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A versatile approach to functionalized cyclic ketones bearing quaternary carbon stereocenters via organocatalytic asymmetric conjugate addition of nitroalkanes to cyclic β-substituted α,β-Enones

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Dedicated to Professor Guo-Qiang Lin in recognition of his significant contributions to organic chemistry.

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ABSTRACT

A versatile organocatalytic asymmetric conjugate addition of nitroalkanes to β-substituted cyclic α,β-enones to yield cyclic ketones bearing all-carbon quaternary stereogenic centers at β-C has been developed. This is an extension of the method that we developed during the total synthesis of (−)-haliclonin A, which features the employment of structurally relatively simple, cheap and easily available primary amine-thiourea derived from (*R,R*)-1,2-diaminocyclohexane as the chiral catalyst. The method shows wide substrate scope, good functional group tolerance, which allows a quick access to multi-functionalized chiral compounds. The synthetic potential of the method was demonstrated by one-step transformations of the nitro-ketone adducts to four other classes of compounds. The absolute configurations of adducts were determined by comparison of both the retention time of chiral HPLC analysis and sense of specific optical rotation with those of a known compound. The enantioselective control mechanism was rationalized based on the DFT computational studies.

1. Introduction

All-carbon quaternary stereocenters are found in many structurally complex natural products and biologically active molecules [1,2], such as antibacterial and cytotoxic marine alkaloid haliclonin A (**1**) [3], diterpenoid alkaloid (−)-arcutinine (**2**) [4], dysentery drug conessine (**3**) [5], and widely employed antitumoral drug Taxol® (**4**) [6] (Fig. 1). During last two decades, many asymmetric strategies have been developed to access to such motifs [2,7,8], however the chemoselective, catalytic enantioselective construction of functionalized molecules bearing all-carbon quaternary stereocenters remains a daunting synthetic challenge.

Recently, we have accomplished the catalytic asymmetric total synthesis of (−)-haliclonin A (**1**), a macrocyclic marine natural product isolated in 2009 from a marine sponge *Haliclona* sp. [9]. The cornerstone of the total synthesis was the enantioselective construction of the all-carbon quaternary stereogenic center by chiral bifunctional thiourea-primary amine catalyst (*R,R*)-**cat-1**-catalyzed enantioselective conjugate addition of nitromethane to 3-substituted cyclohex-2-enone **5** (Scheme 1). The reaction was achieved in good yield (80%) and in excellent enantioselectivity (97% *ee*). Moreover, the reaction could be run at a 10 mmol scale without decreasing enantiopurity of **6**. Besides these inherent advantages, in this strategy nitromethane served as a surrogate of umpolung methylamine carbanion synthon, and the amine group, in turn was used to construct both the bridged ring system and the

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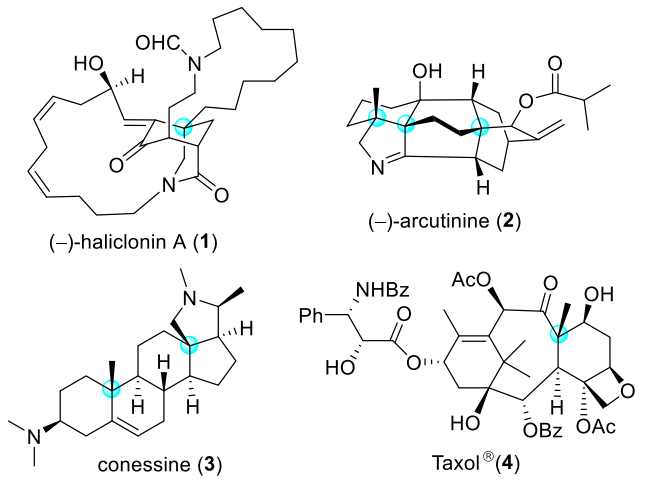
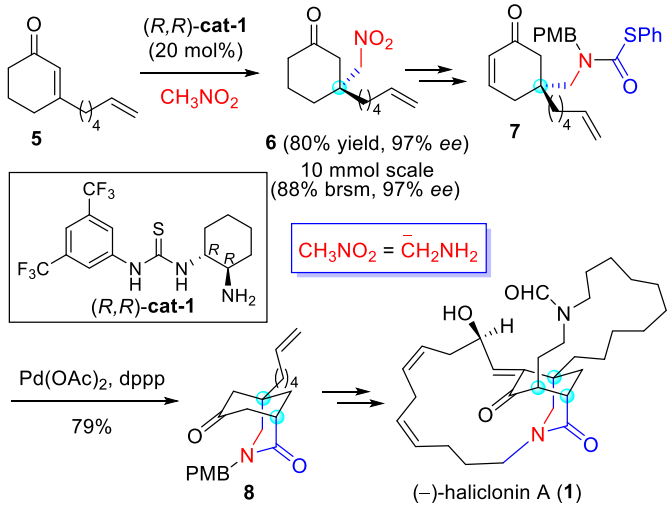
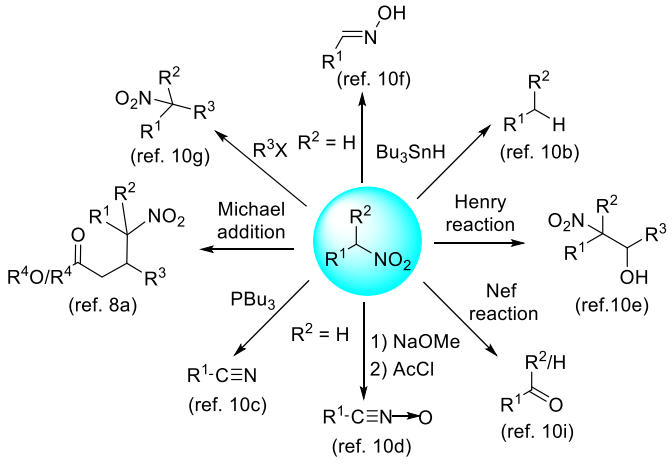


Fig. 1. Selected bioactive natural products containing all-carbon quaternary stereocenters.



Scheme 1. The multiple roles played by the (*R,R*)-**cat-1** catalyzed enantioselective conjugate addition of nitromethane in the total synthesis of (–)-haliclonin A (**1**).



Scheme 2. Some other known transformations of nitroalkanes.

17-membered macrocycle. Lastly, the first chiral center established by nitromethane addition was used to induce the formation of two other chiral centers. In addition, it has been well documented that nitroalkanes could be converted to many other classes of compounds (Scheme 2) [10].

On the other hand, cyclic ketones bearing an all-carbon stereogenic center at β-C are found or can be converted into many natural products such as those shown in Fig. 1. Although many methods for the organocatalytic asymmetric conjugate addition of nitromethane to cyclic α,β-enones have been reported [11], prior to our own work [9], very few examples of catalytic asymmetric addition of nitromethane to β-substituted cyclic α,β-enones leading to functionalized cyclic ketones bearing a quaternary stereogenic center at β-C have been reported [8a-c]. In this context, Ley reported one example of tetrazole derivative of proline **cat-2** catalyzed conjugate addition (Fig. 2) [8a]. Through five examples, Ye and coworkers demonstrated that cinchona-thiourea primary amine **cat-3** [8b] could be used to build the nitromethylated quaternary carbon stereocenters in excellent enantioselectivities. In 2011, Kwiatkowski and coworkers achieved the high-pressure (10 Kbar)-promoted enantioselective addition of nitroalkanes to β-substituted enones by using cinchona-based primary amine catalyst **cat-4**-PhCO$_2$H [8c]. After we had established the method for the catalytic asymmetric addition of nitromethane to cyclohexenone **5**, and turned to the total synthesis of haliclonin A (cf. Scheme 1) [9a], Ye and coworkers reported the vicinal diamine **cat-5**-PhCO$_2$H combination catalyzed asymmetric conjugate addition, which was shown to be versatile and highly enentioselective [8d]. In 2016, Li and coworkers also obtained good to excellent enantioselectivities employing another cinchona-based primary amine catalyst **cat-6**-PhCO$_2$H in combination with proton-sponge additive [8e]. The use of cheap and easily available catalysts is highly desirable in the synthetic organic and medicinal chemistry communities [12]. In 2008 and 2009, Wang/Duan and Chan introduced independently the relatively simple aryl thiourea-primary amine catalysts [2g,13] (*S,S*)-**cat-1** [14], and (*R,R*)-**cat-1** [15], respectively, which are easily available from isothiocyanate and enantiomeric pure 1,2-*trans*-diaminocyclohexane in one step [14–16], and are now commercially available. Wang/Duan also reported the first (*S,S*)-**cat-1**-catalyzed highly enantioselective conjugate addition of nitroalkanes to acyclic enones to form chiral tertiary carbons, and only a cyclic enone, cyclohex-2-enone was examined [17]. On the

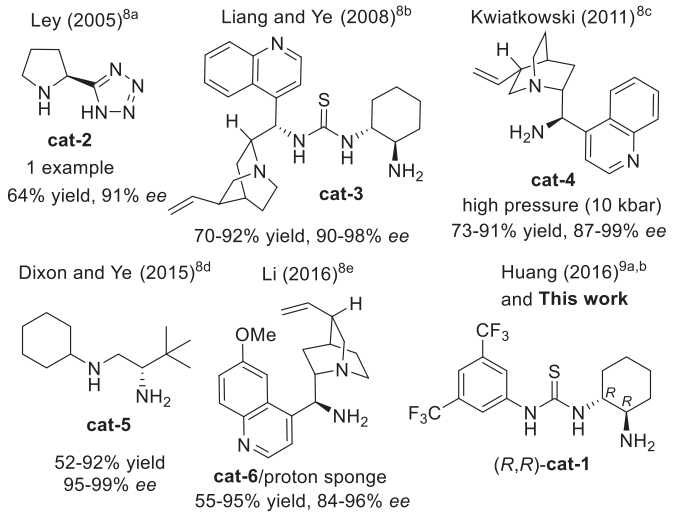


Fig. 2. Reported organocatalysts used for the asymmetric conjugate addition of nitroalkanes to β-substituted cyclic enones.

basis of these considerations, we decided to extend our above-mentioned asymmetric conjugate addition reaction [9] to diverse cyclic enones and nitroalkanes, and tried to get an insight into the catalysis mechanism by computation, and the results are reported herein.

