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Asymmetric 1,4-Michael Addition in Aqueous Medium Using Hydrophobic Chiral Organocatalysts

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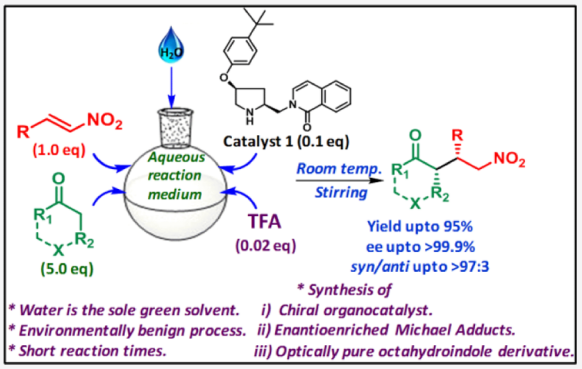
ABSTRACT: Organic transformations exclusively in water as an environmentally friendly and safe medium have drawn significant interest in the recent years. Moreover, transition metal-free synthesis of enantiopure molecules in water will have a great deal of attention as the system will mimic the natural enzymatic reactions. In this work, a new set of proline-derived hydrophobic organocatalysts have been synthesized and utilized for asymmetric Michael reactions in water as the sole reaction medium. Among the various catalysts screened, the catalyst **1** is indeed efficient for stereoselective 1,4-conjugated Michael additions (dr: >97:3, ee up to >99.9%) resulting in high chemical yields (up to 95%) in a very short reaction time (1 h) at room temperature. This methodology provides a robust, green, and convenient protocol and can thus be an important addition to the arsenal of the asymmetric Michael addition reaction. Upon successful implementation, the present strategy also led to the formation of an optically active octahydroindole, the key component found in many natural products.



INTRODUCTION

Enantioselective transformation is a key process in modern organic synthesis and is particularly important in the field of drug discovery research as each enantiomer may differ significantly in exhibiting various pharmacological effects and toxicity.[1] Therefore, the synthesis of a chiral drug substance warrants a new methodology that can result in the formation of specific enantiomers. Asymmetric Michael reactions, in particular, reactions between carbonyl compounds and nitro-olefins, play a significant role in carbon−carbon bond formation reactions as this transformation generates γ-nitro carbonyl compounds with two contiguous stereocenters[2] and these are found to be valuable building blocks in synthesizing various bioactive molecules.[3] Chiral organocatalysts have been broadly developed over the past decade due to its advantageous properties, such as nonmetal in nature and thus having minimal toxicity as well as no contamination in final drug-like substances, stability to air and moisture, and thus convenience in handling.[4−6] In the literature, the development of an asymmetric organocatalytic system has been mostly based on proline or its derivatives and these were found to accelerate the range of transformations such as Michael addition, aldol, and Mannich reaction, to name a few prominent transformations, which were often carried out in organic solvents. D and L forms of proline are inexpensive; besides this, proline has two functional groups, a carboxylic acid and an amine [thus, the reactions usually require polar solvents such as dimethyl sulfoxide (DMSO) or alcohol due to their insoluble nature], and plays a significant role in bi-functional asymmetric catalysis, which has become a successful strategy for facilitating chemical transformations similar to enzymatic catalysis. Thus, proline and its derivatives, to construct stereocenters in organic compounds with better selectivities, are one of the major milestones in the field of organocatalysis.[7−17]

Typically, in any organic reaction, the solvent accounts for 50−60% of the entire mass. Thus, abundant use of volatile organic solvents and their incomplete recovery may be one of the reasons to pollute the environment to a greater extent during the manufacturing process of pharmaceuticals. From the perspective of green chemistry, avoidance of toxic organic solvents and employment of green reaction media are the crucial factors for practical purposes. In this regard, reactions in water as the solvent will be of immense value considering water as an environmentally friendly and safe medium. Moreover, the synthesis of enantiopure molecules in aqueous medium will have great deal of attention as the catalytic system will "mimic" the natural enzymatic reactions. Therefore, exploration of

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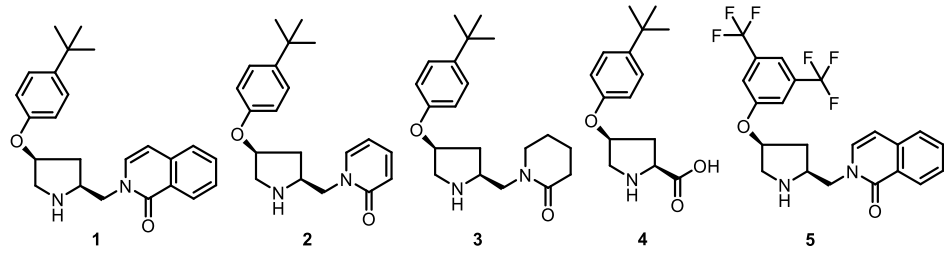
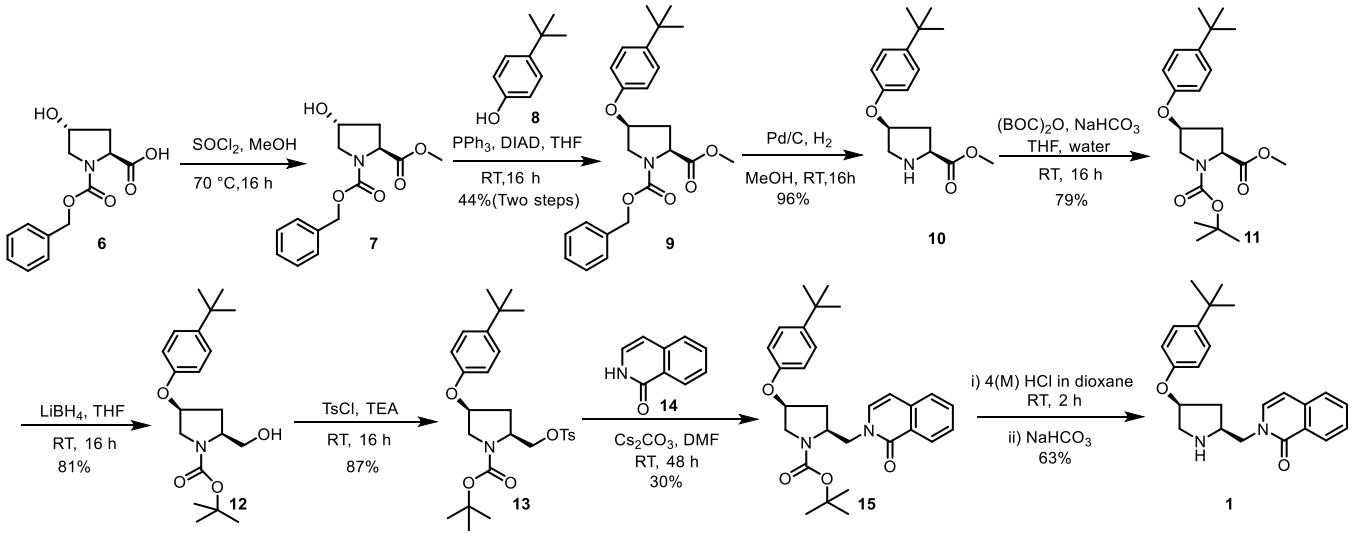
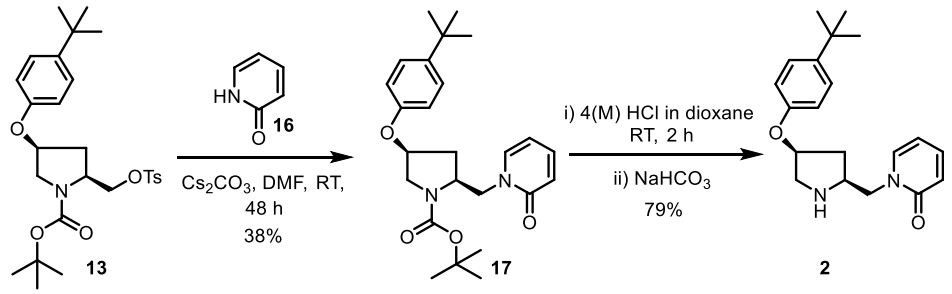


Figure 1. Proline derivatives **1**−**5** as promising organocatalysts.

