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Highly Stereoselective Synthesis of Trisubstituted Cyclohexanols Using a Guanidine-Catalyzed Tandem Henry–Michael Reaction

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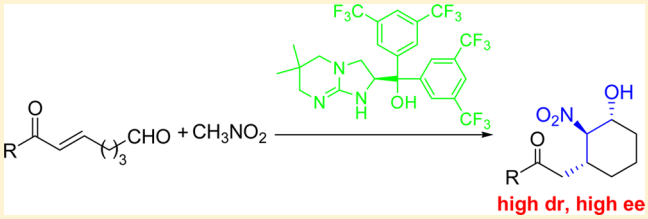
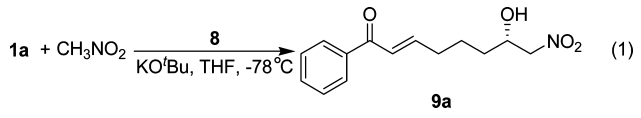
Supporting Information

ABSTRACT: A highly diastereoselective (dr >99:1) and enantioselective (ee value up to 98%) synthesis of trisubstituted cyclohexanols was achieved by using a tandem Henry–-Michael reaction between nitromethane and 7-oxo-hept-5-enals catalyzed by the Misaki–Sugimura guanidine.



In recent years, organocatalyzed tandem reactions have widely been used for constructing complex structures from relatively simple starting materials.[1] Besides their green nature, generally these reactions are also very easy to perform. More importantly, organocatalyzed tandem reactions can tolerate many functional groups so that the use of protecting groups is largely unnecessary.[1] Since cychohexane is a very common structural motif in many natural products,[2] there has been a lot of interest in developing novel organocatalyzed tandem reactions for the stereoselective synthesis of cyclohexane derivatives recently.[1,3] Among the reported methods,[1,3] Michael addition, Henry reaction, and/or aldol reaction are often used in a tandem fashion for obtaining the desired cyclohexane derivatives. Our own interest in organocatalyzed tandem reactions[4] led to our recent realization[5] of a highly diastereo- and enantioselective synthesis of trisubstituted cyclohexanols **2** using a tandem Henry–Michael reaction between (*E*)-7-oxo-hept-5-enals (**1**) and nitromethane. As shown in Scheme 1, using a quinidine thiourea-catalyzed tandem Henry–Michael reaction of (*E*)-7-oxo-hept-5-enals (**1**) and nitromethane, a mixture of three cyclohexanol diastereomers was first obtained with high ee values, and the disatereomers were then converted in situ to a single diastereomer in high ee values using a 1,1,3,3-tetramethylguanidine (TMG)-catalyzed tandem retro-Henry–Henry reaction.[5] Although eventually high product stereoselectivities were achieved using this one-pot sequential catalysis,[6] two catalysts had to be used in the reaction. Moreover, since an incomplete conversion of compound **1** in the first step would lower the final product ee value, a longer reaction time was needed for the first step in order to ensure a full conversion of this substrate. Nonetheless, during the study we also noticed that a single diastereomer of the racemic products may be obtained by using TMG alone as the catalyst (Scheme 1).[5] Based on this observation, we envisioned that an appropriate optically active guanidine derivative[7,8] should be a good catalyst for this reaction. In this paper, we report our finding on a highly stereoselective synthesis of trisubstituted cyclohexanols using the Misaki–Sugimura guanidine catalyst.[9]