2. Results and discussion

We first surveyed the scope of β-substituted cyclic α,β-enones in the (*R,R*)-**cat-1**-catalyzed asymmetric conjugate addition with nitromethane. The protocol established during our total synthesis of haliclonin A (**1**) was employed [9], which consists of exposing a β-substituted cyclohexenone **9** (0.5 mmol, 1.0 equiv) to thiourea catalyst (*R,R*)-**cat-1** (0.1 mmol, 0.2 equiv) in redistilled nitromethane (2.5 mL), and running the reaction at 45 °C under an argon atmosphere for 5–7 days [9].

In view of the widespread use of β-substituted β-methyl cyclohexanones as key intermediates for the synthesis of natural products [1a,4,7a], and active pharmaceutical ingredients (APIs) [18], the conjugate addition of β-methyl-cyclohexenone (**9a**) was first examined (Table 1, entry 1). Subjecting to the above-mentioned conditions, the adduct **10a** was obtained in good yield (78%) and in excellent enantioselectivity (98% *ee*). The asymmetric conjugate addition to β-alkyl (ethyl, *n*-amyl, 4-pentenyl) substituted cyclohexenones **9b-d** (entries 2–4) also proceeded efficiently to give adducts **10b-d** in 80–85% yields and 94–98% *ee*s. As can be seen from entries 5–7, the reaction of cyclohexenones with β-alkyl bearing a functional group such as OTBS, acetal, and ester, proceeded without incidence to give the expected functionalized adducts **10e-g** in good yields (78%, 78%, 88%) and in excellent enantioselectivities (91%, 95%, 98% *ee*). Such good functional group is noteworthy because it affords a simple method to access chiral cyclohexanone derivatives bearing three functional groups in a molecule which are convertible into many compounds. However, the reactions of β-branched substrate **9h** and α-branched β-cyclopropylcyclohexenone **9i** yielded **10h** and **10i** in moderate 79% *ee* and 75% *ee*, respectively (entries 8 and 9). 3,5,5-Trimethylcyclohex-2-enone (**9j**) reacted to give **10j** in 75% yield and 85% *ee* (entry 10). These results implicates that steric hindrance is detrimental for the enantioselectivity of the reaction.

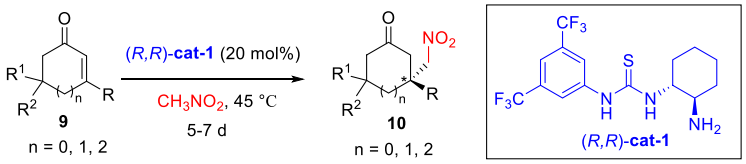
To our delight, β-benzylcyclohexenone **9k** and **9l** turned out to suitable substrates to afford **10k** and **10l** in excellent *ee* (97% and 95%) (entries 11 and 12), whereas the reaction of β-(*p*-methoxybenzyl)cyclohexenone (**9m**) afforded a lower *ee* of 87% (entry 13). Compared with the result obtained from the β-isobutyl derivative **9h**, these results might reflect a beneficial effect of the aryl groups on the asymmetric induction. The reaction of β-phenylcyclohexenone **9n** afforded a moderate yield (58%) and an appreciable *ee* of 89% (entry 14). For β-(*p*-chlorophenyl)cyclohexenone **9o**, both yield and *ee* were moderate (50% yield and 66% *ee*) (entry 15). Interestingly, the reaction can be extended to more rigid β-methylcyclopent-2-enone (**9p**), which yielded compound **10p** in high *ee* (91%) albeit in a moderate yield of 52% (entry 16), whereas for the relative flexible cyclohept-2-enone (**9q**) a good yield (84%) and an excellent enantioselectivity (98% *ee*) were obtained (entry 17).

Next, the asymmetric conjugate addition reaction of 1-nitropropane was examined (Table 2, entry 1). The reaction proceeded smoothly, and two diastereomeric adducts **10r** and **10r'** (more polar) were obtained (55:45 dr) in a good combined yield (86%) and enantioselectivities (91% and 94% *ee*). Finally, the unsubstituted cyclohex-2-enone (**9**r) was evaluated. As expected, the reaction worked well with the less hindered **9**r, which gave adduct **10s** in 79% yield and 98% *ee* (entry 2). The conjugate addition of 1-nitropropane with **9**r yielded two diastereomeric adducts **10t** and **10t'** (more polar) (17: 83 dr) in excellent combined yield (93%) and enantioselectivities (99% and 97% *ee*) (entry 3). To our surprise, the reaction of more hindrance 2-nitropropane also afforded **10u** in a good yield of 87% and in excellent enantioselectivity (98% *ee*).

In our previous work, after derivatization, and by single crystal X-ray diffraction analysis, the absolute configuration of the major product **6** obtained from the (*R,R*)-**cat-1** catalyzed asymmetric conjugate addition of nitromethane to 5-hexenyl cyclohexenone (**5**) was determined to be (*R*)-**6** [9a]. This result indicates that with the structure displayed in Scheme 1, the conjugate addition takes place from *re*-face of enone **5**. A similar α–face enantioselective addition was expected for enones shown in Tables 1 and 2 Notably, for different β-substituted cyclohexenones the same α–face approach could be named *re*-face or *si*-face assigned according to the Cahn-Ingold-Prelog sequence rule. The chiral HPLC analysis (Chiralcel AD-H) indicated that the major enantiomer (*R*)-**6** has a shorter retention time (t_R = 8.7 min) than the minor enantiomer (t_R = 10.1 min) (Table 3, entry 1). In agreement with this result, as can be seen from entries 2–21 of Table 3, all the major enantiomers (**10a**-**10t**) have shorter a retention time. This allows deducing that all the products **10a**-**10t** were formed by additions of nitroalkanes to the specific cyclic enones from same side, namely, the major enantiomers of **10a**-**10t** have the absolute configurations at β-C shown in Tables 1 and 2 This is confirmed by a comparison of the sense of specific optical rotation of (*R*)-**6** with those of the major enantiomers of **10a**-**10s** (Table 3, column 4, entries 1 versus 2–20). The exceptional negative specific optical rotation of the mixture of adducts **10t** and **10t'** can be rationalized via comparisons of the sense of specific optical rotations of (*R,S*)-**10t** and (*R,R*)-**10t'**. (*R,S*)-**10t** is less polar and has a positive specific optical rotation {$[\alpha]_D = +29.3$ (c = 1.2, $CHCl_3$, 91% *ee*)}, on the contrary, more polar (*R,R*)-**10t'** has negative value {$[\alpha]_D = -13.2$ (c = 1.1, $CHCl_3$, 74% *ee*)} [11b]. It is suggested that major diastereomer (*R,R*)-**10t'** (17:83 dr, entry 3, Table 2) has a greater contribution to the observed rotation resulting in a negative rotation. The HPLC retention times of enantiomers of **10u** behave differently, which didn't allow determining the absolute configurations, but could be assigned via comparison of sense of specific rotation data as (*R*)-**10u** for the major enantiomer. It is worth noting that although the conclusion is that all the major enantiomers of **10a**-**10u** have the structures displayed in Tables 1 and 2, the absolute configurations should be assigned as *R* or *S* according to the Cahn-Ingold-Prelog sequence rule.

When an aldehyde is used as a pro-nucleophile in the thiourea-primary amine catalyzed reaction, it was proposed that an enamine was formed as a nucleophilic intermediate [19]. In the case of a ketone, acid additive is needed to promote the formation of a nucleophilic enamine intermediate [20]. On the other hand, for the primary amine-catalyzed conjugate addition of an active methylene compound [21] or a nitroalkane [8d] to an enone under acidic conditions, an electrophilic eniminium intermediate was proposed. As regarding the acid-free thiourea-primary amine catalyzed nitromethane addition to enone at rt, Wang/Duan suggested nitromethane carbanion and H-bonding activated enone as nucleophilic and electrophilic species, respectively [17], although the mechanism was questioned by Kwiatkowski based on the results from the primary amine/acid dual-catalyzed reaction of enone [21]. More recently, Miura et al. postulated an transition state involving both nitroalkane carbanion and (*Z*)-eniminium species in the thiourea primary amine-sulfonamide-catalyzed addition reactions of nitroalkanes to acyclic enones [12c]. Moreover, it has been demonstrated that even the α-proton [pK_a (DMSO) = 26.4] [22] of cyclohexanone can be deprotonated by pyrrolidine [ammonium pK_a (DMSO) = 11.1] [23] to form enolate serving as reactive intermediate (eq. 1) [24]. In view of the much higher acidity of the

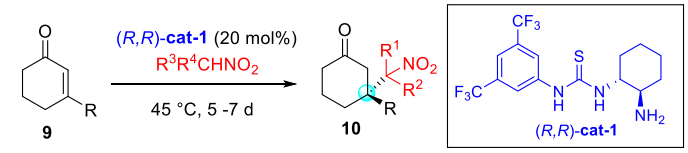
Table 1
(*R,R*)-**Cat-1**-catalyzed asymmetric conjugate additions of nitromethane to β-substituted cyclic α,β-enones.