Scheme 1. Synthesis of Catalyst 1



Scheme 2. Synthesis of Catalyst 2



carbon−carbon bond formation reactions in water will presumably be of high interest in terms of functional group tolerance and late stage chemical modification of biologically relevant molecules.[18] Interestingly though, for a long time, it was assumed that reactions performed in water led to slow reaction rates and yields.[19] However, a revolution occurred with studies reported by Breslow, introducing that Diels−Alder reactions could be performed in water,[20] and Hayashi, for the first time, introduced organocatalytic aldol reactions using prolinamide in the presence of water as an exclusive reaction medium.[21]

In view of developing a new generation of organocatalysts to be effective only in aqueous medium, we recently have shown that a novel pyrrolidine−oxadiazolone conjugate can successfully give the desired Michael adduct from nitrostyrene and cyclohexanone with >97:3 diastereoselectivity in water as a sole medium, although the enantiomeric excess for the *syn*isomer was found to be only 87%.[22] The use of proline and proline derivatives as catalysts of multicomponent reactions performed in aqueous media has been summarized in a recent review.[2e] As an example, asymmetric Michael addition exclusively in water or brine has been reported albeit with very long reaction time and/or resulting in low enantioselectivities in many adducts.[14,16b] In continuation of our studies and to improve on the enantioselectivity in water as a reaction medium in short reaction time, we here synthesized a set of new chiral proline-based compounds **1**−**5** (Figure 1) as promising organocatalysts containing a bulky hydrophobic substituent at the 4-position and methylene-heterocycle at the 2-position (except cat. 4) of the pyrrolidine ring to examine the performance of these catalysts **1**−**5** in Michael addition between nitroolefins and carbonyl compounds solely in water medium.

RESULTS AND DISCUSSION

The new chiral catalyst **1** was synthesized from a commercially available 4-hydroxy derivative of L-proline **6**, as represented in

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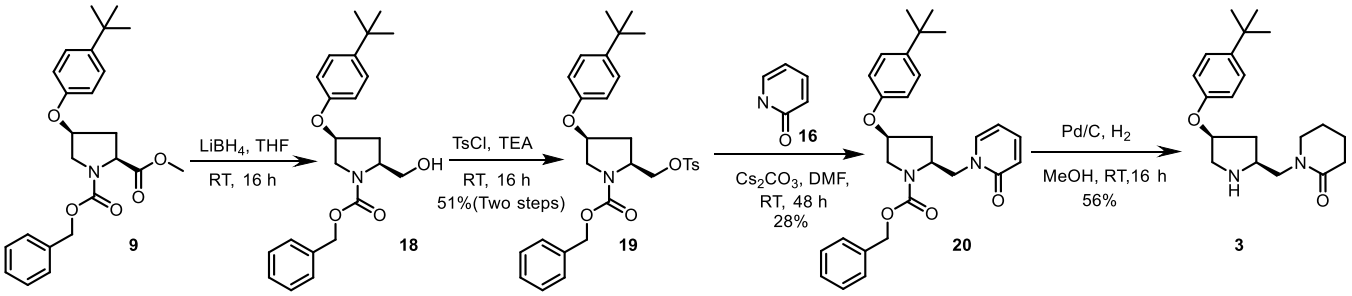
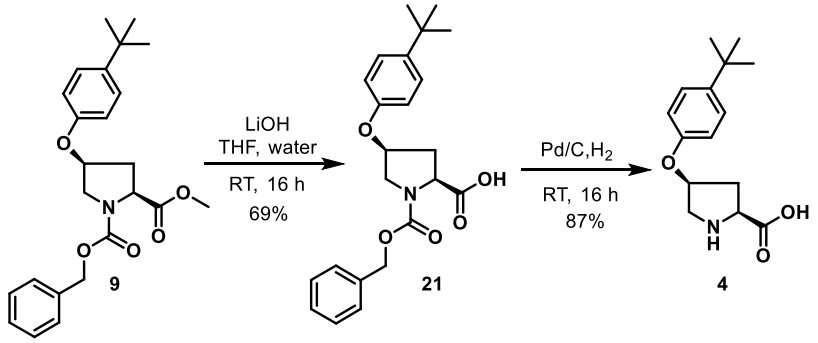
J. Org. Chem. 2021, 86, 5213−5226

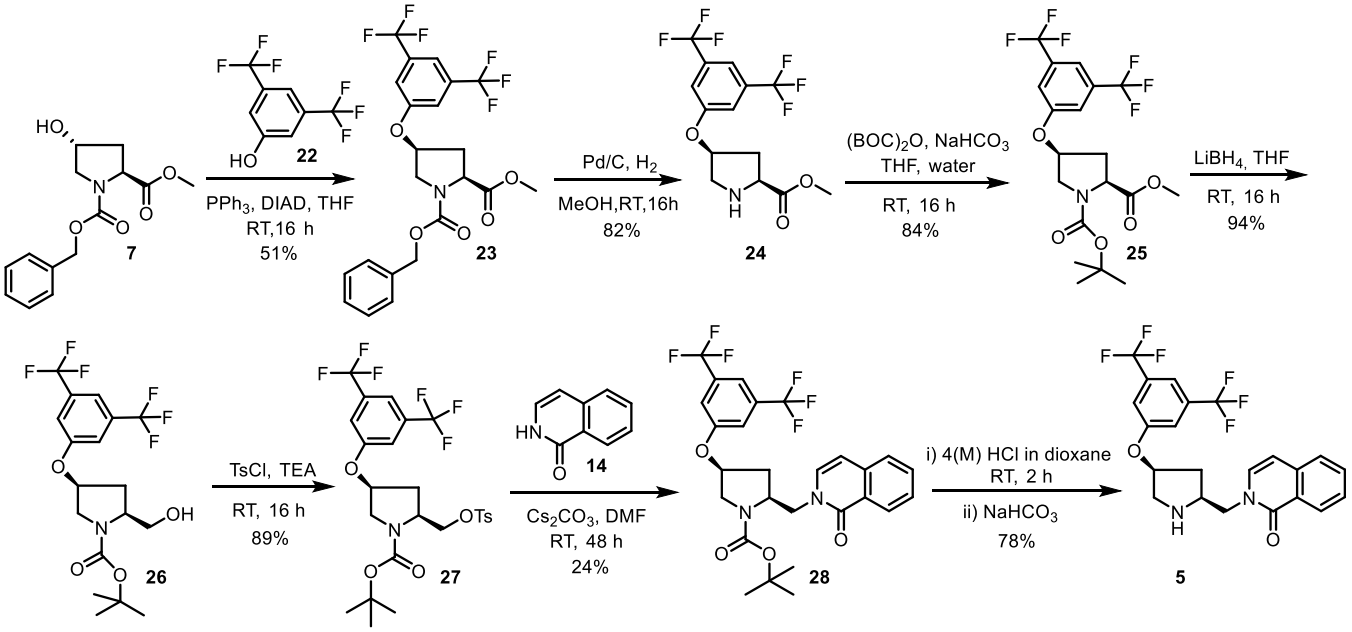
Scheme 3. Synthesis of Catalyst 3



Scheme 4. Synthesis of Catalyst 4



Scheme 5. Synthesis of Catalyst 5



Scheme 1. Accordingly, **6** was converted to (*tert*-butyl)-phenoxyprolinate derivative **9** using the Mitsunobu reaction (via proline intermediate **7**).

N-Boc-protected compound **11** was obtained via Cbz-deprotected proline ester **10** followed by O-tosylation using *p*-tosyl chloride in dichloromethane with the presence of TEA (via prolinol derivative **12**).[12,22] The tosyl derivative **13** was then coupled with isoquinolone **14** using Cs_2CO_3 as a base in dimethylformamide (DMF) to provide the adduct **15**. Deprotection of the Boc-group was performed by 4 (M) HCl in 1,4-dioxane and the crude material was basified with $NaHCO_3$ to afford pyrrolidine-isoquinolone conjugate **1** as a sticky liquid. Catalyst **2** was synthesized from intermediate **13** (Scheme 2), following a similar synthetic route, as discussed in Scheme 1.

A new chiral organocatalyst **3** was synthesized from intermediate **9**, as depicted in Scheme 3. Accordingly, **9** was converted to *N*-Cbz-protected prolinol derivative **18** followed by O-tosylation using *p*-tosyl chloride in dichloromethane in the presence of TEA as a base.[12,22] The tosyl derivatives **19** was then coupled with 2-pyridone (**16**) using Cs_2CO_3 in DMF to provide the adduct **20**. Finally, deprotection of the Cbz-group along with simultaneous reduction of the pyridine ring resulted in our desired compound 1-(((2*S*,4*S*)-4-(4-(*tert*-

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J. Org. Chem. 2021, 86, 5213−5226

butyl)phenoxy)pyrrolidin-2-yl)methyl)piperidin-2-one **3** as a brownish sticky liquid.

Chiral organocatalyst **4** was synthesized from (2*S*,4*S*)-1-benzyl 2-methyl 4-(4-(*tert*-butyl)phenoxy)pyrrolidine-1,2-dicarboxylate **9**, as depicted in Scheme 4, hydrolysis followed by hydrogenation.

Catalyst **5** was synthesized (Scheme 5) following a similar synthetic route, as described for the synthesis of catalysts **1** and **2**.

After successful synthesis of the catalysts **1**−**5**, we commenced our investigations to check the efficiency of the catalysts in water following the benchmark Michael addition of donor **30** to acceptor **29a** at room temperature (Scheme 6, Table 1).