Using (*E*)-7-oxo-7-phenylhept-5-enal (**1a**) as the substrate, we first screened several reported guanidine derivatives as the catalyst (Scheme 2). The results are summarized in Table 1. As the data in Table 1 show, when the pseudo-C_2-symmetric guanidine catalyst **3**[10] was used in CH_2Cl_2 at rt, the desired tandem Henry–Michael product **2a** was obtained as a single diastereomer in 98% yield and 60% ee (entry 1). This compound has identical relative and absolute stereochemistry as that obtained in the sequential catalysis[5] according to its NMR and optical rotation data. Similarly, Feng's guanidine catalyst **4**[11] gave **2a** in 48% ee (entry 2). On the other hand, guanidine catalyst **5**[12] led to the formation of the opposite enantiomer of **2a** in 95% yield and 59% ee (entry 3). When Misaki–Sugimura guanidine catalysts **6** and **7** were applied,[9] slightly improved ee values were obtained for the product **2a** (65% and 73% ee, respectively, entries 4 and 5). It should be pointed out that only a single diastereomer was obtained with all the above catalysts. Together with *t*-BuOK, the Ooi's phopshonium salt **8** has been reported to be a very good catalyst for the Henry reaction.[13] Thus, we also screened this combination in our reaction. However, with this catalyst combination in THF at −78 °C, no desired tandem Henry–Michael product was observed. Instead, the *S*-enantiomer of the Henry product **9a**[5] was obtained in 97% yield and 55% ee (entry 6, eq 1). The desired tandem reaction product was not



obtained probably because this catalytic system was not basic enough. Since Misaki–Sugimura catalyst **7** generated the highest enantioselectivity among these screened catalysts, it was chosen for further optimizations. First the solvent effects on the reaction were evaluated. It was found that in $CHCl_3$, the

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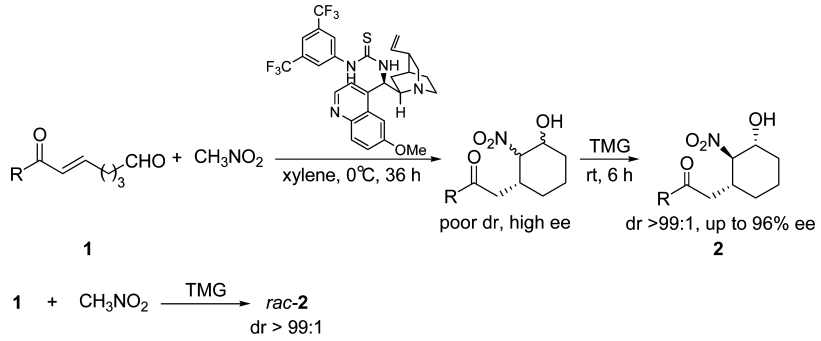
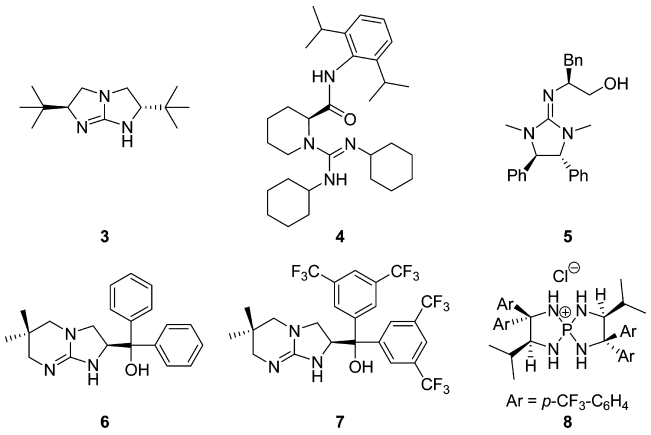
Scheme 1. Organocatalyzed synthesis of Trisubstituted Cyclohexanols Using a Tandem Henry–Michael Reaction



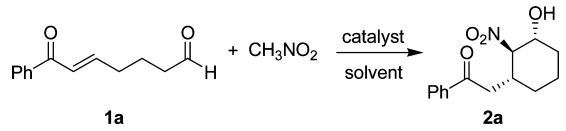
Scheme 2. Catalysts Screened in the Tandem Henry–Michael Reaction of 1a and Nitromethane



product ee value was slightly improved to 84% (entry 7), while the other halogenated and nonhalogenated solvents screened all led to inferior results (entries 8–12). Gratifyingly, when the reaction was conducted at 0 °C, the enantioselectivity of this reaction was improved to 91% ee (entry 13), although the reaction became a little slower at this temperature. Further dropping the reaction temperature to −15 °C, an even higher ee value of 98% was obtained for compound **2a** (entry 14). No further improvement in the asymmetric induction was observed when the reaction temperature was lowered further (data not shown). On the other hand, reducing the loading of the catalyst was found to cause some minor loss of the product ee values (entries 15 and 16).