Entry	cyclic enone	Product (yield,[a] *ee*[b])	Entry	cyclic enone	Product (yield,[a] *ee*[b])
1	**9a**	**10a** (76%, 98% *ee*)	10	**9j**	**10j** (75%, 85% *ee*)
2	**9b**	**10b** (82%, 98% *ee*)	11	**9k**	**10k** (78%, 97% *ee*)
3	**9c**	**10c** (85%, 98% *ee*)	12	**9l**	**10l** (81%, 95% *ee*)
4	**9d**	**10d** (80%, 94% *ee*)	13	**9m**	**10m** (85%, 87% *ee*)
5	**9e**	**10e** (78%, 91% *ee*)	14	**9n**	**10n** (58%, 89% *ee*)
6	**9f**	**10f** (78%, 95% *ee*)	15	**9o**	**10o** (50%, 66% *ee*)
7	**9g**	**10g** (88%, 98% *ee*)	16	**9p**	**10p** (52%, 91% *ee*)
8	**9h**	**10h** (78%, 79% *ee*)	17	**9q**	**10q** (84%, 98% *ee*)
9	**9i**	**10i** (76%, 75% *ee*)			

[a]Isolated yield. [b]Determined by HPLC analysis using AD-H or OD-H column, column temperature 30 °C, flow phase *n*-hexane/*i*-PrOH, flow rate 1.0 mL/ min.

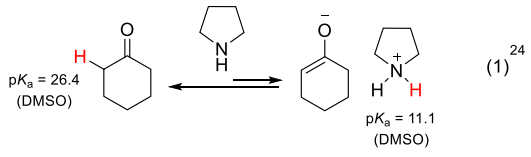
Table 2
(*R*,*R*)-**Cat-1**-catalyzed conjugate additions of nitroalkanes to cyclohexenones.



Entry	Enone	Nu	Product (yield,[a] *ee*[b])
1	**9a**	$CH_3CH_2CH_2NO_2$	**10r+10r'** (86%) (55 : 45 dr, 91%, 94% ee)
2	**9r**	CH_3NO_2	**10s** (79%, 98% *ee*)
3	**9r**	$CH_3CH_2CH_2NO_2$	**10t+10t'** (93%) (17 : 83 dr, 99%, 97% ee)
4	**9r**	$(CH_3)_2CHNO_2$	**10u** (87%, 98% *ee*)

[a]Isolated yield. [b]Determined by HPLC analysis using AD-H or OD-H column, column temperature 30 °C, flow phase *n*-hexane/*i*-PrOH, flow rate 1.0 mL/ min.

nitromethane [pK_a (DMSO) = 17.2] [25] as compared with cyclohexanone, the generation of nitromethane carbanion as a reactive specie in the equilibrium is reasonable (eq. 2) [26]. Under such circumstance, the generation of a substantial amount of an enimi-nium species as reactive intermediate is less plausible.



To gain an insight into the mechanism of enantioselection, we conducted DFT calculations on the key chirality-generating C—C bond formation step at M062X-D3/def2-TZVPP-PCM//B3LYP-D3/6-31G*-PCM level (Fig. 3, **9b** employing as model substrate). Through hydrogen bonding the pre-formed thiourea-ammonium organized the nitromethane carbanion and 3-ethylcyclohex-2-enone **9b** to form the transition state structures. For this assembling process two possible hydrogen-bond binding patterns among the three species were investigated. **Pattern 1** (***R*-TS1**, ***S*-TS1**): Hydrogen bonds were formed between two oxygen atoms of nitromethane carbanion and H—N of thiourea and ammonium, and between carbonyl oxygen of **9b** and ammonium hydrogen, which led to the transition states ***R*-TS1** (nitromethane carbanion attacked from *re*-face of **9b** to afford *R*-configuration product), ***S*-TS1** (attacked from *si* face of **9b** to afford *S*-configuration product). **Pattern 2** (***R*-TS2**, ***S*-TS2**): Alternatively, hydrogen bonds between carbonyl oxygen of **9b** and H—N of thiourea, and between two oxygen atoms of nitromethane carbanion and ammonium hydrogen were formed to generate ***R*-TS2** (attacked from *re* face to afford *R*-configuration product), ***S*-TS2** (attacked from *si*-face to afford *S*-configuration product). And transition state ***R*-TS1** was more favored than ***S*-TS1**, ***R*-TS2**, ***S*-TS2** by 3.55, 4.93, 2.48 kcal/mol, respectively. According to these differences of free energies the calculated *ee* value was determined to 96%, which was in good agreement with the experimental value (98% *ee*). The results can be rationalized by the hydrogen bond interaction and the repulsive interaction between cyclohexanone ring and nitromethane carbanion in the transition states. As the H-bond binding ternary complex of ***S*-TS1** shown, the attacking nitromethane carbanion

Table 3
Retention time (t_R) and optical rotation of the enantiomeric adducts.

Entry	Adduct	t_R[a]/min of major enantiomer	t_R[a]/min of minor enantiomer	Optical rotation {$[\alpha]_D$ (c = 1.0, $CHCl_3$)}
1	(*R*)-6 [9a]	8.7	10.1	+33 (97% *ee*)
2	(*R*)-10a	17.1	18.2	+7.9 (98% *ee*)
3	(*R*)-10b	13.5	14.3	+3.0 (98%, *ee*)
4	(*R*)-10c	4.3	4.9	+2.6 (98% *ee*)
5	(*R*)-10d	10.0	11.8	+4.3 (94% *ee*)
6	(*R*)-10e	6.7	7.2	+1.7 (91% *ee*)
7	(*S*)-10f	46.6	53.4	+1.0(95% *ee*)
8	(*R*)-10g	*29.1*	*44.1*	+5.9 (98% *ee*)
9	(*S*)-10h	5.4	5.9	+4.3 (79% *ee*)
10	(*S*)-10i	15.0	16.8	+2.7 (75% *ee*)
11	(*R*)-10j	15.1	17.1	+3.3 (85% *ee*)
12	(*S*)-10k	11.6	18.2	+9.5 (97% *ee*)
13	(*S*)-10l	20.7	21.8	+10.4 (95% *ee*)
14	(*S*)-10m	24.7	25.8	+9.1 (87% *ee*)
15	(*R*)-10n	11.8	16.0	+11.3 (89% *ee*)
16	(*R*)-10o	15.9	23.3	+11.5 (66% *ee*)
17	(*R*)-10p	62.2	64.4	+8.0 (91% *ee*)
18	(*R*)-10q	29.1	30.4	+5.9 (98% *ee*)
19	(*R*)-10r + (*R*)-10r′	7.7	26.1	+2.4 (97, 99% *ee*, 55: 45 dr)
		11.4	12.9	
20	(*R*)-10s	14.0	16.2	+7.9 (98% *ee*)
21	(*R,S*)-10t + (*R,R*)-10t' [11b]	10.0	11.1	−2.4 (99, 97% *ee*, 17: 83 dr)
		10.4	11.8	
22	(*R*)-10u	12.6	11.8	+20.5 (98% *ee*)

[a] HPLC analysis using AD-H or OD-H column, column temperature: 30 °C, flow phase *n*-hexane/*i*-PrOH, flow rate 1.0 mL/min.

was arranged on the upside of cyclohexenone ring. Correspondingly, in ***R*-TS1** the nitromethane carbanion was approaching the electrophilic site from one side of cyclohex-2-enone ring, thus resulting in a less repulsive interaction between molecular planes of nitromethane carbanion and cyclohexanone than those occurring in ***S*-TS1** (*cf.* the Newman projections through the forming C1−C2 bond). Similar behavior was observed in ***R*-TS2** and ***S*-TS2**. Hence, ***R*-TS1** and ***S*-TS2** were more favored than ***S*-TS1** and ***R*-TS1** by 3.55 and 2.45 kcal/mol, respectively. In addition, ***R*-TS1** preferred over ***S*-TS2** by 2.48 kcal/mol may be ascribe to the relatively strong hydrogen-bonding interaction featured by the exhibited shorter O···HN distances (***R*-TS1**: 1.822, 2.161, 1.867, 1.574 Å *vs* ***S*-TS2**: 1.837, 1.843, 2.381, 1.700 Å) and more linear O···H···N angles (***R*-TS1**: 169°, 146°, 161°, 170° *vs* ***S*-TS2**: 157°, 156°, 114°, 167°) [27]. These results are in support of our suggestion that nitroalkane carbanion and H-bond activated cyclic enone are reactive intermediates in the asymmetric conjugate addition, which is in agreement with the model proposed by Wang [17].

