4.01 (dd, J = 4.2, 12.3 Hz, 1H), 2.62−2.56(m, 2H), 2.17 (td, J = 2.1, 14.1 Hz, 1H), 1.99 (dt, J = 3.9, 14.1 Hz, 1H), 1.47−1.24 (m, 4H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 30 °C) δ = 201.0, 140.5, 137.3, 134.5, 129.7, 129.2, 128.9, 127.9, 127.4, 92.4, 66.3, 45.6, 41.5, 34.2, 33.0, 32.2, 19.8, 14.0; IR (KBr) 3555, 2961, 2923, 1685, 1589, 1544, 1272, 1093, 702 cm^{-1}; HR-MS ESI exact mass calcd for $C_{22}H_{23}NO_4Cl$ [M − H]$^-$ 400.1316, found 400.1320; $[\alpha]^{25}_D$ = −102 (c = 0.01 in chloroform, 98% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak OD column, 20% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times minor 9.5 min, major 11.5 min.

*((1R,2S,3S,4S,6S)-6-Hydroxy-3-nitro-2-phenyl-4-propylcyclohexyl)-p-tolylmethanone (**13g**):* yield 51% (109 mg); white crystal; mp = 192 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.85 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 7.8 Hz, 2H), 7.17−7.09 (m, 5H), 5.09 (dd, J = 1.8, 12.3 Hz, 1H), 4.99 (t, J = 4.2 Hz, 1H), 4.40 (d, J = 2.1 Hz, 1H), 4.02 (dd, J = 4.2, 12.3 Hz, 1H), 2.72 (br s, 1H), 2.62−2.56(m, 1H), 2.41 (s, 3H), 2.16 (td, J = 1.8, 15.9 Hz, 1H), 1.99 (dt, J = 3.9, 13.8 Hz, 1H), 1.47−1.24 (m, 4H), 0.93 (t, J = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 30 °C) δ = 201.9 145.1, 137.5, 133.7, 129.6, 128.8, 128.5, 127.7, 127.4, 92.6, 66.4, 45.2, 41.5, 33.2, 33.1, 32.1, 21.7, 19.8, 14.0; IR (KBr) 3491, 2960, 2926, 1682, 1668, 1606, 1548, 1280, 1181, 700 cm^{-1}; HR-MS ESI exact mass calcd for $C_{23}H_{27}NO_4Cl$ [M + Cl]$^-$ 416.1629, found 416.1627; $[\alpha]^{25}_D$ = −116 (c = 0.01 in chloroform, >99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak IA column, 30% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times minor 9.0 min, major 13.3 min.

*((1R,2S,3S,4S,6S)-4-Ethyl-6-hydroxy-3-nitro-2-phenylcyclohexyl)-phenylmethanone (**13k**):* yield 65% (128 mg); white crystal; mp = 172 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.95 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 7.15−7.10 (m, 5H), 5.13 (dd, J = 2.1, 12.3 Hz, 1H), 5.04 (t, J = 4.2 Hz, 1H), 4.43 (d, J = 2.4 Hz, 1H), 4.03 (dd, J = 4.2, 12.3 Hz, 1H), 2.52−2.45 (m, 2H), 2.18 (dd, J = 2.1, 14.1 Hz, 1H), 2.01 (dt, J = 3.9, 14.1 Hz, 1H), 1.45−1.29 (m, 2H), 1.03 (t, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 30 °C) δ = 202.3, 137.4, 136.1, 133.9, 128.88, 128.85, 128.3, 127.8, 127.5, 92.1, 66.3, 45.4, 41.5, 35.1, 32.0, 25.1, 11.4; IR (KBr) 3531, 2967, 1686, 1541, 1371, 1286, 1273, 698 cm^{-1}; HR-MS ESI exact mass calcd for $C_{21}H_{22}NO_4$ [M − H]$^-$ 352.1549, found 352.1550; $[\alpha]^{25}_D$ = −72 (c = 0.01 in chloroform, >99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak IA column, 10% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times minor 15.5 min, major 17.1 min.