Once the reaction conditions were optimized, the scope of this reaction was established. The results are presented in Table 2. It was found that the electronic nature of the substituent on the phenyl ring of (*E*)-7- aryl-7-oxohept-5-enals (**1a–k**) has almost no influence on either the diastereoselectivity or the enantioselectivity of this reaction (entries 1–8). The corresponding tandem Henry–Michael products **2** were consistently obtained as a single diastereomer in high ee values. Similarly, the position of these substituents on the phenyl ring is of almost no influence on the stereoselectivities of this reaction (entries 3, 9, and 10; 4 and 11). In contrast, when 7-methyl- and 7-cyclopropyl-substituted enals (**1l** and **1m**) were used as the substrates, the products were obtained in much lower enantioselectivities, although the high diastereoselectivity of this reaction was retained (entries 12 and 13). Nevertheless, a high ee value of 90% was achieved when a *tert*-butyl-substituted enal **1n** was applied. These results indicate that the enantioselectivity of the 7-alkyl-substituted substrates is

Table 1. Catalyst Screening and Reaction Condition Optimization[a]



1a 2a

entry	catalyst	solvent	*T* (°C)	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**3**	CH_2Cl_2	rt	4	98	>99:1	60
2	**4**	CH_2Cl_2	rt	4	98	>99:1	48
3	**5**	CH_2Cl_2	rt	4	95	>99:1	59[e]
4	**6**	CH_2Cl_2	rt	4	99	>99:1	65
5	**7**	CH_2Cl_2	rt	4	99	>99:1	73
6	**8**[f]	THF	−78	24	0[g]		
7	**7**	$CHCl_3$	rt	4	99	>99:1	84
8	**7**	$ClCH_2CH_2Cl$	rt	4	99	>99:1	70
9	**7**	CCl_4	rt	4	97	>99:1	65
10	**7**	THF	rt	4	99	>99:1	66
11	**7**	Et_2O	rt	4	95	>99:1	38
12	**7**	toluene	rt	4	99	>99:1	67
13	**7**	$CHCl_3$	0	12	99	>99:1	91
14	**7**	$CHCl_3$	−15	12	99	>99:1	98
15	**7**[h]	$CHCl_3$	−15	12	99	>99:1	95
16	**7**[i]	$CHCl_3$	−15	12	99	>99:1	89

[a]Unless otherwise noted, all reactions were carried out with **1a** (0.10 mmol), nitromethane (0.20 mmol), and the catalyst (0.010 mmol, 10 mol %) in the indicated solvent (0.2 mL). [b]Yield of isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by HPLC analysis on ChiralPak AD-H column. The absolute configuration of the product was determined by comparison of the measured optical rotation with the reported data (ref 5). [e]The opposite enantiomer was obtained. [f]*t*-BuOK (10 mol %) was used together with **8** in this reaction as the catalyst. [g]The *R*-enantiomer of the Henry reaction product was obtained (see text). [h]The loading of the catalyst was 5 mmol %. [i]The loading of the catalyst was 2 mmol %.

mainly depending on the size of the substituent at the C7 position. This is in drastic contrast to the results obtained with the quinidine thiourea-TMG sequential catalysis (Scheme 1), in which the enantioselectivity was not sensitive to steric factors for these substrates.[5] Overall, except for substrates **1l** and **1m**, the enantioselectivities obtained with this new catalytic system is either better than or at least comparable to those of the sequential catalysis.[5]

We believe the current reaction also follows our previously reported tandem Henry–Michael mechanism.[5] In order to elucidate the reaction mechanism some control experiments were carried out. According to the reported mechanism, the

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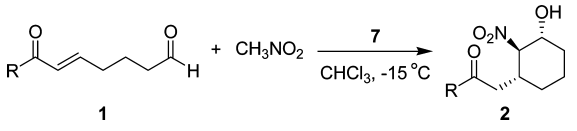
Table 2. Scope of the Guanidine-Catalyzed Tandem Henry–Michael Reaction[a]