To demonstrate the utility of this methodology, one-step conversions of **10a** into carboxylic acid **11**, oxime **12**, and an active pharmaceutical ingredient (API) **13** [18] were performed. The nitromethane oxidation using sodium nitrite in the presence of acetic acid provided **11** in a yield of 72% (Scheme 3−1) [28]. Treatment of **10a** with tributyltin hydride in the presence of 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) in toluene at 90 °C produced oxime **12** in good yield (75%) (Scheme 3−2) [29]. Ketal **13** was obtained in 94% yield by the $BF_3 \cdot Et_2O$-promoted reaction with glycol and trimethyl orthoformate (Scheme 3−3). In addition, the tandem deprotection of acetal in **10f** and intramolecular aldol condensation of the keto-aldehyde intermediate were achieved by treating with a 3 M HCl to give **14** in 71% yield (Scheme 4). It is worth mentioning that the bicyclo[4.3.0]nonane core skeleton **14** is possessed by many bioactive nature products such as acutifolone A [30] and (+)-axamide-4 [31].

3. Conclusions

In summary, on the basis of our previous work in the total synthesis of (−)-haliclonin A (**1**), we have developed a versatile enantioselective approach to cyclic ketones bearing all-carbon quaternary stereogenic centers at β-C based on a structurally relatively simple, cheap and easily available chiral primary amine-thiourea catalyst. Excellent enantioselectivities were obtained from β−substituted cyclohex-2-enones with α′ and β′-unbranched alkyl groups, and from 3-benzylcyclohex-2-enone. The reaction is amenable to cyclohex-2-enone, β−substituted cyclopent-2-enones and cyclohept-2-enones, and to other nitroalkanes. We have shown that absolute configurations of adducts could be determined according to the retention times of two enantiomers of each adduct by chiral HPLC analysis. Additionally, DFT computational results of transition states at the chirality generation step suggested that the enantioselection control mechanism of the catalytic conjugate addition involved the hydrogen-bonding modes between substrates (nitromethane, cyclic enone) and catalyst, and the intra-complex repulsive interaction.

4. Experimental section

4.1. General

Melting points were determined on a Büchi M560 Automatic Melting Point apparatus and are uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film pellet techniques. Optical rotation data were measured on an Anton Paar MCP 500 polarimeter at 589 nm and at 20 or 25 °C, using a 50 mm path-length cell in the solvent and at the concentration indicated. HPLC analyses were carried out on an Agilent 1260 series system with Daicel CHIRALPAK® or Daicel CHIRALCEL® columns (4.6 × 250 mm, particle size 3 μm). ^1H and ^{13}C NMR spectra were

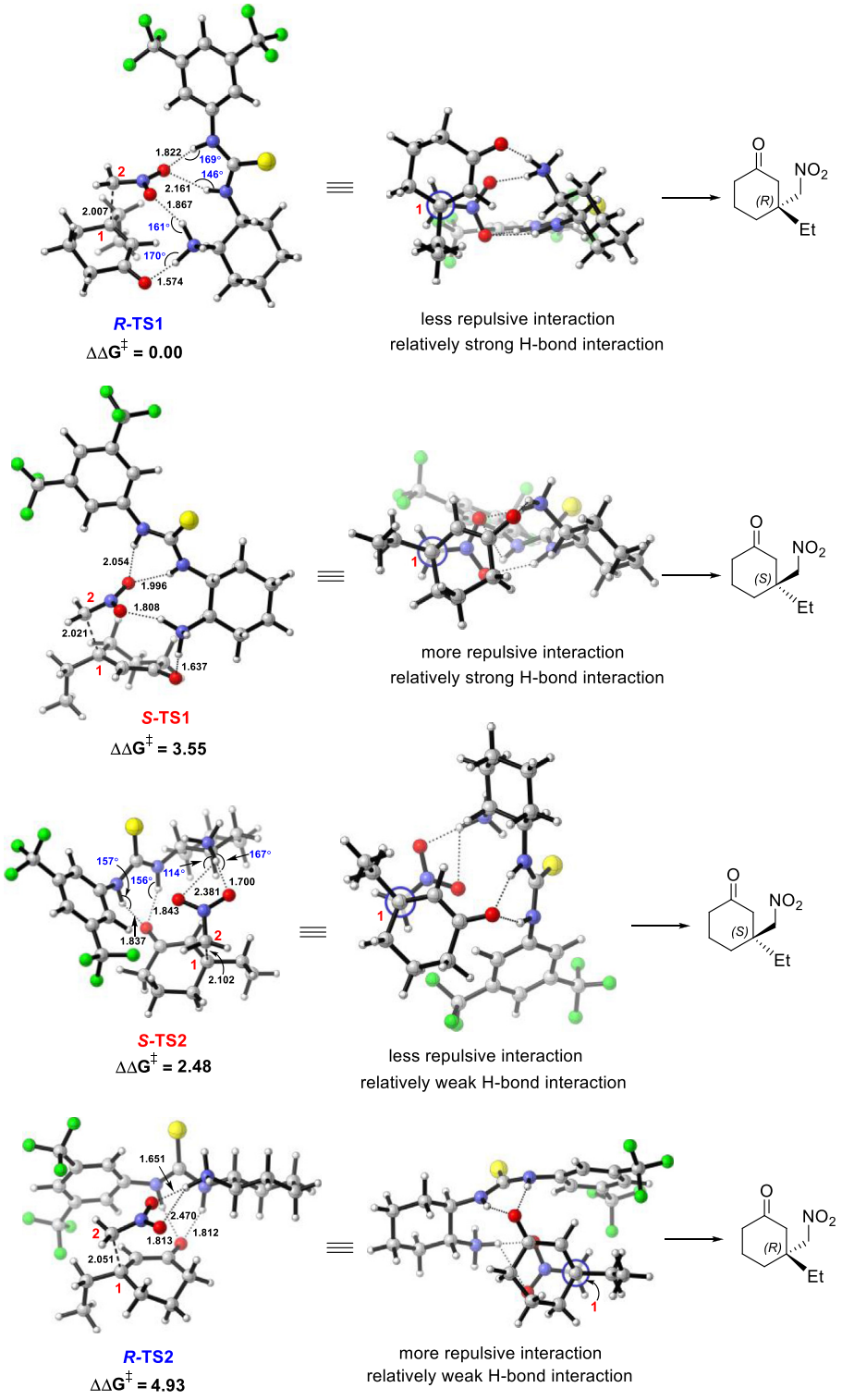
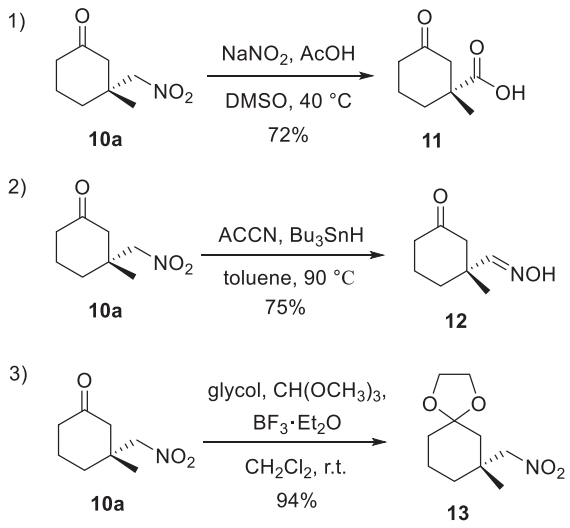
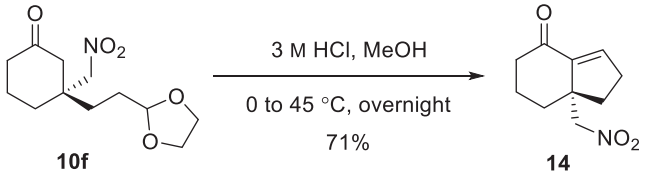


Fig. 3. The DFT-calculated geometries, the corresponding Newman projections of through the forming C1−C2 bond, and relative free energies (ΔΔ*G*, 318 K) of transition states for the C−C bond forming step in (*R*,*R*)-**cat-1** catalyzed conjugate addition of nitromethane to the model β-ethylcyclohexenone under acid-free conditions. The energies are given in kcal/mol. Selected distances and angles are denoted in angstroms (Å) and degrees, respectively.

recorded at 500 and 125 MHz, respectively. Chemical shifts (δ) are reported in ppm and respectively referenced to internal standard Me_4Si and solvent signals (Me_4Si, 0.0 ppm for ^1H NMR and $CDCl_3$, 77.0 ppm for ^{13}C NMR). Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus LC-MS apparatus (ESI direct injection). HRMS spectra were recorded on a 7.0T FT-MS apparatus. Silica gel (300−400 mesh) was used for flash column chromatography, eluting with EtOAc/*n*-hexane mixture. Reactions were performed in oven-dried glassware under an argon atmosphere.



Scheme 3. One-step conversions of nitro ketone **10a** into keto carboxylic acid **11**, keto oxime **12**, and nitro ketal **13**.



Scheme 4. One-step construction of bicyclo[4.3.0]nonane skeleton **14** from **10f**.

4.2. Synthesis of starting materials 9a-9q

3-Substituted cyclic enones were prepared by addition of a Grignard reagent to a 3-ethoxy cyclic enone according to the literature procedure [11a].