Scheme 6. Asymmetric Organocatalysis Reaction in Water

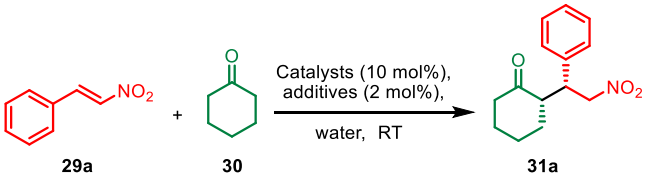

Table 1. Catalyst Optimization Reaction between Cyclohexanone and *β*-Nitrostyrene[a]

entry	catalysts	time (h)	additives	isolated yield (%)	*syn*/*anti* [dr]	% ee
1	**1**	15		68	>97:3	98
2	**1**	**1**	**TFA**	**81**	**>97:3**	**98**
3	1	24	AcOH	20% conversion		
4	1	1.5	PNBA	70	>97:3	97
5	1	2.5	TsOH	75	>97:3	97
6	**2**	7	TFA	75	>97:3	80
7	**3**	10	TFA	80	>97:3	92
8	proline	24	TFA			
9	**4**	24	TFA	12		29
10	**5**	1	TFA	80	>97:3	97
11[b]	**1**	3	TFA	75	>97:3	95

[a]Reaction conditions (entries 1−10): nitrostyrene (1.0 mmol), cyclohexanone (5.0 mmol), catalysts (10 mol %), additives (2 mol %), water (2.0 mL), RT. dr determined by the ^{1}H NMR of the crude product; the ratio >97:3 has been kept despite there was no detectable *anti*-isomer present. % ee determined by chiral HPLC corresponds to the *syn* diastereomer. [b]Reaction was carried out under solvent-free conditions.

We thus initiated our investigation on the 1,4-conjugated Michael addition between nitrostyrene **29a** and cyclohexanone (**30**) utilizing 10 mol % of catalyst **1** without the presence of additive trifluoroacetic acid (TFA) in water (Table 1, entry 1). The reaction took sufficiently longer time (15 h) to produce the Michael adduct **31a** in moderate yield (68%), although the enantioselectivity (98% ee—*syn* isomer) and diastereoselectivity (>97:3— *syn*/*anti*) were quite high. Subsequently, we carried out the same reaction with 2 mol % of TFA as an additive keeping other parameters the same (Table 1, entry 2). We were pleased to observe that the product **31a** was formed in high yield (81%) within a very short reaction time (1 h) with excellent enantioselectivity (98% ee—*syn* isomer) and diastereoselectivity (>97:3—*syn*/*anti*) (Table 1, entry 2). In organocatalytic reactions, an additive is known to increase catalyst efficiency and thus other additives were screened (Table 1, entries 3−5) and we identified that among the various additives, TFA was the best in terms of both yield and asymmetric induction. For a head-to-head comparison, catalyst **2**−**4** and proline were also tested but did not show any significant outcome (Table 1, entries 6−9). Although catalyst **5** was equally effective (Table 1, entry 10) to catalyst **1**, we choose catalyst **1** to proceed for all our future reactions and the overall studies concluded that a brew of 10 mol % of catalyst **1** and 2 mol % of TFA in water as a greener solvent at room temperature was found to be optimal to facilitate the asymmetric 1,4-Michael addition to afford the desired product **31a** in high yield (Table 1, entry 2). This aqueous medium reaction was further encouraging as the reaction under solvent-free conditions (neat condition) with additive TFA was found relatively slow (3 h) with lesser yield (75%) and stereoselectivity (95% ee, *syn* isomer) of **31a** (Table 1, entry 11). Prompted by the abovementioned observations, we next turned our attention to explore the scope and generality of the aqueous medium protocol (Table 1, entry 2) with steric and electronically diverse nitroolefin substrates (**29**, Table 2).

As evident from Table 2, a wide range of nitrostyrenes were found amenable to the organocatalytic asymmetric Michael addition using cyclohexanone as a donor and dispensed the corresponding Michael adducts in high yields and having good-to-excellent enantioselectivity (**31c**−**g**). The protocol also worked well with nitroolefins containing naphthyl group and heteroaryl groups in terms of both chemical yield and stereoselectivity, providing desired adducts (**31b**, **h**−**j**). Pleasingly, a nitroolefin containing 3-pyridyl unit resulted in the desired adduct **31h** with >99.9% ee. Remarkably, nonaromatic Michael acceptor **29k** (R = cyclopropyl) was also consistent with the formation of product **31k** providing high diastereo- and enantioselectivity. These results not only highlight the exquisite stereoselectivity of our protocol but also strengthened the ability of newly developed proline derivatives as promising organocatalysts for Michael reactions in water as a sole reaction medium.

Fruitful results of this transformation encouraged us to further investigate the utility of catalyst **1** in exploring the breadth of other ketones and aldehyde for the Michael reaction with nitrostyrene **29a** and the corresponding results are displayed in Table 3.

Delightfully, from this study, we uncovered that the ketones used were compliant to our catalytic condition. Notably, pyran-4-one and thiopyran-4-one were more suitable affording the products **33a,b** in short reaction time with high diastereo- and enantioselectivity (Table 3). *N*-Boc 4-azacyclohexanone and acetone took relatively longer reaction time to afford adducts **33c,d** with moderate yield and enantioselectivity, whereas as expected, 2-butanone resulted in regioisomeric products (according to NMR of the crude reaction mass—not shown) but **33e** was isolated as a major product in the pure form with moderate yield and enantioselectivity. When isobutaraldehyde was used as a Michael donor, it rendered the Michael adduct **33f** with low yield and moderate enantioselectivity.

On the basis of the existing literature on mechanistic studies[23] and some experimental observations in the present studies, a plausible mechanism has been proposed for the formation of Michael adduct **31a** (Scheme 7), which can be considered as a general mechanism for the formation of other adducts also. The present reacting systems are found to be biphasic with water and the organic part (nitroolefins, carbonyl

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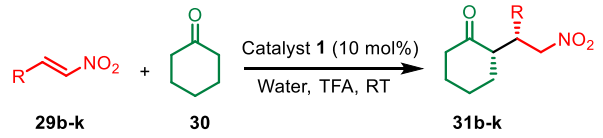
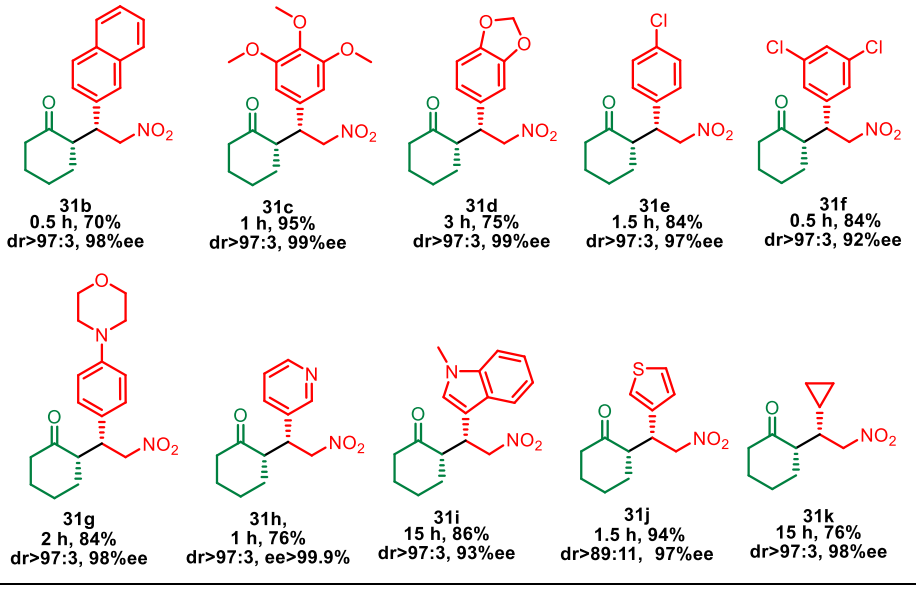
Table 2. Stereoselective Michael Reaction of Cyclohexanone with Different Olefins[a,b]

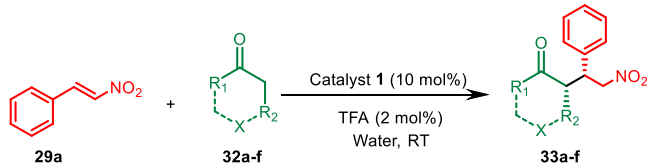


29b-k + 30 → 31b-k

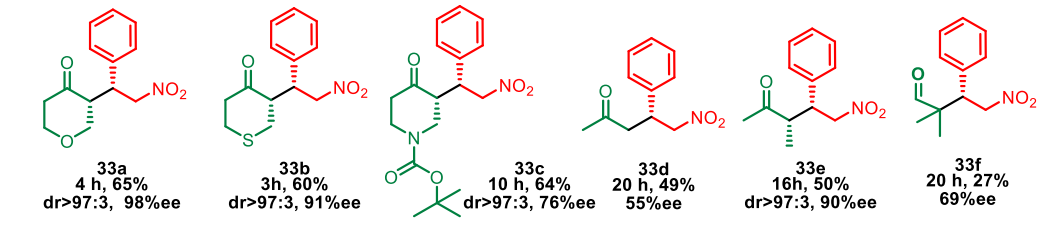


[a]Reaction conditions: nitrostyrene (1.0 mmol), cyclohexanone (5.0 mmol), catalyst **1** (10 mol %), TFA (2 mol %), water (2.0 mL), RT. [b]Isolated yields. dr determined by the ^{1}H NMR of the crude product; the ratio >97:3 has been kept despite there was no detectable *anti*-isomer present. % ee determined by chiral HPLC corresponds to the *syn* diastereomer.