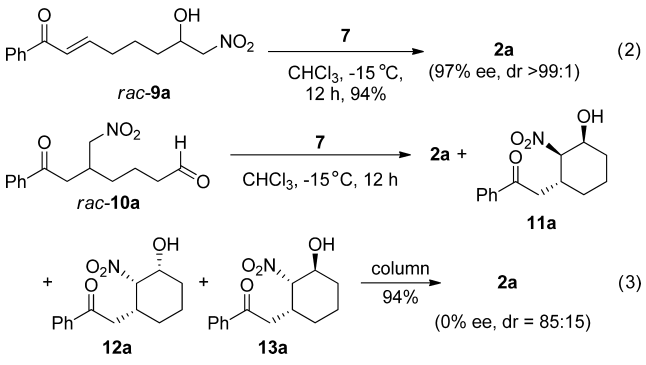


1 2

entry	R	1/2	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	**a**	99	>99:1	98
2	4-FC_6H_4	**b**	98	>99:1	96
3	4-ClC_6H_4	**c**	95	>99:1	96
4	4-BrC_6H_4	**d**	99	>99:1	97
5	4-CNC_6H_4	**e**	98	>99:1	98
6	4-$NO_2C_6H_4$	**f**	99	>99:1	92
7	4-MeC_6H_4	**g**	98	>99:1	97
8	4-$MeOC_6H_4$	**h**	99	>99:1	98
9	2-ClC_6H_4	**i**	99	>99:1	96
10	3-ClC_6H_4	**j**	98	>99:1	96
11	3-BrC_6H_4	**k**	99	>99:1	96
12[e]	Me	**l**	98	>99:1	60
13	*c*-C_3H_5	**m**	95	>99:1	76
14	*t*-Bu	**n**	98	>99:1	90

[a]Unless otherwise noted, all reactions were carried out with **1a** (0.10 mmol), nitromethane (0.20 mmol), and catalyst **7** (0.010 mmol, 10 mol %) in $CHCl_3$ (0.2 mL) at −15 °C for 12 h. [b]Yield of isolated product after column chromatography. [c]Determined by ^1H NMR analysis of the crude product. [d]Determined by HPLC analysis. [e]The reaction time was 24 h.

enantioselectivity of this reaction is generated in the intramolecular Michael addition step.[5] Moreover, under base catalysis, all of the diastereomers formed in the Michael reaction step can be converted to the thermodynamically more stable product **2**.[5] On the basis of this assumption, even if a racemic Henry product is used as the starting material, compound **2** should be obtained in similar diastereo- and enantioselectivities.[5] Indeed, when the reaction was carried out with *rac*-**9a** using catalyst **7** under the optimized conditions, **2a** was obtained as a single diastereomer in 94% yield and 97% ee (eq 2). In contrast, similar reaction conducted with the racemic



Michael addition product (*rac*-**10a**) as the starting material led to the formation of a mixture of all four possible diastereomers **2a**, **11a**,[5] **12a**,[5] and **13a** in a ratio of 3:17:40:40. After column, most of these diastereomers were also converted to the more stable diastereomer **2a**, which was isolated in 94% yield as a racemic compound with a dr of 85:15 (eq 3). These results clearly indicate our two-component reaction follows a tandem Henry-Michael mechanism instead of a tandem Michael–Henry reaction.

In summary, we have developed a new protocol for the highly stereoselective synthesis of trisubstituted cyclohexanols using a guanidine-catalyzed tandem Henry–Michael reaction between 7-oxo-hept-5-enals and nitromethane. Misaki–Sugimura guanidine catalyst **7** has been demonstrated to be the best catalyst for this reaction and, after optimizations of the reaction conditions, the desired trisubstituted cyclohexanols may be obtained in both high enantioselectivities (up to 98% ee) and diastereoselectivities (>99:1 dr).

EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer (75 MHz for ^{13}C). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quintet), and m (multiplet), and coupling constants (*J*) are reported in hertz. Splitting patterns that could not be easily interpreted are designated as multiplet (m). TLC was performed with silica gel GF254 precoated on plastic plates, and spots were visualized with UV. HPLC analysis was performed on an HPLC instrument equipped with a UV–vis detector. Dry solvents were freshly distilled under argon from an appropriate drying agent before use. Catalysts were synthesized by following the published procedures.[9−13] (*E*)-7-Alkyl-7-oxohept-5-enals (**1a–n**) were prepared according to literature procedures,[14] which are known compounds except for compounds **1e**, **1i**, **1m**, and **1n**.

*(E)-7-(4-Cyanophenyl)-7-oxohept-5-enal (**1e**):* colorless oil, 1.27 g, 56% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 9.79 − 9.75 (m, 1H), 8.00–7.93 (m, 2H), 7.77–7.72 (m, 2H), 7.04 (dt, *J* = 15.4, 6.9 Hz, 1H), 6.88–6.80 (m, 1H), 2.52 (td, *J* = 7.1, 1.2 Hz, 2H), 2.40–2.33 (m, 2H), 1.90–1.82 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.4, 189.1, 150.1, 140.9, 132.4, 128.8, 125.8, 117.9, 115.8, 42.9, 31.9, 20.2; IR ν_{max} (neat, cm^{-1}) 3054, 2863, 1724, 1673, 1622, 1264. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.96; H, 5.64; N, 6.19.

*(E)-7-(2-Chlorophenyl)-7-oxohept-5-enal (**1i**):* colorless oil, 1.65 g, 70% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.3 Hz, 1H), 7.36 (dddd, *J* = 8.2, 7.6, 3.3, 1.4 Hz, 4H), 6.66 (dt, *J* = 15.8, 6.7 Hz, 1H), 6.47 (dt, *J* = 15.8, 1.3 Hz, 1H), 2.51 (td, *J* = 7.2, 1.2 Hz, 2H), 2.33 (td, *J* = 8.0, 1.3 Hz, 2H), 1.84 (dd, *J* = 14.7, 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 193.8, 150.4, 138.6, 131.1, 130.9, 130.8, 130.0, 128.9, 126.6, 43.0, 31.8, 20.2; IR ν_{max} (neat, cm^{-1}) 2254, 1724, 1657, 1296. Anal. Calcd for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.54. Found: C, 65.90; H, 5.67.

*(E)-7-Cyclopropyl-7-oxohept-5-enal (**1m**):* colorless oil, 1.25 g, 75% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (t, *J* = 1.4 Hz, 1H), 6.77 (dt, *J* = 15.7, 6.9 Hz, 1H), 6.16 (dt, *J* = 15.8, 1.5 Hz, 1H), 2.44 (td, *J* = 7.2, 1.4 Hz, 2H), 2.28–2.16 (m, 2H), 2.06 (tt, *J* = 7.8, 4.6 Hz, 1H), 1.76 (dq, *J* = 14.6, 7.4 Hz, 2H), 1.04–0.95 (m, 2H), 0.88–0.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 199.6, 144.8, 130.7, 42.8, 31.4, 20.3, 18.7, 11.0; IR ν_{max} (neat, cm^{-1}) 2830, 2253, 1723, 1680, 1659, 1625, 1443, 1391, 1207, 1090. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.38; H, 8.54.

*(E)-8,8-Dimethyl-7-oxonon-5-enal (**1n**):* colorless oil, 1.31 g, 72% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 9.67 (d, *J* = 1.2 Hz, 1H), 6.78 (dt, *J* = 14.1, 6.9 Hz, 1H), 6.43 (dd, *J* = 15.2, 1.1 Hz, 1H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.18 (q, *J* = 7.3 Hz, 2H), 1.73 (p, *J* = 7.4 Hz, 2H), 1.06 (d, *J* = 1.0 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.6, 201.3, 145.4, 124.6, 42.9, 42.7, 31.4, 26.0, 20.4; IR ν_{max} (neat, cm^{-1}) 2967, 2871, 2722, 1723, 1687, 1623, 1461, 1365, 1241, 1108, 1046. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.36; H, 9.97.