4.3. General synthetic method of 10a-10u

Into a dry 10-mL Schlenk tube equipped with a magnetic stirring bar were added successively a 3-substituted cyclic enone **9** (0.5 mmol, 1.0 equiv), thiourea catalyst (*R,R*)-**cat-1** (0.1 mmol, 0.2 equiv) in 2.5 mL of redistilled nitromethane at room temperature under an argon atmosphere. And then the reaction was heated to 45 °C and stirred for 5–7 days. The reaction mixture was cooled to room temperature and quenched with 1 M HCl (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-Hexane) to afford product **10**. The enantiomeric excess was determined by HPLC analysis on a chiral column.

4.3.1. (+)-(R)-3-Methyl-3-(nitromethyl)cyclohexan-1-one (10a)

Following the general procedure, the reaction of cyclohexenone **9a** (55 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:8), the known compound (*R*)-**10a** [8c] (65 mg, yield: 76%) as a yellow oil. 98% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 95: 5, 1.0 mL/min, λ = 220 nm), t_R (major) = 17.1 min, t_R (minor) = 18.2 min, $[\alpha]_D^{20}$ = +7.9 (*c* = 1.0, $CHCl_3$, 98% *ee*) [lit [8c]. $[\alpha]_D^{25}$ = +1.7 (*c* = 2.0, $CHCl_3$, 98% *ee*); (*S*)-**10a**: lit [8d]. $[\alpha]_D^{30}$ = −6.6 (*c* = 1.0, CH_2Cl_2, 99% *ee*)]; IR (film) ν_{max}: 2921, 2852, 1738, 1503, 1379, 1296, 1080, 437 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.52–1.60 (m, 1H), 1.62–1.69 (m, 1H), 1.71–1.79 (m, 1H), 1.80–1.90 (m, 1H), 2.08 (d, *J* = 13.9 Hz, 1H), 2.14–2.23 (m, 2H), 2.27 (d, *J* = 13.9 Hz, 1H), 4.16 (d, *J* = 10.8 Hz, 1H), 4.20 (d, *J* = 10.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 23.1, 33.5, 39.8, 40.5, 50.7, 84.9, 208.8 ppm; MS (ESI) *m/z* 194 ($M + Na^+$, 100%).

4.3.2. (+)-(R)-3-Ethyl-3-(nitromethyl)cyclohexan-1-one (10b)

Following the general procedure, the reaction of cyclohexenone **9b** (62 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:8), the known compound (*R*)-**10b** [8d] (75 mg, yield: 82%) as a yellow oil. 98% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 95: 5, 1.0 mL/min, λ = 220 nm), t_R (major) = 13.5 min, t_R (minor) = 14.3 min, $[\alpha]_D^{20}$ = +3.0 (*c* = 1.0, $CHCl_3$, 98% *ee*) [(*S*)-**10b**: lit [8d]. $[\alpha]_D^{30}$ = −5.7 (*c* = 1.0, CH_2Cl_2, 99% *ee*)]; IR (film) ν_{max}: 2966, 2883, 1712, 1545, 1381, 1315, 1230, 1044, 756, 530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.5 Hz, 3H), 1.41–1.51 (m, 2H), 1.67–1.80 (m, 2H), 1.82–1.92 (m, 1H), 1.93–2.00 (m, 1H), 2.26–2.36 (m, 3H), 2.38 (d, *J* = 14.2 Hz, 1H), 4.31 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 7.1, 20.8, 28.0, 30.9, 40.5, 42.5, 49.0, 81.3, 209.1 ppm; MS (ESI) *m/z* 208 ($M + Na^+$, 100%).

4.3.3. (+)-(R)-3-Hexyl-3-(nitromethyl)cyclohexan-1-one (10c)

Following the general procedure, the reaction of cyclohexenone **9c** (90 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:10), the known compound (*R*)-**10c** [8d] (102 mg, yield: 85%) as a yellow oil. 98% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 90: 10, 2.0 mL/min, λ = 220 nm), t_R (major) = 4.3 min, t_R (minor) = 4.9 min, $[\alpha]_D^{20}$ = +2.6 (*c* = 1.0, $CHCl_3$, 98% *ee*) [(*S*)-**10c**: lit [8d]. $[\alpha]_D^{30}$ = −1.5 (*c* = 1.0, CH_2Cl_2, 99% *ee*)]; IR (film) ν_{max}: 2932, 2858, 1713, 1549, 1431, 1314, 1229, 1081, 724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.22–1.29 (m, 8H), 1.33–1.43 (m, 2H), 1.68–1.81 (m, 2H), 1.82–1.92 (m, 1H), 1.94–2.03 (m, 1H), 2.27–2.42 (m, 4H), 4.32 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 20.9, 22.5, 22.6, 29.4, 31.3, 31.5, 35.4, 40.5, 42.4, 49.5, 81.9, 209.1 ppm; HRMS (ESI) *m/z* calcd for $[C_{13}H_{23}NNaO_3]^+$ ($M + Na^+$): 264.1570; found: 264.1569.

4.3.4. (+)-(R)-3-(Nitromethyl)-3-(pent-4-en-1-yl)cyclohexan-1-one (10d)

Following the general procedure, the reaction of cyclohexenone **9d** (82 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:10), compound (*R*)-**10d** (90 mg, yield: 80%) as a yellow oil. 94% *ee* was determined by chiral (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 95: 5, 1.0 mL/min, λ = 220 nm), t_R (major) = 10.0 min, t_R (minor) = 11.8 min, $[\alpha]_D^{20}$ = +4.3 (*c* = 1.0, $CHCl_3$, 94% *ee*); IR (film) ν_{max}: 3077, 2941, 1707, 1640, 1542, 1459, 1316, 1230, 993, 915, 724, 667, 509 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.30–1.43 (m, 4H), 1.67–1.79 (m, 2H), 1.80–1.92 (m, 1H), 1.92–2.06 (m, 3H), 2.24–2.41 (m, 4H), 4.30 (s, 2H), 4.88–5.03 (m, 2H), 5.62–5.83 (m, 1H) pm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 21.9, 31.2, 33.6, 34.7, 40.4, 42.2, 49.3, 81.7, 115.3, 137.6, 208.9 ppm; HRMS (ESI) *m/z* calcd for $[C_{11}H_{19}NNaO_3]^+$ ($M + Na^+$): 248.1257; found: 248.1259.

4.3.5. (+)-(R)-3-(4-((tert-Butyldimethylsilyl)oxy)butyl)-3-(nitromethyl)cyclohexan-1-one (10e)

Following the general procedure, the reaction of cyclohexenone **9e** (141 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:11), compound (*R*)-**10e** (151 mg, yield: 78%) as a yellow oil. 91% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 97: 3, 1.0 mL/min,

λ = 220 nm), t_R (major) = 6.7 min, t_R (minor) = 7.2 min, $[\alpha]_D^{20}$ = +1.7 (*c* = 1.0, $CHCl_3$, 91% *ee*); IR (film) ν_{max}: 2952, 2857, 1715, 1551, 1471, 1432, 1255, 1101, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.00 (s, 6H), 0.87 (s, 9H), 1.28−1.49 (m, 6H), 1.73−1.99 (m, 4H), 2.24−2.40 (m, 4H), 3.57 (t, *J* = 6.2 Hz, 2H), 4.32 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.4 (2C), 18.2, 19.1, 20.8, 25.9 (3C), 31.2, 32.8, 35.2, 40.5, 42.4, 49.5, 62.4, 81.8, 209.0 ppm; HRMS (ESI) *m/z* calcd for $[C_{17}H_{33}NNaO_4Si]^+$ (M + Na^+): 366.2071; found: 366.2072.

4.3.6. (+)-(S)-3-(2-(1, 3-Dioxolan-2-yl)ethyl)-3-(nitromethyl) cyclohexan-1-one (10f)

Following the general procedure, the reaction of cyclohexenone **9f** (98 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:2), compound (*S*)-**10f** (100 mg, yield: 78%) as a yellow oil. 95% *ee* was determined by chiral HPLC (Chiralcel OD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 90: 10, 1.5 mL/min, λ = 220 nm), t_R (minor) = 46.6 min, t_R (major) = 53.4 min, $[\alpha]_D^{20}$ = +1.0 (*c* = 1.0, $CHCl_3$, 95% *ee*); IR (film) ν_{max}: 2955, 2885, 1712, 1549, 1457, 1382, 1279, 1142, 1079, 1033, 894, 640 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.47−1.57 (m, 2H), 1.62−1.68 (m, 2H), 1.73−1.80 (m, 2H), 1.83−1.98 (m, 2H), 2.24−2.42 (m, 4H), 3.77−3.83 (m, 2H), 3.87−3.92 (m, 2H), 4.29 (s, 2H) 4.80 (t, *J* = 4.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7, 27.2, 29.2, 31.1, 40.4, 41.8, 49.4, 64.9 (2C), 81.5, 103.6, 208.7 ppm; HRMS (ESI) *m/z* calcd for $[C_{12}H_{19}NNaO_5]^+$ (M + Na^+): 280.1155; found: 280.1156.