Table 3. Asymmetric Michael Addition with Different Ketones Using Catalyst 1[a,b]



29a + 32a-f → 33a-f



[a]Reaction conditions: ketones and aldehydes (5.0 mmol), nitrostyrene (1.0 mmol), catalyst **1** (10 mol %), TFA (2 mol %), water (2.0 mL), RT. [b]Isolated yields. dr determined by the ^{1}H NMR of the crude product. % ee determined by chiral HPLC.

compounds, and hydrophobic catalysts) and form an emulsion during the reaction under stirring (Supporting Information, Figure S1). As the reaction is biphasic, the hydrophobic interaction drives the substrates and the catalyst in the organic phase and facilitates the reaction at the water−organic interface. As per literature precedents,[2e,4b,15,23] the catalytic system operates via the formation of enamine (**I**) between the pyrrolidine ring and a ketone such as cyclohexanone. E-*anti* is the energetically preferred conformation of enamine **I** where the E double bond is in antiorientation with the 2-substituent group in the pyrrolidine ring (Scheme 7).[23b] In enamine **I**, the top face, that is, the Re face is sterically crowded due to the presence of a bulky quinolone moiety (−HetAr) at 2-position and the 4-*tert*-butyl-4-(3,5-bis(trifluoromethyl)phenoxy) group (−OAr) at 4-position of the pyrrolidine unit for catalysts **1** and **5**. On the other hand, the bottom face of enamine **I** (i.e., Si face) is not sterically crowded. Therefore, it is likely that the *trans*-*β*-nitrostyrene will approach to the double bond of enamine **I** from sterically less-hindered bottom face (Si face) for the chemical reaction. This orientation of approach may be further assisted by the dipole−dipole interactions between the carbonyl group of the quinolone moiety and nitro groups. As

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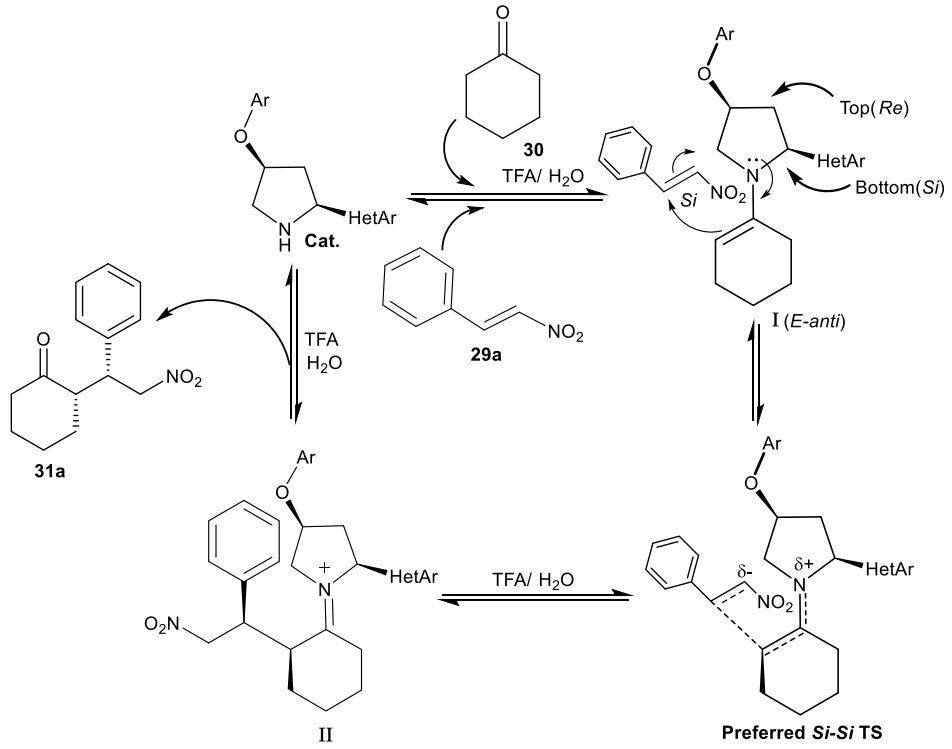
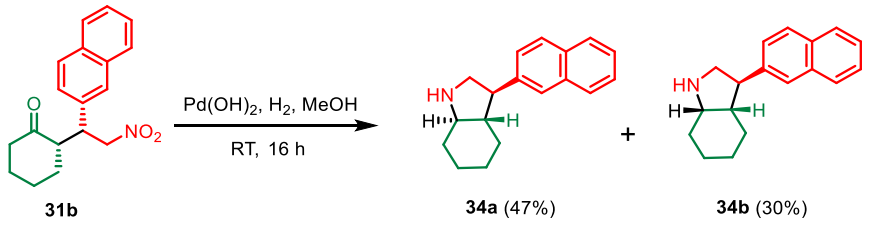
Scheme 7. Proposed Reaction Mechanism



Scheme 8. Synthesis of Octahydroindole Derivatives 34a,b



shown in Scheme 7, the Si face of *trans*-β-nitrostyrene and the Si face of enamine **I** will come close for reaction which is sterically favored and lead to the formation of the stable Si−Si transition state. The corresponding iminium intermediate **II** finally produces the *syn* Michael adduct **31a** through hydrolysis in high enantio- and diastereoselectivity, particularly in the case of catalysts **1** and **5** due to high steric crowding in the Re face.

It was observed that the reaction in the absence of TFA in water medium took 15 h to produce the adduct **31a** in 68% yield, whereas the presence of TFA as an additive remarkably reduced the reaction time (1 h) with an improved yield of **31a** (81%), although the enantio- and diastereoselectivity were the same in both cases (Table 1, entries 1 and 2). The addition of TFA in water accelerates the reaction and improves the yield of **31a** by catalyzing the enamine **I** formation as well as the hydrolysis of iminium intermediate **II** at the water−organic interface.[23] When the reaction was carried out under solvent-free conditions (neat condition) with additive TFA, the adduct **31a** was formed at a relatively slower rate (3 h) with lesser yield (75%) and stereoselectivity (95% ee, *syn* isomer) (Table 1, entry 11). Thus, in line with the literature precedent,[23a] these observations emphasize the role of TFA−water combination for efficient catalysis of the hydrolysis of iminium intermediate **II** to regenerate the organocatalyst for the next cycle of the reaction (Scheme 7). Stabilization of the transition state due to strong hydrophobic interactions in water may accelerate the reaction by reducing the activation energy. Strong association between substrates and catalyst arising from hydrophobic interactions in water may also cause high stereoselectivity in product formation as observed in the case of catalysts **1** and **5**. Longer reaction time, lesser yield, and lower stereoselectivity in the formation of **31a** with catalysts **2** and **3** (Table 1, entries 6 and 7) may be due to a less bulky nature and lower hydrophobicity of the −HetAr group in these catalysts (Figure 1).

The synthetic potentiality of the reaction was also showcased through an application where enantioenriched nitroketone **31b** was subjected to hydrogenation followed by reductive amination and cyclization to give the octahydroindole scaffolds **34a** and **34b** (yield = 65%, *trans*/*cis* ∼3:2) (Scheme 8), which are found to be a key component of several bioactive natural products such as glycosidase inhibitors and glycomimetics, to name a few.