Representative Procedure for the Enantioselective Organocatalytic Tandem Reaction. A solution of catalyst **7** (6.1 mg, 0.010 mmol, 10 mol %) and (*E*)-7-oxo-7-phenylhept-5-enal (**1a**) (20.2 mg, 0.10 mmol) in $CHCl_3$ (0.2 mL) was stirred at −15 °C for 10 min. To the above mixture was added nitromethane (12.2 mg, 0.20 mmol) in one portion. The reaction mixture was further stirred at this temperature for 12 h (monitored by TLC). After the reaction was completed, the volatile components were removed under reduced pressure and the residue was purified by column chromatography on

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silica gel (1:2 EtOAc/hexanes as the eluent) to afford the desired product **2a**.

(1*R*,2*R*,3*R*)-2-Nitro-3-(2-oxo-2-phenylethyl)cyclohexanol (**2a**):[5] 26.0 mg, 99% yield.

(1*R*,2*R*,3*R*)-3-[2-(4-Fluorophenyl)-2-oxoethyl]-2-nitrocyclohexanol (**2b**):[5] 27.6 mg, 98% yield.

(1*R*,2*R*,3*R*)-3-[2-(4-Chlorophenyl)-2-oxoethyl]-2-nitrocyclohexanol (**2c**):[5] 28.3 mg, 95% yield.

(1*R*,2*R*,3*R*)-3-[2-(4-Bromophenyl)-2-oxoethyl]-2-nitrocyclohexanol (**2d**):[5] 33.8 mg, 99% yield.

(1*R*,2*R*,3*R*)-3-[2-(4-Cyanophenyl)-2-oxoethyl]-2-nitrocyclohexanol (**2e**):[5] 28.2 mg, 98% yield.

(1*R*,2*R*,3*R*)-2-Nitro-3-[2-(4-nitrophenyl)-2-oxoethyl]cyclohexanol (**2f**):[5] 30.5 mg, 99% yield.

(1*R*,2*R*,3*R*)-3-[2-(4-Methylphenyl)-2-oxoethyl]-2-nitrocyclohexanol (**2g**):[5] 27.2 mg, 98% yield.

(1*R*,2*R*,3*R*)-3-[2-(4-Methoxyphenyl)-2-oxoethyl]-2-nitrocyclohexanol (**2h**):[5] 29.1 mg, 99% yield.

(1*R*,2*R*,3*R*)-3-[2-(2-Chlorophenyl)-2-oxoethyl]-2-nitrocyclohexanol (**2i**):[5] 29.5 mg, 99% yield.

(1*R*,2*R*,3*R*)-3-[2-(3-Chlorophenyl)-2-oxoethyl]-2-nitrocyclohexanol (**2j**):[5] 29.2 mg, 98% yield.

(1*R*,2*R*,3*R*)-3-[2-(3-Bromophenyl)-2-oxoethyl]-2-nitrocyclohexanol (**2k**):[5] 33.9 mg, 99% yield.

(1*R*,2*R*,3*R*)-2-Nitro-3-(2-oxopropyl)cyclohexanol (**2l**):[5] 19.8 mg, 98% yield.

(1*R*,2*R*,3*R*)-3-(2-Cyclopropyl-2-oxoethyl)-2-nitrocyclohexanol (**2m**):[5] 21.5 mg, 95% yield.

(1*R*,2*R*,3*R*)-3-(3,3-Dimethyl-2-oxobutyl)-2-nitrocyclohexanol (**2n**):[5] 23.8 mg, 98% yield.

Gram-Scale Synthesis of Compound ***2a***. A solution of catalyst **7** (303.5 mg, 0.50 mmol, 10 mol %) and (*E*)-7-oxo-7-phenylhept-5-enal (**1a**) (1.01 g, 5.0 mmol) in $CHCl_3$ (10 mL) was stirred at −15 °C for 10 min. To the above mixture was added nitromethane (610 mg, 10.0 mmol) in one portion. The reaction mixture was further stirred at this temperature for 12 h (monitored by TLC). After the reaction was completed, the volatile components were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (1:2 EtOAc/hexanes as the eluent) to afford product **2a** (1.21 g, 92% yield).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra for the compounds obtained in this study as well as HPLC chromatograms of the tandem Henry−Michael products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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