4.3.7. (+)-Ethyl (R)-2-(1-(nitromethyl)-3-oxocyclohexyl) acetate (10g)

Following the general procedure, the reaction of cyclohexenone **9g** (91 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:10), compound (*R*)-**10g** (107 mg, yield: 88%) as a yellow oil. 98% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 96.2: 3.8, 1.0 mL/min, λ = 220 nm), t_R (major) = 29.1 min, t_R (minor) = 44.1 min, $[\alpha]_D^{20}$ = +5.6 (*c* = 1.0, $CHCl_3$, 98% *ee*); IR (film) ν_{max}: 2957, 2924, 2855, 1722, 1631, 1550, 1462, 1188, 1081, 964, 814, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.76−1.83 (m, 1H), 1.87−1.96 (m, 2H), 1.96−2.04 (m, 1H), 2.31−2.41 (m, 2H), 2.44−2.54 (m, 4H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 20.8, 31.5, 38.9, 40.4, 41.2, 48.9, 60.8, 80.8, 169.9, 208.0 ppm; HRMS (ESI) *m/z* calcd for $[C_{11}H_{17}NNaO_5]^+$ (M + Na^+): 266.0999; found: 266.0999.

4.3.8. (+)-(S)-3-Isobutyl-3-(nitromethyl)cyclohexan-1-one (10h)

Following the general procedure, the reaction of cyclohexenone **9h** (83 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:10), the known compound (*S*)-**10h** [8c] (83 mg, yield: 78%) as a yellow oil. 79% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 95: 5, 2.0 mL/min, λ = 220 nm), t_R (major) = 5.4 min, t_R (minor) = 5.9 min, $[\alpha]_D^{20}$ = +4.3 (*c* = 1.0, $CHCl_3$, 79% *ee*) [lit [8c]. $[\alpha]_D^{25}$ = −1.8 (*c* = 2.0, CH_2Cl_2, 97% *ee*)]; IR (film) ν_{max}: 2958, 2872, 1713, 1549, 1378, 1228, 1080, 963, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.96 (d, *J* = 6.6 Hz, 6H), 1.30−1.42 (m, 2H), 1.69−1.85 (m, 3H), 1.87−2.03 (m, 2H), 2.27−2.42 (m, 4H), 4.35 (d, *J* = 11.0 Hz, 1H), 4.38 (d, *J* = 11.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0, 23.6, 24.9, 25.0, 31,7, 40.5, 43.2, 44.4, 49.7, 82.2, 209.2 ppm; HRMS (ESI) *m/z* calcd for $[C_{11}H_{19}NNaO_3]^+$ (M + Na^+): 236.1257; found: 236.1259.

4.3.9. (+)-(S)-3-Cyclopropyl-3-(nitromethyl)cyclohexan-1-one (10i)

Following the general procedure, the reaction of cyclohexenone **9i** (78 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:10), compound (*S*)-**10i** (89 mg, yield: 76%) as a yellow oil. 75% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 95: 5, 1.0 mL/min, λ = 220 nm), t_R (major) = 15.0 min, t_R (minor) = 16.8 min, $[\alpha]_D^{20}$ = +2.7 (*c* = 1.0, $CHCl_3$, 75% *ee*); IR (film) ν_{max}: 2924, 2854, 1710, 1632, 1548, 1277, 1080, 965, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.18−0.25 (m, 1H), 0.29−0.36 (m, 1H), 0.37−0.44 (m, 1H), 0.46−0.53 (m, 1H), 0.76−0.85 (m, 1H), 1.71−1.84 (m, 2H), 1.87−1.97 (m, 1H), 2.02 (d, *J* = 15.0 Hz, 1H), 2.05−2.12 (m, 2H), 2.18 (d, *J* = 15.0 Hz, 1H), 2.22−2.40 (m, 2H), 4.29 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 1.2, 1.7, 18.4, 20.6, 32.1, 40.5, 41.3, 45.3, 83.4, 209.5 ppm; HRMS (ESI) *m/z* calcd for $[C_{11}H_{19}NNaO_3]^+$ (M + Na^+): 220.0944; found: 220.0943.

4.3.10. (+)-(R)-3, 3, 5-Trimethyl-5-(nitromethyl)cyclohexan-1-one (10j)

Following the general procedure, the reaction of cyclohexenone **9j** (70 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:15), the known compound (*R*)-**10j** [8c] (75 mg, yield: 75%) as a yellow oil. 85% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 96.2: 3.8, 1.0 mL/min, λ = 220 nm), t_R (major) = 15.1 min, t_R (minor) = 17.1 min, $[\alpha]_D^{20}$ = + 3.3 (*c* = 1.0, $CHCl_3$, 85% *ee*) [lit [8c]. $[\alpha]_D^{25}$ = +7.6 (*c* = 2.0, $CHCl_3$, 99% *ee*); (*S*)-**10j**: lit [8d]. $[\alpha]_D^{30}$ = −8.6 (*c* = 1.0, CH_2Cl_2, 96% *ee*)]; IR (film) ν_{max}: 2959, 2925, 1715, 1551, 1461, 1429, 1283, 1248, 1081, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.05−1.09 (m, 6H), 1.20 (s, 3H), 1.65 (d, *J* = 14.4 Hz, 1H), 1.79 (d, *J* = 14.4 Hz, 1H), 2.18−2.25 (m, 3H), 2.44−2.50 (m, 1H), 4.26 (d, *J* = 10.9 Hz, 1H), 4.29 (d, *J* = 10.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.8, 30.0, 32.4, 35.5, 39.6, 46.7, 49.5, 53.6, 86.3, 209.2 ppm; MS (ESI) *m/z* 222 (M + Na^+, 100%).

4.3.11. (+)-(S)-3-Benzyl-3-(nitromethyl)cyclohexan-1-one (10k)

Following the general procedure, the reaction of cyclohexenone **9k** (93 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:5), the known compound (*S*)-**10k** [8c] (96 mg, yield: 78%) as a yellow oil. 97% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 90: 10, 1.0 mL/min, λ = 220 nm), t_R (major) = 11.6 min, t_R (minor) = 18.2 min, $[\alpha]_D^{20}$ = +9.5 (*c* = 1.0, $CHCl_3$, 97% *ee*) [lit [8c]. $[\alpha]_D^{25}$ = +20.0 (*c* = 2.0, $CHCl_3$, 97% *ee*); (*S*)-**10k**: lit [8d]. $[\alpha]_D^{30}$ = −18 (*c* = 1.0, CH_2Cl_2, 99% *ee*)]; IR (film) ν_{max}: 3029, 2926, 2855, 1712, 1650, 1548, 1378, 1228, 1079, 962, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.75−1.89 (m, 2H), 2.02−2.11 (m, 2H), 2.25−2.30 (m, 1H), 2.34−2.43 (m, 3H), 2.77−2.84 (m, 2H), 4.21 (d, *J* = 11.5 Hz, 1H), 4.28 (d, *J* = 11.5 Hz, 1H), 7.19−7.23 (m, 2H), 7.26−7.36 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 31.4, 40.5, 41.9, 43.4, 48.2, 80.9, 127.2, 128.5 (2C), 130.7 (2C), 134.9, 209.3 ppm; MS (ESI) *m/z* 270 (M + Na^+, 100%).

4.3.12. (+)-(S)-3-(4-Fluorobenzyl)-3-(nitromethyl)cyclohexan-1-one (10l)

Following the general procedure, the reaction of cyclohexenone **9l** (102 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:5), compound (*S*)-**10l** (107 mg, yield: 81%) as a yellow oil. in 95% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 93: 7, 1.0 mL/min, λ = 220 nm), t_R (major) = 20.7 min, t_R (minor) = 21.8 min, $[\alpha]_D^{20}$ = +10.4 (*c* = 1.0, $CHCl_3$, 95% *ee*); IR (film) ν_{max}: 2925, 1712, 1604, 1550, 1509, 1248, 1226, 1161, 842, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.72−1.79 (m, 1H), 1.79−1.86 (m, 1H), 2.00−2.07 (m, 2H), 2.20−2.26 (m, 1H), 2.31−2.38 (m, 3H), 2.73−2.80 (m, 2H), 4.18 (d, *J* = 11.7 Hz, 1H), 4.24 (d, *J* = 11.7 Hz, 1H), 6.97−7.02 (m, 2H), 7.15−7.21 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 31.6, 40.5, 40.9, 43.5, 48.1, 80.6, 115.4 (d, $J_{C\text{-}F}$ = 21.0 Hz, 2C), 130.6 (d, $J_{C\text{-}F}$ = 3.5 Hz), 132.3 (d, $J_{C\text{-}F}$ = 7.9 Hz, 2C), 162.0 (d, $J_{C\text{-}F}$ = 246.2 Hz), 209.0 ppm; HRMS (ESI) *m/z* calcd for

$[C_{14}H_{16}FNNaO_3]^+$ (M + Na^+): 288.1006; found: 288.1007.