*((1R,2S,3S,4S,6S)-6-Hydroxy-3-nitro-2,4-diphenylcyclohexyl)-phenylmethanone (l-**13l**):* yield 27% (61 mg); white crystal; mp = 234 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.99 (d, J = 7.5 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.34−7.27 (m, 5H), 7.15 (br s, 5H), 5.22 (d, J = 12.0 Hz, 1H), 5.13 (br s, 1H), 4.62 (br s, 1H), 4.26 (dd, J = 3.6, 12.0 Hz, 1H), 3.98 (br d, J = 13.2 Hz, 1H), 3.00 (t, J = 13.5 Hz, 1H), 2.81 (br s, 1H), 2.20 (br d, J = 13.8 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 30 °C) δ = 202.1, 138.5, 137.1, 136.1, 134.0, 128.94, 128.89, 128.3, 127.86, 127.84, 127.4, 127.3, 94.2, 66.4, 45.1, 41.9, 39.1, 30.6; IR (KBr) 3448, 1655, 1551, 1208, 1057, 701, 688 cm^{-1}; HR-MS ESI exact mass calcd for $C_{25}H_{22}NO_4$ [M − H]$^-$ 400.1549, found 400.1550; $[\alpha]^{25}_D$ = −116 (c = 0.01 in chloroform, >99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak IB column, 10% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times major 12.7 min, minor 19.0 min.

*((1R,2S,6S)-2-Hydroxy-3-methyl-5-nitro-6-phenylcyclohexyl)-phenylmethanone (**13m−m″**) isomer mixture.* We were not able to separate isomers from each other via chromatography. The structures of the diastereomers were assigned by NMR techniques. The overall yield of the mixture was 90% (171 mg). The ratio of diastereomers was 19:19:62. To exact mass and enantiomeric excess, the major isomer could be determined from an enriched sample obtained by preparative thin-layer chromatography.

Major component: ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C, major isomer) δ = 7.94 (m, 2H), 7.57 (m, 1H), 7.45 (overlapping triplets, 2H),7.13−7.07 (m, 5H), 5.12 (dd J = 12.3, 1.9 Hz, 1H), 5.03 (td, J = 4.7, 1.8 Hz, 1H), 4.11 (br t, J = 1.9 Hz, 1H), 3.97 (dd, J = 12.3, 4.6 Hz, 1H), 2.49 (m, 1H), 2.27 (ddd, J = 15.0, 12.9, 5.0 Hz, 1H), 2.02 (ddd, J

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J. Org. Chem. 2015, 80, 8990−8996

= 15.0, 3.8, 1.8 Hz, 1H), 1.06 (d, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, 30 °C) δ = 201.6, 137.5, 136.1, 133.9, 129.0, 128.8, 128.4, 128.1, 127.7, 88.8, 70.2, 46.7, 40.3, 31.5, 30.8, 17.6; HR-MS ESI exact mass calcd for $C_{20}H_{20}NO_4$ $[M - H]^-$ 338.1392, found 338.1395. Enantioselectivity was determined by HPLC analysis with a Chiralpak OD column, 10% ethyl alcohol in hexane, 0.5 mL/min, λ = 211 nm, retention times major 18.2 min, minor 21.4 min. The relative configuration of isomers were determined by NMR spectroscopy.

(3S,4R)-4-Nitro-1,3-diphenyloctane-1,7-dione ***(13p)****:* yield 88% (167 mg); white crystal; mp = 68 °C; ^1H NMR (300 MHz, $CDCl_3$, 30 °C, major isomer) δ = 7.82 (d, J = 7.2 Hz, 2H), 7.55−7.50 (m, 1H), 7.43−7.38 (m, 2H), 7.34−7.23 (m, 5H), 4.90 (dd J = 3.3, 10.2 Hz, 1H), 3.96 (dd, J = 3.6, 9.9 Hz, 1H), 3.60−3.51 (m, 1H), 3.21 (dd, J = 3.6, 17.1 Hz, 1H), 2.42−2.37 (m, 2H), 2.07 (s, 3H), 2.03−1.85 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 30 °C) δ = 206.2, 196.3, 138.2, 136.5, 133.3, 129.0, 128.6, 128.3, 127.9, 127.8, 91.5, 44.8, 41.6, 38.9, 29.9, 25.8; IR (KBr) 3415, 1718, 1692, 1682, 1541, 1370, 751, 704 cm^{-1}; HR-MS ESI exact mass calcd for $C_{20}H_{20}NO_4$ $[M - H]^-$ 338.1392, found 338.1396; $[\alpha]^{25}_D$ = −32 (c = 0.01 in chloroform, 92% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak AD column, 10% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times minor 37.5 min, major 48.5 min. The relative configuration was determined by NMR spectroscopy.