CONCLUSIONS

In summary, we have divulged the synthesis and application of differently substituted pyrrolidine conjugates as new organocatalysts to give enantiopure Michael adducts (up to >99.9% ee and *syn*/*anti*>97:3) in excellent chemical yields (up to 95%). The reaction protocol is operational-handy, tolerates variety of

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substrates, fast, and most notably can be performed exclusively in aqueous medium. In comparison to proline, a bulky hydrophobic substituent at 4-position of the pyrrolidine ring as well as $-CH_2$-quinolone unit in the place of the $-CO_2H$ group (catalyst **1**) proved to catalyze Michael addition more efficiently leading to excellent stereoselectivities. Plausibly, the steric shielding and dipolar interactions due to the carbonyl and nitro groups make nitroolefin acceptors to approach the enamine double bond from the nonshielded side to give the desired Michael adducts in high enantio- and diastereoselectivity. Moreover, the additive TFA in water medium efficiently catalyzes the reaction at the water−organic interphase to produce the Michael adducts in excellent yields within a short reaction time. Impeccably, this methodology provides a robust, green, and convenient protocol and compatible with an array of common organic functional groups to perform 1,4-conjugate addition reactions, where the product could be isolated just by simple extractions from the reaction mixture. Despite significant research in the organocatalysis field, in most recent years, organocatalytic methodologies for the synthesis of enantioenriched medicinally important compounds have been gaining momentum and applicability of organocatalysts to the total synthesis of marketed drugs such as oseltamivir, paroxetine, maraviroc, and so forth,[24] where efforts mainly focused on addressing issues such as catalyst loading, substrate scope, and bulk availability of designer catalysts to remove some of the barriers for scale up of the drug substances. We believe that, along with the advantages said above, our results will open new avenues on a green organocatalytic approach in synthesizing some of these essential medicines.

EXPERIMENTAL SECTION

General Information. Commercial-grade reagents and solvents were used without further purification. Column chromatography was carried out using silica gel (100−200 mesh). TLC was performed on aluminum-backed plates coated with Silica gel 60 with an F_{254} indicator. The ^{1}H NMR spectra were recorded with 400 MHz and ^{13}C NMR spectra were recorded with 100 MHz using $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are expressed in parts per million (δ) relative to $CDCl_3$ (δ = 7.26) and DMSO-d_6 (δ = 2.49); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the $CDCl_3$ resonance (δ = 77.0) and DMSO-d_6 (δ = 39.7). GCMS experiments were carried out on an Agilent 6890 series GC coupled mass selective detector, with an HP-5MS capillary column. Purity was determined using a Shimadzu Prominence LC-20AD Binary pump, Shimadzu SIL-HTC autosampler, and Applied biosystem API-2000 triple quadruple mass spectrometer equipped with an ESI source. Chiral HPLC analyses were carried out on a CHIRALPAK or CHIRACEL column using either ethanol or a mixture of solvents, viz., hexane, ethyl acetate, and adding diethyl amine, where appropriate, as an eluent. Elemental analyses (C, H, and N) were recorded using a PerkinElmer 2400 elemental analyzer. HRMS spectra were recorded using a Xevo G2-S QTof instrument.

*1-Benzyl 2-Methyl (2S,4R)-4-Hydroxypyrrolidine-1,2-dicarboxylate (**7**).* Compound **7** (20.0 g) was prepared from **6** (25.0 g, 94.3 mmol) following the literature procedure[22] as a light-yellow semisolid, which was used directly in the following step mentioned below without purification.

*(2S,4S)-1-Benzyl 2-Methyl 4-(4-(tert-Butyl)phenoxy)pyrrolidine-1,2-dicarboxylate (**9**).* Compound **9** was prepared from **7** (20.0 g, 71.65 mmol) following the literature procedure[22] in 44% (two steps) yield (17.0 g) as a light-yellow liquid. $[\alpha]_D^{25}$ −49.19 (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.25 (m, 7H), 6.70 (d, *J* = 8.36 Hz, 2H), 5.21−5.06 (m, 2H), 4.87 (brs, 1H), 4.61−4.51 (m, 1H), 3.81−3.73 (m, 4H), 3.63 (s, 1H), 2.53−2.40 (m, 2H), 1.27 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.13 and 171.80 (rotamers), 154.71, 154.33 and 154.13 (rotamers), 144.2, 136.47 and 136.43 (rotamers), 128.4, 128.36 and 128.0 (rotamers), 127.94 and 127.84 (rotamers), 126.3, 115.11 and 115.04 (rotamers), 75.3, 74.3, 69.9, 67.18 and 67.04 (rotamers), 57.99 and 57.75 (rotamers), 52.29 and 52.13 (rotamers), 52.11 and 51.77 (rotamers), 36.5, 35.5, 34.0, 31.4, 21.89 and 21.65 (rotamers); LC−MS (ESI): 412.5 $[M + H]^+$.

*(2S,4S)-Methyl 4-(4-(tert-Butyl)phenoxy)pyrrolidine-2-carboxylate (**10**).* Compound **10** was prepared from **9** (10.0 g, 24.3 mmol) following the literature procedure[22] in 96% yield (6.5 g) as a colorless liquid. $[\alpha]_D^{25}$ −25.56 (*c* 0.87, $CHCl_3$); IR (neat): $\bar{\nu}$ 1738 (−NCO−) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.24 (m, 2H), 6.75−6.71 (m, 2H), 4.78−4.76 (m, 1H), 3.84−3.80 (m, 1H), 3.72 (s, 3H), 3.33 (d, *J* = 12.32 Hz, 1H), 3.02 (dd, *J* = 12.32 Hz and 4.24 Hz, 1H), 2.43−2.36 (m, 1H), 2.29−2.23 (m, 1H), 1.27 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 174.5, 154.5, 143.6, 126.1, 114.9, 59.1, 52.7, 52.2, 36.7, 34, 31.4; LC−MS (ESI): 278.4 $[M + H]^+$.

*(2S,4S)-1-tert-Butyl 2-Methyl 4-(4-(tert-Butyl)phenoxy)-pyrrolidine-1,2-dicarboxylate (**11**).* Compound **11** was prepared from **10** (8.4 g, 30.30 mmol) following the literature procedure[22] in 79% yield (9.03 g) as a colorless liquid. $[\alpha]_D^{25}$ −29.5 (*c* 0.5, $CHCl_3$); IR (neat): $\bar{\nu}$ 1754 (−NCO−) cm^{-1}, 1702 (−CCO) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 at 100 °C): δ 7.29 (d, *J* = 8.76 Hz, 2H), 6.79 (d, *J* = 8.72 Hz, 2H), 4.96−4.95 (m, 1H), 4.38 (dd, *J* = 9.32 and 3.0 Hz, 1H), 3.77−3.73 (m, 1H), 3.67 (s, 3H), 3.43 (dd, *J* = 11.72 and 2.28 Hz, 1H), 2.62−2.55 (m, 1H), 2.20−2.17 (m, 1H), 1.41 (s, 9H), 1.28 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 172.6 and 172.17 (rotamers), 154.31 and 154.18 (rotamers), 153.8, 144.0, 126.3, 115.04 and 114.93 (rotamers), 80.3, 80.15 and 80.08 (rotamers), 75.3, 74.4, 57.87 and 57.48 (rotamers), 52.16 and 52.0 (rotamers), 51.95 and 51.48 (rotamers), 36.4, 35.5, 34.0, 31.4, 28.35 and 28.24 (rotamers); LC−MS (ESI): 378.2 $[M + H]^+$.

*(2S,4S)-tert-Butyl 4-(4-(tert-Butyl)phenoxy)-2-(hydroxymethyl)-pyrrolidine-1-carboxylate (**12**).* Compound **12** was prepared from **11** (5.7 g, 15.11 mmol) following the literature procedure[22] in 81% yield (3.8 g) as a colorless sticky liquid. $[\alpha]_D^{25}$ −34 (*c* 0.5, $CHCl_3$); IR (neat): $\bar{\nu}$ 1676 (−NCO−) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.64 Hz, 2H), 6.77 (dd, *J* = 11.84 Hz and 3.08 Hz, 2H), 4.80 (brs, 1H), 4.40 (brs, 1H), 4.15−4.10 (m, 1H), 3.90−3.84 (m, 1H), 3.71−3.58 (m, 3H), 2.38−2.31 (m, 1H), 1.96 (brs, 1H), 1.46 (s. 9H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 156.9, 154.3, 144.2, 136.2, 128.5, 128.13 and 128.03 (rotamers), 126.9, 126.4, 126.37 and 126.17 (rotamers), 115.47 and 114.82 (rotamers), 76.7, 75.0, 67.45 and 67.27 (rotamers), 60.1, 52.97 and 52.70 (rotamers), 34.25 and 34.04 (rotamers), 31.4, 29.96 and 29.63 (rotamers), 21.9; LC−MS (ESI): 350.4 $[M + H]^+$.

*(2S,4S)-4-(4-tert-Butyl-phenoxy)-2-(toluene-4-sulfonyloxymethyl)-pyrrolidine-1-carboxylic Acid tert-Butylester (**13**).* Compound **13** was prepared from **12** (10.31 g, 29.50 mmol) following the literature procedure[22] in 87% yield (13 g) as a colorless liquid. $[\alpha]_D^{25}$ −46.5 (*c* 0.74, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.30−7.23 (m, 4H), 6.63 (brs, 2H), 4.79 (brs, 1H), 4.30 (brs, 1H), 4.06−4.04 (m, 2H), 3.63 (brs, 1H), 3.48 (d, *J* = 12.36 Hz, 1H), 2.41 (s, 3H), 2.27−2.18 (m, 2H), 1.41 (s, 9H), 1.29 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C 154.29 and 153.9 (rotamers), 144.73 and 144.02 (rotamers), 132.8, 130.0 and 129.79 (rotamers), 128.9, 127.9, 126.31 and 125.95 (rotamers), 115.14 and 114.79 (rotamers), 80.45 and 80.14 (rotamers), 75.89 and 75.14 (rotamers), 66.99 and 69.42 (rotamers), 55.2, 52.46 and 52.11 (rotamers), 34.04 and 33.87 (rotamers), 33.1, 31.4, 28.3, 21.5; LC−MS (ESI): 504.1 $[M + H]^+$.