4.3.13. (+)-(S)-3-(4-Methoxybenzyl)-3-(nitromethyl)cyclohexan-1-one (10m)

Following the general procedure, the reaction of cyclohexenone **9m** (108 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:4), compound (*S*)-**10m** (117 mg, yield: 85%) as a yellow oil. 87% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 92: 8, 1.0 mL/min, λ = 220 nm), t_R (major) = 24.7 min, t_R (minor) = 25.8 min, $[\alpha]_D^{20}$ = +9.1 (*c* = 1.0, $CHCl_3$, 87% *ee*); IR (film) ν_{max}: 2925, 2853, 1711, 1611, 1549, 1512, 1381, 1249, 1033, 840, 644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.70–1.85 (m, 2H), 1.96–2.08 (m, 2H), 2.20–2.27 (m, 1H), 2.30–2.38 (m, 3H), 2.71 (s, 2H), 3.77 (s, 3H), 4.17 (d, *J* = 11.5 Hz, 1H), 4.24 (d, *J* = 11.5 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0, 31.3, 40.4, 40.9, 43.5, 48.1, 55.1, 80.9, 113.8 (2C), 126.7, 131.7 (2C), 158.6, 209.3 ppm; HRMS (ESI) *m/z* calcd for $[C_{15}H_{19}NNaO_4]^+$ (M + Na^+): 300.1206; found: 300.1207.

4.3.14. (+)-(R)-3-(Nitromethyl)-3-phenylcyclohexan-1-one (10n)

Following the general procedure, the reaction of cyclohexenone **9n** (86 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:5), the known compound (*R*)-**10n** [8c] (68 mg, yield: 58%) as a yellow solid. 89% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 90: 10, 1.0 mL/min, λ = 220 nm), t_R (major) = 11.8 min, t_R (minor) = 16.0 min, $[\alpha]_D^{20}$ = +11.3 (*c* = 1.0, $CHCl_3$, 89% *ee*) [lit [8c]. $[\alpha]_D^{25}$ = +63.6 (*c* = 2.0, $CHCl_3$, 98% *ee*); (*S*)-**10n**: lit [8d]. $[\alpha]_D^{30}$ = −23 (*c* = 0.55, CH_2Cl_2, 98% *ee*)]; mp: 91–93 °C; IR (film) ν_{max}: 2955, 2924, 2854, 1711, 1650, 1548, 1462, 1375, 1185, 1080, 948, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.45–1.57 (m, 1H), 1.88–1.97 (m, 1H), 2.07–2.17 (m, 1H), 2.28–2.36 (m, 2H), 2.40–2.48 (m, 1H), 2.75 (d, *J* = 14.8 Hz, 1H), 3.21 (d, *J* = 14.8 Hz, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.59 (d, *J* = 11.1 Hz, 1H) 7.27–7.41 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6, 33.4, 40.4, 46.6, 48.4, 85.8, 126.5, 127.9, 129.2, 139.1, 208.3 ppm; MS (ESI) *m/z* 256 (M + Na^+, 100%).

4.3.15. (+)-(R)-3-(4-Chlorophenyl)-3-(nitromethyl)cyclohexan-1-one (10o)

Following the general procedure, the reaction of cyclohexenone **9o** (103 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:5), compound (*R*)-**10o** (66 mg, yield: 50%) as a yellow solid. 66% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 90: 10, 1.0 mL/min, λ = 220 nm), t_R (major) = 15.9 min, t_R (minor) = 23.3 min, $[\alpha]_D^{20}$ = +11.5 (*c* = 1.0, $CHCl_3$, 66% *ee*); mp: 117–119 °C; IR (film) ν_{max}: 2956, 2925, 2854, 1711, 1681, 1453, 1361, 1190, 1082, 847, 771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.46–1.57 (m, 1H), 1.88–1.98 (m, 1H), 2.06–2.16 (m, 1H), 2.26–2.42 (m, 3H), 2.74 (d, *J* = 14.6 Hz, 1H), 3.16 (d, *J* = 14.6 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6, 33.5, 40.3, 46.4, 48.5, 85.6, 128.1 (2C), 129.4 (2C), 134.0, 137.6, 207.9 ppm; HRMS (ESI) *m/z* calcd for $[C_{13}H_{14}ClNNaO_3]^+$ (M + Na^+): 290.0554; found: 290.0559.

4.3.16. (+)-(R)-3-Methyl-3-(nitromethyl)cyclopentan-1-one (10p)

Following the general procedure, the reaction of cyclopentenone **9p** (55 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:4), the known compound (*R*)-**10p** [8c] (41 mg, yield: 52%) as a yellow oil. 91% *ee* was determined by chiral HPLC (Chiralcel OD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 95: 5, 1.0 mL/min, λ = 220 nm), t_R (minor) = 62.2 min, t_R (major) = 64.4 min, $[\alpha]_D^{20}$ = + 8.0 (*c* = 1.0, $CHCl_3$, 91% *ee*) [lit [8c]. $[\alpha]_D^{25}$ = +77.5 (*c* = 2.1, $CHCl_3$, 88% *ee*); (*S*)-**10p**: lit [8d]. $[\alpha]_D^{30}$ = −28 (*c* = 1.0, CH_2Cl_2, 96% *ee*)]; IR (film) ν_{max}: 2964, 2924, 1743, 1550, 1381, 1255, 1168, 1034, 639, 518 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.24 (s, 3H), 1.91–1.98 (m, 1H), 1.99–2.07 (m, 1H), 2.18–2.25 (m, 1H), 2.35–2.41 (m, 3H), 4.38–4.45 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.5, 33.0, 36.0, 40.2, 49.7, 84.3, 215.7 ppm; MS (ESI) *m/z* 180 (M + Na^+, 100%).

4.3.17. (+)-(R)-3-Methyl-3-(nitromethyl)cycloheptan-1-one (10q)

Following the general procedure, the reaction of cycloheptenone **9q** (62 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:6), the known compound (*R*)-**10q** [8c] (78 mg, yield: 84%) as a yellow oil. 98% *ee* was determined by chiral HPLC (Chiralcel OD-H, column temperature: 30 °C, *n*-hexane: *i*-PrOH = 95: 5, 1.0 mL/min, λ = 220 nm), t_R (minor) = 29.1 min, t_R (major) = 30.4 min, $[\alpha]_D^{20}$ = +5.9 (*c* = 1.0, $CHCl_3$, 98% *ee*) [lit [8c]. $[\alpha]_D^{25}$ = +28.8 (*c* = 2.2, $CHCl_3$, 99% *ee*); (*S*)-**10q**: lit [8d]. $[\alpha]_D^{30}$ = −31 (*c* = 1.0, CH_2Cl_2, 98% *ee*)]; IR (film) ν_{max}: 2924, 2853, 1693, 1549, 1462, 1377, 1186, 964, 818, 654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.05 (s, 3H), 1.55–1.65 (m, 2H), 1.67–1.88 (m, 4H), 2.33–2.44 (m, 2H), 2.47 (d, *J* = 12.3 Hz, 1H), 2.67 (d, *J* = 12.3 Hz, 1H), 4.22 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.6 (2C), 23.7, 36.5, 39.4, 43.7, 51.5, 85.2, 211.1 ppm; MS (ESI) *m/z* 208 (M + Na^+, 100%).

4.3.18. (+)-(R)-3-Methyl-3-((S/R)-1-nitropropyl)cyclohexan-1-one (10r + 10r′)

Following the general procedure, the reaction of cyclohexenone **9a** (55 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/n-hexane = 1:4), a mixture of inseparable diastereomers (*R*)-**10r** and (*R*)-**10r′** [11c] (86 mg, yield: 86%, dr = 55: 45, determined by ^1H NMR) as a yellow oil. 91, 94% *ee* were determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, hexane: *i*-PrOH = 90: 10, 1.0 mL/min, λ = 230 nm), t_R (major) = 7.7 min, t_R (minor) = 26.1 min, t_R (major) = 11.4 min, t_R (minor) = 12.9 min, $[\alpha]_D^{25}$ = +2.4 (*c* = 1.0, $CHCl_3$, 91, 94% *ee*). IR (film) ν_{max}: 2948, 1712, 1546, 1364, 1232, 810, 510 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) mixture: δ 0.83 (td, *J* = 7.2, 2.8 Hz, 3.15H), 0.90 (d, *J* = 10.4 Hz, 3.12H), 1.38–1.55 (m, 1.11H), 1.63–1.77 (m, 3.18H), 1.82–2.01 (m, 2.67H), 2.10–2.29 (m, 3.20H), 2.43 (d, *J* = 13.7 Hz, 0.55H), 4.18 (ddd, *J* = 11.8, 6.7, 2.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) mixture: δ 10.6, 20.0, 20.1, 20.8, 20.9, 21.0, 32.4, 32.6, 40.2, 40.3, 40.9, 41.4, 48.6, 49.8, 98.1, 99.2, 209.0 ppm; HRMS (ESI) *m/z* calcd for $[C_{10}H_{17}NO_3Na]^+$ (M + Na^+): 222.1101; found: 222.1098.

4.3.19. (+)-(R)-3-(Nitromethyl)cyclohexan-1-one (10s)

Following the general procedure, the reaction of cyclohexenone **9r** (48 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/n-hexane = 1:10), the known compound (*R*)-**10s** [12c] (62 mg, yield: 79%) as a yellow oil. 98% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, hexane: *i*-PrOH = 90: 10, 1.0 mL/min, λ = 210 nm), t_R (major) = 14.0 min, t_R (minor) = 16.2 min, $[\alpha]_D^{25}$ = +7.9 (*c* = 1.0, $CHCl_3$, 98% *ee*) [lit [12c]. $[\alpha]_D^{25}$ = +10.6 (*c* = 0.5, $CHCl_3$, 96% *ee*)]; IR (film) ν_{max}: 2962, 2924, 2853, 1261, 1019, 799 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.42–1.60 (m, 1H), 1.67–1.82 (m, 1H), 1.95–2.04 (m, 1H), 2.08–2.21 (m, 2H), 2.25–2.36 (m, 1H), 2.41–2.54 (m, 2H), 2.59–2.72 (m, 1H), 4.28–4.51 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.1, 28.2, 37.1, 40.8, 44.4, 80.0, 208.1 ppm; HRMS (ESI) *m/z* calcd for $[C_7H_{11}O_3Na]^+$ (M + Na^+): 180.0631; found: 180.0630.