(R)-3-((1′R,2′S)-1′-Nitro-4′-oxo-2′,4′-diphenylbutyl)-cyclohexanone ***(13q)****:* yield 45% (92 mg); white crystal; mp = 167 °C; ^1H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.80 (d, J = 7.2 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.33−7.23 (m, 5H), 4.94 (dd J = 4.5, 10.5 Hz, 1H), 4.09 (td, J = 3.0, 11.7 Hz, 1H), 3.58−3.49 (m, 1H), 3.15 (dd, J = 3.0, 16.8 Hz, 1H), 2.61−2.55 (m, 1H), 2.40−2.30 (m, 2H), 2.23−2.12 (m, 1H), 2.06−1.89 (m, 3H), 1.52−1.42 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 30 °C) δ = 208.5, 196.2, 137.6, 136.4, 133.3, 129.3, 128.6, 128.01, 127.97, 127.92, 95.6, 41.5, 41.4, 41.2, 41.7, 38.3, 28.6, 24.2; IR (KBr) 3414, 1715, 1681, 1541, 1447, 1363, 1252, 748, 700 cm^{-1}; HR-MS ESI exact mass calcd for $C_{22}H_{22}NO_4$ $[M - H]^-$ 364.1549, found 364.1552; $[\alpha]^{25}_D$ = −36 (c = 0.01 in chloroform, >99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak IB column, 10% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times minor 6.9 min, major 7.5 min. The relative configuration was determined by NMR spectroscopy.

(R)-3-((1′R,2′S)-1′-Nitro-4′-oxo-2′,4′-diphenylbutyl)-cyclopentanone ***(13r)****:* yield 54% (106 mg); white crystal; mp = 143 °C; ^1H NMR (300 MHz, $CDCl_3$, 30 °C) δ = 7.81 (d, J = 7.8 Hz, 2H), 7.54−7.49 (m, 1H), 7.42−7.37 (m, 2H), 7.33−7.23 (m, 5H), 4.96 (dd J = 6.3, 9.9 Hz, 1H), 4.05 (td, J = 3.0, 9.9 Hz, 1H), 3.65−3.56 (m, 1H), 3.22 (dd, J = 3.0, 17.1 Hz, 1H), 2.49−2.41 (m,1H), 2.34−2.22 (m, 3H), 2.15−1.91 (m, 2H), 1.06−1.43 (m, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, 30 °C) δ = 214.9, 196.2, 138.1, 136.3, 133.3, 129.1, 128.5, 127.96, 127.95, 127.85, 94.8, 43.1, 41.1, 39.6, 38.3, 38.2, 26.3; IR (KBr) 2900, 1738, 1694, 1548, 1446, 1368, 1348, 1235, 1197,747, 698, 543 cm^{-1}; HR-MS ESI exact mass calcd for $C_{21}H_{20}NO_4$ $[M - H]^-$ 350.1392, found 350.1397; $[\alpha]^{25}_D$ = −132 (c = 0.01 in chloroform, >99% ee). Enantioselectivity was determined by HPLC analysis with a Chiralpak AD column, 10% ethyl alcohol in hexane, 1.0 mL/min, λ = 211 nm, retention times minor 75.4 min, major 94.7 min. The relative configuration was determined by NMR spectroscopy.

Michael Reaction with Nitroethane and Cyclohex-2-enone. A 4 mL vial equipped with a magnetic stirring bar was charged with nitroethane (83 mg, 1.1 mmol), cyclohex-2-enone (54 mg, 0.56 mmol **14c**), and chloroform-d_3 (0.25 mL). Then, catalyst (30 mg, 0.05 mmol, 10 mol % **1a**) was added. The stirring had been maintained at room temperature for 64 h. The Michael adduct was not detected by either TLC analysis or NMR spectroscopy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01474.

Determination of relative configuration of compounds **13a**, **13m**−**m″**, and **13p**−**r**; copies of ^1H and ^{13}C NMR spectra and HPLC chromatograms of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +36-1-382-6401. E-mail: soos.tibor@ttk.mta.hu.

Notes

The authors declare no competing financial interest.

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