*(2S,4S)-tert-Butyl-4-(4-(tert-butyl)phenoxy)-2-((1-oxoisoquinolin-2(1H)-yl)methyl)pyrrolidine-1-carboxylate (**15**).* To a stirred solution of isoquinolin-1(2*H*)-one (1.5 g, 10.33 mmol) in dry DMF (5 mL) was added solid CS_2CO_3 (6.73 g, 20.67 mmol) at 0 °C and the mixture was stirred at rt for 30 min. A solution of (2*S*,4*S*)-*tert*-butyl 4-(4-(*tert*-butyl)phenoxy)-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (5.19 g, 8.26 mmol) in dry DMF (10 mL) was added at 0 °C and stirred at rt for 48 h. After completion of the reaction, the mixture was quenched with ice water and the organic parts were extracted with ethyl acetate (3 × 100 mL), washed with brine solution, dried over sodium sulphate, and concentrated. The crude

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J. Org. Chem. 2021, 86, 5213−5226

material was purified by silica gel flash chromatography using a mixture of 70% ethyl acetate in hexane to give (2*S*,4*S*)-*tert*-butyl-4-(4-(*tert*-butyl)phenoxy)-2-((1-oxoisoquinolin-2(1*H*)-yl)methyl)-pyrrolidine-1-carboxylate **15** in 30% yield (1.2 g) as a white solid. $[\alpha]_D^{25}$ +102.47 (*c* 0.94, $CHCl_3$); IR (neat): $\bar{\nu}$ 1693 (−NCO^{t}Bu), 1655(−NCO−), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 at 100 °C): δ_H 8.23 (d, *J* = 8.04 Hz, 1H), 7.66 (t, *J* =7.4 Hz, 1H), 7.58 (d, *J* = 7.76 Hz, 1H), 7.48−7.44 (m, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 7.36 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.49 (d, *J* = 7.32 Hz, 1H), 4.98−4.95 (m, 1H), 4.43−4.40 (m, 1H), 4.30−4.25 (m, 1H), 4.16−4.12 (m, 1H), 3.85 (dd, *J* = 12.28 and 5.72 Hz, 1H), 3.43 (d, *J* = 13.68 Hz, 1H), 2.37−2.30 (m, 1H), 2.05 (d, *J* = 14.04 Hz, 1H), 1.29 (s, 9H), 1.23 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 162.62 and 162.35 (rotamers), 154.55 and 154.42 (rotamers), 144.14 and 143.82 (rotamers), 137.2, 133.01 and 132.6 (rotamers), 132.11 and 131.86 (rotamers), 127.95 and 127.77 (rotamers), 126.58 and 126.48 (rotamers), 126.19 and 125.74 (rotamers), 114.77 and 114.58 (rotamers), 105.63 and 105.48 (rotamers), 80.04 and 79.83 (rotamers), 75.6, 56.30, 55.19, 53.21, 52.67 and 52.45 (rotamers), 51.8, 34.8, 34.33 and 34.07 (rotamers), 31.46, 28.30 and 27.91 (rotamers); Chiral HPLC using CHIRALPAK IC, (EtOH), flow rate 0.5 mL/min, t_R = 10.01 min; LC−MS (ESI): 477.3 $[M + H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M\text{-BOC} + H]^+$ calcd for $C_{24}H_{29}N_2O_2$, 377.2230; found, 377.2255.

*2-(((2S,4S)-4-(4-(tert-Butyl)phenoxy)pyrrolidin-2-yl)methyl)-isoquinolin-1(2H)-one (**1**).* 4 (M) HCl in 1,4-dioxane (10 mL) was added to (2*S*,4*S*)-*tert*-butyl 4-(4-(*tert*-butyl)phenoxy)-2-((1-oxoisoquinolin-2(1*H*)-yl)methyl)pyrrolidine-1-carboxylate **15** (600 mg, 1.26 mmol) under ice-cold conditions and stirred at room temperature for 4 h. After completion of the reaction, the solvent was evaporated under reduced pressure. The crude reaction mixture was diluted with water and basified by saturated sodium bicarbonate solution and the organic parts were extracted with dichloromethane (2 × 100 mL). The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulphate, and concentrated under reduced pressure to give 2-(((2*S*,4*S*)-4-(4-(*tert*-butyl)phenoxy)-pyrrolidin-2-yl)methyl)isoquinolin-1(2*H*)-one (**1**) in 63% yield (300 mg) as a light-brown sticky liquid. $[\alpha]_D^{25}$ +39 (*c* 0.6, $CHCl_3$); IR (neat): $\bar{\nu}$ 1649 (−NCO−) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 8.20 (d, *J* = 7.96 Hz, 1H), 7.70−7.62 (m, 2H), 7.50−7.44 (m, 2H), 7.26 (d, *J* = 8.68 Hz, 2H), 6.79 (d, *J* = 8.68 Hz, 2H), 6.56 (d, *J* = 7.36 Hz, 1H), 4.80−4.79 (m, 1H), 4.09 (dd, *J* = 13.08 and 4.84 Hz, 1H), 3.91 (dd, *J* = 13.02 and 8.34 Hz, 1H), 3.47−3.44 (m, 1H), 3.07 (dd, *J* = 11.98 and 5.78 Hz, 1H), 2.94 (dd, *J* = 11.92 and 2.36 Hz, 1H), 2.32−2.25 (m, 1H), 1.58−1.52 (m, 1H), 1.24 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 162.4, 155.0, 143.4, 137.1, 132.6, 132.1, 127.7, 126.7, 126.2, 126.0, 125.8, 114.7, 105.7, 57.3, 54.2, 52.9, 36.6, 34.0, 31.4; Chiral HPLC using CHIRALPAK IC, (EtOH), flow rate 0.5 mL/min, t_R = 11.76 min; LC−MS (ESI): 377.3 $[M + H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{29}N_2O_2$, 377.2230; found, 377.2256.

*(2S,4S)-tert-Butyl 4-(4-(tert-Butyl)phenoxy)-2-((2-oxopyridin-1(2H)-yl)methyl)pyrrolidine-1-carboxylate (**17**).* Compound **17** was prepared from **13** (100 mg, 1.05 mmol) following the above-mentioned protocol used for compound **15** in 38% yield (162 mg) as a colorless sticky liquid purified by flash chromatography using a silica gel column and eluted with hexane/EtOAc, 7/3. $[\alpha]_D^{25}$ +69.2 (*c* 1.05, $CHCl_3$); IR (neat): $\bar{\nu}$ 1697 (−NCO−) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.32−7.28 (m, 3H), 7.15 (brs, 1H), 6.79 (d, *J* = 8.72 Hz, 2H), 6.54 (d, *J* = 9.2 Hz, 1H), 6.06−6.03 (m, 1H), 4.92 (brs, 1H), 4.57 (brs, 1H), 4.45 (brs, 1H), 4.18−4.01 (m, 2H), 3.90 (brs, 1H), 3.63 (d, *J* = 12.84 Hz, 1H), 2.22−2.14 (m, 1H), 1.39−1.24 (m, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 162.8, 154.6 and 154.3 (rotamers), 139.7 and 138.9 (rotamers), 126.5 and 126.4 (rotamers), 120.9, 115.5 and 114.8 (rotamers) 105.5, 80.30, 75.6, 54.9, 53.7 and 52.5 (rotamers), 34.6 and 34.1 (rotamers), 31.5, 29.6, 28.1; Chiral HPLC using CHIRALPAK IA, (hexane/EtOH/IP amine: 80:20:0.1), flow rate 1.0 mL/min, t_R = 6.12 min; LC−MS (ESI): 427.0; HRMS (ESI-TOF) *m*/*z*: $[M\text{-BOC} + H]^+$ calcd for $C_{20}H_{27}N_2O_2$, 327.2073; found, 327.2058.