4.3.20. (+)-(R)-3-((S)-1-Nitropropyl)cyclohexan-1-one (10t) + (−)-(R)-3-((R)-1-Nitropropyl)cyclohexan-1-one (10t′)

Following the general procedure, the reaction of cyclohexenone **9r** (48 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:8), a mixture of inseparable diastereomers (*R,S*)-**10t** and (*R,R*)-**10t′** [11b] (86 mg, yield: 93%, dr = 17: 83, determined by ^1H

NMR) as a yellow oil. 99, 97% *ee* were determined by chiral HPLC (Chiralcel OD-H, column temperature: 30 °C, hexane: *i*-PrOH = 90: 10, 1.0 mL/min, λ = 210 nm), t_R (major) = 10.0 min, t_R (minor) = 11.1 min; t_R (major) = 10.4 min, t_R (minor) = 11.8 min); $[\alpha]_D^{25} = -2.4$ (c = 1.0, $CHCl_3$, 97, 99% *ee*) [lit [11b]. less polar (*R*,*S*)-**10t**: $[\alpha]_D = +29.3$ (c = 1.2, CHCl3, 91% *ee*), more polar (*R*,*R*)-**10t'**: $[\alpha]_D = -13.2$ (c = 1.1, $CHCl_3$, 74% *ee*)]; IR (film) ν_{max}: 2924, 2854, 1713, 1546, 1462, 1260, 1098, 804 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) mixture: δ 0.77 (td, J = 7.3, 3.1 Hz, 3H), 1.27–1.35 (m, 1H), 1.41–1.57 (m, 1H), 1.61–2.06 (m, 5H), 2.06–2.31 (m, 4H), 4.14–4.26 (m, 1H) ppm; Major disastereomer: ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.7, 23.6, 23.9, 26.9, 40.3, 40.8, 43.0, 93.9, 208.2 ppm; Minor disastereomer: ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.8, 23.4, 23.7, 26.9, 40.3, 41.0, 43.1, 93.7, 208.3 ppm HRMS (ESI) *m/z* calcd for $[C_9H_{15}NO_3Na]^+$ (M + Na^+): 208.0944; found: 208.0942.

4.3.21. (+)-(R)-3-(2-Nitropropan-2-yl)cyclohexan-1-one (10u)

Following the general procedure, the reaction of cyclohexenone **9r** (48 mg, 0.5 mmol) gave, after FC on silica gel (eluent: EtOAc/*n*-hexane = 1:10), the known compound (*R*)-**10u** [11d] (81 mg, yield: 87%) as a white solid. 98% *ee* was determined by chiral HPLC (Chiralcel AD-H, column temperature: 30 °C, hexane: *i*-PrOH = 90: 10, 1.0 mL/min, λ = 210 nm), t_R (major) = 12.6 min, t_R (minor) = 11.8 min, $[\alpha]_D^{25} = +20.5$ (c = 1.0, $CHCl_3$, 98% *ee*) [lit [11d]. $[\alpha]_D^{26} = -13.7$ (c = 1.0, $CHCl_3$)]; mp: 64–65 °C; IR (film) ν_{max}: 2923, 2854, 1714, 1533, 1457, 1261, 1092, 1022, 800 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.33–1.45 (m, 1H), 1.52 (d, J = 7.8 Hz, 6H), 1.57–1.63 (m, 1H), 1.71–1.82 (m, 1H), 2.02–2.13 (m, 2H), 2.15–2.42 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.5, 23.1, 24.2, 25.8, 40.6, 42.4, 46.4, 90.5, 208.8 ppm; HRMS (ESI) *m/z* calcd for $[C_9H_{15}NO_3Na]^+$ (M + Na^+): 208.0944; found: 208.0946.

4.4. (R)-1-Methyl-3-oxocyclohexane-1-carboxylic acid (11)

A mixture of compound **10a** (86 mg, 0.5 mmol), sodium nitrite (104 mg, 1.5 mmol), and acetic acid (300 mg, 5.0 mmol) in dimethylsulfoxide (2.0 mL) was stirred at 40 °C for 6 h [28]. The reaction mixture was cooled to room temperature, diluted with water (3 mL) and acidified with hydrochloric acid (3 M) to pH 2. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/*n*-Hexane = 1:1) to afford the desired product **11** (56 mg, yield: 72%) as a pale yellow oil; IR (film) ν_{max}: 3321, 2965, 2925, 1730, 1463, 1413, 1260, 1102, 1113, 803 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.65–1.98 (m, 3H), 2.10–2.46 (m, 4H), 2.75 (d, J = 14.5 Hz, 1H), 8.69 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 24.5, 34.2, 40.2, 46.3, 49.5, 181.7, 209.2 ppm; HRMS (ESI) *m/z* calcd for $[C_8H_{12}O_3Na]^+$ (M + Na^+): 179.0679; found: 179.0670.

4.5. (R,E)-1-Methyl-3-oxocyclohexane-1-carbaldehyde oxime (12)

A solution of compound **10a** (86 mg, 0.5 mmol), 1,1′-azobis(cyanocyclohexane) (122 mg, 0.5 mmol), and *n*-Bu_3SnH (728 mg, 2.5 mmol) in toluene (5 mL) was stirred at 90 °C for 6 h. The reaction mixture was cooled to room temperature and quenched with H_2O (5 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/*n*-Hexane = 1:4) to afford the desired product **12** (58 mg, yield: 75%) as a yellow oil; IR (film) ν_{max}: 3277, 2964, 2923, 2853, 1709, 1462, 1260, 1187, 963, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.63–1.71 (m, 1H), 1.78–1.91 (m, 3H), 2.14–2.25 (m, 2H), 2.30–2.38 (m, 1H), 2.59 (d, J = 13.9 Hz, 1H), 7.30 (s, 1H), 8.60 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.2, 25.6, 34.5, 40.4, 41.0, 49.9, 156.1, 210.3 ppm; HRMS (ESI) *m/z* calcd for $[C_8H_{13}NO_2Na]^+$ (M + Na^+): 178.0838; found: 178.0842.

4.6. (R)-7-Methyl-7-(nitromethyl)-1,4-dioxaspiro[4.5]decane (13)

To a solution of compound **10a** (86 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added ethylene glycol (621 mg, 10 mmol), trimethyl orthoformate (1061 mg, 10.0 mmol) and $BF_3{\cdot}OEt_2$ (28 mg, 0.2 mmol) at room temperature under an argon atmosphere for 12 h. The reaction was quenched with $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/*n*-Hexane = 1:8) to afford the desired product **13** (101 mg, yield: 94%) as a yellow oil; IR (film) ν_{max}: 2942, 2882, 1547, 1462, 1376, 1177, 1140, 1098, 1054, 1043, 943, 832, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.04 (s, 3H), 1.19–1.26 (m, 1H), 1.46–1.54 (m, 2H), 1.58–1.67 (m, 4H), 1.71 (d, J = 14.1 Hz, 1H), 3.79–3.96 (m, 4H), 4.38 (d, J = 10.8 Hz, 1H), 4.51 (d, J = 10.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.4, 26.2, 34.6, 34.7, 36.6, 43.4, 64.0, 64.4, 83.5, 108.2 ppm; HRMS (ESI) *m/z* calcd for $[C_{10}H_{17}NO_4Na]^+$ (M + Na^+): 238.1050; found: 238.1051.

4.7. (S)-7a-(Nitromethyl)-1, 2, 5, 6, 7, 7a-hexahydro-4H-inden-4-one (14)

To a solution of compound **10f** (64 mg, 0.5 mmol) in MeOH (5 mL) was added 3 M HCl (5 mL) at 0 °C. The reaction was heated to 45 °C for 24 h. The resulting mixture was quenched with saturated aqueous solution of $NaHCO_3$ (5 mL). The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/*n*-Hexane) to afford the desired product **14** (70 mg, yield: 71%) as a yellow oil, $[\alpha]_D^{20} = -1.1$ (c = 1.0, $CHCl_3$); IR (film) ν_{max}: 2923, 2851, 1705, 1614, 1455, 1378, 1318, 1169, 1082 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.59–1.70 (m, 1H), 1.79–1.89 (m, 1H), 1.97–2.10 (m, 2H), 2.16–2.24 (m, 1H), 2.25–2.37 (m, 1H), 2.49–2.59 (m, 3H), 2.60–2.68 (m, 1H), 4.19 (d, J = 11.1 Hz, 1H), 4.45 (d, J = 11.1 Hz, 1H), 6.71 (t, J = 2.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.3, 29.6, 33.0, 36.9, 39.8, 52.1, 77.6, 141.6, 143.8, 198.0 ppm; HRMS (ESI) *m/z* calcd for $[C_{10}H_{13}NNaO_3]^+$ (M + Na^+): 218.0788; found: 218.0785.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132005.

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