*1-(((2S,4S)-4-(4-(tert-Butyl)phenoxy)pyrrolidin-2-yl)methyl)-pyridin-2(1H)-one (**2**).* Compound **2** was prepared from **17** (160 mg, 0.376 mmol) following the abovementioned protocol used for compound **1** in 79% yield (96 mg) as a light-brown sticky liquid. $[\alpha]_D^{25}$ +44 (*c* 0.34, $CHCl_3$); IR (neat): $\bar{\nu}$ 1653 (−NCO−) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.63 (d, *J* = 4.64 Hz, 1H), 7.39 (t, *J* = 6.68 Hz, 1H), 7.28 (d, *J* = 8.56 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.35 (d, *J* = 9.08 Hz, 1H), 6.15 (t, *J* = 6.68 Hz, 1H), 4.80 (brs, 1H), 4.03 (dd, *J* = 12.96 and 4.68 Hz, 1H), 3.81−3.75 (m, 1H), 3.40 (brs, 1H), 3.09 (dd, *J* = 12.2 and 6.12 Hz, 1H). 2.93 (d, *J* = 9.68 Hz, 1H), 2.33−2.24 (m, 1H), 1.51 (brs, 1H), 1.25 (s, 9H), 0.85 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 163.0, 154.9, 143.7, 139.8, 138.7, 126.3, 120.7, 114.8, 105.8, 77.4, 56.9, 54.6, 52.6, 36.4, 34.0, 31.5; Chiral HPLC using CHIRALPAK IC, (hexane/EtOH/IP amine: 80:20:0.1), flow rate 1.0 mL/min, t_R = 8.57 min; LC−MS (ESI): 327.3; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{27}N_2O_2$, 327.2073; found, 327.2083.

*(2S,4S)-Benzyl 4-(4-(tert-Butyl)phenoxy)-2-(hydroxymethyl)-pyrrolidine-1-carboxylate (**18**).*[22] Compound **18** (485 mg) was prepared from **9** (525 mg, 1.27 mmol) following the abovementioned protocol used for compound **12** as a colorless sticky liquid which was used directly in the following step mentioned below without purification.

*(2S,4S)-Benzyl 4-(4-(tert-Butyl)phenoxy)-2-((tosyloxy)methyl)-pyrrolidine-1-carboxylate (**19**).* This compound was prepared from **18** (485 mg, 1.26 mmol) following the literature procedure[22] in 51% (two steps) yield (351 mg) as a colorless liquid. $[\alpha]_D^{25}$ −37.6 (*c* 0.6, $CHCl_3$); IR (neat): $\bar{\nu}$ 1706 (−NCO−) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (d, *J* = 7.64 Hz, 1H), 7.65 (d, *J* = 7.72 Hz, 1H), 7.34−7.32 (m, 5H), 7.33−7.25 (m, 4H), 6.66−6.60 (m, 2H), 5.09−5.00 (m, 2H), 4.80 (brs, 1H), 4.36−4.31 (m, 1H), 4.23−4.03 (m, 2H), 3.69 (brs, 1H), 3.57−3.54 (m, 1H), 2.39 (s, 3H), 2.21−2.18 (m, 2H), 1.29 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 154.6 and 154.4 (rotamers), 154.3 and 154.2 (rotamers), 144.6, 144.1, 136.2 and 136.1 (rotamers), 132.8 and 132.7 (rotamers), 129.8, 128.5 and 128.4 (rotamers), 128.1 and 128.0 (rotamers), 127.9 and 127.8 (rotamers), 127.7 and 127.6 (rotamers), 126.3, 114.8, 75.79 and 75.01 (rotamers), 69.7 and 69.2 (rotamers), 67.2 and 67.1 (rotamers), 55.6 and 55.2 (rotamers), 52.6 and 52.3 (rotamers), 34.0 and 33.9 (rotamers), 31.4, 21.89 and 21.58 (rotamers); Chiral HPLC using CHIRALPAK IG hexane/DCM/EtOH/IP amine: 60/20/20/0.1, flow rate 1.0 mL/min, t_R = 6.24 min; LC−MS (ESI): 538.2 $[M + H]^+$; Anal. Calcd. for $C_{30}H_{35}NO_6S$: C, 67.02; H, 6.56; N, 2.61. Found: C, 66.96; H, 6.61; N, 2.57.

*(2S,4S)-Benzyl 4-(4-(tert-Butyl)phenoxy)-2-((2-oxopyridin-1(2H)-yl)methyl)pyrrolidine-1-carboxylate (**20**).* Compound **20** was prepared from **19** (107 mg, 1.18 mol) following the literature procedure[22] in 28% yield (151 mg) as a colorless liquid purified by flash chromatography using a silica gel column and eluted with hexane/EtOAc, 3/7.$[\alpha]_D^{25}$ +61.2 (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6 at 100 °C): δ_H 7.32−7.27 (m, 9H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.29 (d, *J* = 9.2 Hz, 1H), 6.02 (t, *J* = 6.72 Hz, 1H), 5.07 (d, *J* = 12.8 Hz, 1H), 4.98 (brs, 1H), 4.90 (d, *J* = 12.4 Hz, 1H), 4.44 (d, *J* = 6.8 Hz, 1H), 4.24−4.19 (m, 1H), 4.11−4.06 (m, 1H), 3.91−3.87 (m, 1H), 3.49 (d, *J* = 12.0 Hz, 1H), 2.36−2.31 (m, 1H), 2.06−2.02 (m, 1H), 1.29 (s, 9H); ^{13}C $\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 162.93 and 162.68 (rotamers), 154.9, 154.36 and 154.16 (rotamers), 144.18 and 144.02 (rotamers), 139.8, 139.32 and 139.14 (rotamers), 138.4, 136.39 and 136.05 (rotamers), 128.7, 128.3 and 128.0 (rotamers), 127.87 and 127.60 (rotamers), 126.4, 120.7, 120.5 and 120.4 (rotamers), 114.7, 105.55 and 105.30 (rotamers), 75.6 and 75.3 (rotamers), 67.0 and 66.8 (rotamers), 65.4, 57.50 and 56.56 (rotamers), 55.01, 53.9, 52.9 and 52.8 (rotamers), 52.5, 34.8, 34.2 and 33.9 (rotamers), 31.3; Chiral HPLC using CHIRALPAK IA, (hexane/EA/EtOH/IP amine: 70:15:15:0.1), flow rate 1 mL/min, t_R (*S*) = 8.50 min; LC−MS (ESI): 461.0 $[M + H]^+$; Anal. Calcd. for $C_{28}H_{32}N_2O_4$: C, 73.02; H, 7.00; N, 6.08. Found: C, 73.07; H, 7.04; N, 6.01.

*1-(((2S,4S)-4-(4-(tert-Butyl)phenoxy)pyrrolidin-2-yl)methyl)-piperidin-2-one (**3**).* To a stirred solution of **20** (100 mg, 0.21 mmol)

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J. Org. Chem. 2021, 86, 5213−5226

in methanol (5 mL) was added 10% Pd/C (100 mg/1.0 g) and the mixture was stirred under a hydrogen atmosphere at room temperature for 16 h. After completion of the reaction, the mixture was filtered through Celite bed and the filtrate was concentrated in vacuo to give 1-(((2*S*,4*S*)-4-(4-(*tert*-butyl)phenoxy)pyrrolidin-2-yl)-methyl)piperidin-2-one **3** in 56% yield (39 mg) as a colorless sticky liquid. $[\alpha]_D^{25}$ +2.18 (*c* 0.4, $CHCl_3$); IR (neat): $\overline{\nu}$ 1618 (−NCO−) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.27 (d, *J* = 8.56 Hz, 2H), 6.80 (d, *J* = 8.48 Hz, 2H), 4.80 (brs, 1H), 3.31 (brs, 5H), 3.06 (dd, *J* = 12.32 and 6.16 Hz, 1H), 2.98 (d, *J* = 11.64 Hz, 1H), 2.32−2.25 (m, 1H), 2.19 (brs, 2H), 1.68 (brs, 4H), 1.47 (brs, 1H), 1.24 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 171.4, 154.8, 143.7, 126.3, 114.9, 57.6, 52.6, 52.1, 49.3, 36.7, 34.0, 32.1, 31.5, 29.6, 23.1, 21.0; Chiral HPLC using CHIRALPAK IC, (hexane/EA/EtOH/IPA: 70/15/15/0.1) flow rate 1.0 mL/min, t_R (*S*) = 8.66 min; LC−MS (ESI): 331.31 $[M + H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{31}N_2O_2$, 331.2386; found, 331.2398.

*(2S,4S)-1-((Benzyloxy)carbonyl)-4-(4-(tert-butyl)phenoxy)-pyrrolidine-2-carboxylic Acid (**21**).*[25] To a stirred solution of **9** (400 mg, 0.97 mmol) in a mixture of THF/water (1:1) was added lithium hydroxide monohydrate (81 mg, 1.94 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 16 h. The reaction was monitored by TLC and LCMS. After completion of the reaction, the organic parts were washed with diethyl ether. The aqueous part was acidified (pH ∼ 3), and the organic parts were extracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried over sodium sulphate and concentrated to give **21** in 69% yield (270 mg) as a colorless semisolid. $[\alpha]_D^{25}$ −22.5 (*c* 0.5, $CHCl_3$); IR (neat): $\overline{\nu}$ 1709(−NCO−). 1607 (−COO−) cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6): δ_H 12.55 (brs, 1H), 7.37−7.26 (m, 7H), 6.79−6.78 (m, 2H), 5.13−4.99 (m, 3H), 4.44−4.35 (m, 1H), 3.82−3.74 (m, 1H), 3.46 (d, *J* = 11.84 Hz, 1H), 2.32−2.18 (m, 1H), 1.90 (s, 1H), 1.24 (s, 9H); Chiral HPLC using CHIRALPAK IC, hexane/IPA/TFA: 70/30/0.1, flow rate 1.0 mL/min, t_R (*S*) = 5.21 min; LC−MS (ESI): 398.4 $[M + H]^+$.

*(2S,4S)-4-(4-(tert-Butyl)phenoxy)pyrrolidine-2-carboxylic Acid (**4**).*[25] Catalyst **4** was prepared from **21** (260 mg, 0.65 mmol) following the abovementioned protocol used for catalyst **3** in 87% yield (150 mg) as a white solid; IR (neat): $\overline{\nu}$ 1638 (−COO−) cm^{-1}; ^1H NMR (400 MHz, MeOD): δ_H 7.30 (d, *J* = 8.68 Hz, 2H), 6.85 (d, *J* = 8.64 Hz, 2H), 5.06 (brs, 1H), 4.08 (t, *J* = 7.1 Hz, 1H), 3.66 (d, *J* = 12.6 Hz, 1H), 3.46−3.42 (m, 1H), 2.54−2.52 (m, 2H), 1.25 (s, 9H); Chiral HPLC using CHIRALPAK IG, ACN/MeOH/TFA: 50/50/0.1, flow rate 0.5 mL/min, t_R (*S*) = 5.57 min; LC−MS (ESI): 264.4 $[M + H]^+$.

*(2S,4S)-1-Benzyl 2-Methyl 4-(3,5-Bis(trifluoromethyl)phenoxy)-pyrrolidine-1,2-dicarboxylate (**23**).* To a stirred solution of (2*S*,4*R*)-1-benzyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate **7** (5.0 g, 17.90 mmol) in THF (60 mL) were added 3,5-bis(trifluoromethyl)phenol **22** (6.17 g, 26.85 mmol), triphenyl phosphine (7.0 g, 26.85 mmol), and DEAD (40% in THF) (13.42 mL, 26.85 mmol) sequentially at 0 °C. Then, the resulting reaction mixture was stirred at room temperature for 16 h. The reaction was monitored by TLC and LCMS. After completion of the reaction, the solvent was removed and 20% diethyl ether in pentane was added, then the precipitate was filtered, and the filtrate was concentrated and purified by silica gel (100−200 mesh) column chromatography using 30% ethyl acetate in hexane as an eluent to get (2*S*,4*S*)-1-benzyl 2-methyl 4-(3,5-bis(trifluoromethyl)phenoxy)pyrrolidine-1,2-dicarboxylate **23** in 51% yield (4.5 g) as a light-yellow liquid. $[\alpha]_D^{25}$ −30 (*c* 0.96, $CHCl_3$); IR (neat): $\overline{\nu}$ 1755 (−NCO−), 1712 (−NCO−CH_2−), 3436 (−NH−) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 at 100 °C): δ_H 7.59 (brs, 1H),7.48 (brs, 2H), 7.39−7.30 (m, 5H), 5.37−5.34 (m, 1H), 5.16−5.07 (m, 2H), 4.55 (dd, *J* = 9.60 and 2.40 Hz, 1H), 3.91 (dd, *J* = 12.00 and 4.80 Hz, 1H), 3.63 (s, 3H), 3.60−3.57 (m, 1H), 2.72−2.65 (m, 1H), 2.33−2.25 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −63.02 (s, 3F), −63.04 (s, 3F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 171.73 and 171.45 (rotamers), 157.07 and 157.06 (rotamers), 154.57 and 154.28 (rotamers), 136.3, 133.1 (q, $^2J_{C-F}$ = 33.4 Hz), 128.50 and 128.44 (rotamers), 128.18 and 128.10 (rotamers), 127.95, 122.9 (q, $^1J_{C-F}$ = 271.0 Hz), 115.75 and 115.71 (rotamers), 115.6, 75.4, 67.44 and 67.34 (rotamers), 57.81 and 57.54 (rotamers), 52.43 and 52.29 (rotamers), 52.01 and 51.68 (rotamers), 36.16 and 35.10 (rotamers), 21.7; Chiral HPLC using CHIRALPAK IC, (hexane/DCM/EtOH: 60:20:20), flow rate 1.0 mL/min, t_R = 3.59 min; LC−MS (ESI): 292.36 $[M + H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{22}H_{19}F_6NO_5Na$, 514.1065; found, 514.1093.

*(2S,4S)-Methyl 4-(3,5-Bis(trifluoromethyl)phenoxy)pyrrolidine-2-carboxylate (**24**).* To a stirred solution of (2*S*,4*S*)-1-benzyl 2-methyl 4-(3,5-bis(trifluoromethyl)phenoxy)pyrrolidine-1,2-dicarboxylate **23** (3.0 g, 6.11 mmol) in MeOH (50 mL) was added Pd/C (100 mg/g) and the mixture was stirred at room temperature for 16 h under a hydrogen atmosphere. After completion of the reaction, the mixture was filtered through Celite bed and washed with ethyl acetate and the filtrate was concentrated to give **24** in 82% yield (1.81 g) as a colorless liquid. $[\alpha]_D^{25}$ +54.6 (*c* 0.7, MeOH); IR (neat): $\overline{\nu}$ 1739 (−NCO−) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.45 (s, 1H), 7.21 (s, 2H), 4.88 (brs, 1H), 3.89−3.84 (m, 1H), 3.72 (s, 3H), 3.37 (d, *J* = 12.56 Hz, 1H), 3.13 (dd, *J* = 12.56 and 4.20 Hz, 1H), 2.51−2.44 (m, 1H), 2.29−2.24 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, MeOD): δ_C 169.3, 157.3, 133.4 (q, $^2J_{C-F}$ = 33.58 Hz), 123.4 (q, $^1J_{C-F}$ = 270.1 Hz), 115.5, 115.4, 76.6, 58.8, 53.2, 51.5, 34.4; Chiral HPLC using CHIRALPAK IC, (EtOH), flow rate 0.05 mL/min, t_R (*S*) = 6.44 min; LC−MS (ESI): 357.7 $[M + H]^+$; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{14}F_6NO_3$, 358.0879; found, 358.0858.

*(2S,4S)-1-tert-Butyl 2-Methyl 4-(3,5-Bis(trifluoromethyl)-phenoxy)pyrrolidine-1,2-dicarboxylate (**25**).* To a stirred solution of **24** (1.4 g, 3.92 mmol) in THF (40 mL) was added di-*tert*-butyl dicarbonate (1.34 mL, 5.88 mmol) at 0 °C. Then, a solution of $NaHCO_3$ (659 mg, 7.84 mmol) in water (40 mL) was added at the same temperature and the resulting mixture was stirred at room temperature for 16 h. After completion of the reaction, the mixture was diluted with water and the organic parts were extracted with ethyl acetate, washed with saturated sodium chloride solution, dried over anhydrous sodium sulphate, and concentrated under reduced pressure. The crude material was purified by silica gel (100−200 mesh) column chromatography using 30% ethyl acetate in hexane as an eluent. After evaporation of the solvent, (2*S*,4*S*)-1-*tert*-butyl 2-methyl 4-(3,5-bis(trifluoromethyl)phenoxy)pyrrolidine-1,2-dicarboxylate **25** was obtained in 84% yield (1.52 g) as a colorless liquid. $[\alpha]_D^{25}$ −20 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6 at 100 °C): δ_H 7.59 (s, 1H), 7.49 (s, 2H), 5.31 (brs, 1H), 4.41 (d, *J* = 9.20 Hz, 1H), 3.80 (d, *J* = 12.12 Hz, 1H), 3.65 (s, 3H), 3.49 (d, *J* = 12.08 Hz, 1H), 2.66 (brs, 1H), 2.21 (d, *J* = 14.08 Hz, 1H), 1.41 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −61.41 (s, 6F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 172.14 and 171.79 (rotamers), 157.2, 153.96 and 153.63 (rotamers), 133.03 (q, $^2J_{C-F}$ = 33.06 Hz), 122.9 (q, $^1J_{C-F}$ = 271 Hz), 115.67 and 114.95 (rotamers), 80.56 and 80.49 (rotamers), 75.4, 57.64 and 57.29 (rotamers), 52.22 and 52.08 (rotamers), 51.80 and 51.37 (rotamers), 36.01, 35.02, 28.28 and 28.16 (rotamers); Chiral HPLC using CHIRALPAK IG, (hexane/IPA/TFA: 70:30:0.1), flow rate 1.0 mL/min, t_R (*S*) = 3.49 min; LC−MS (ESI): 458.3 $[M + H]^+$; HRMS (ESI-TOF) *m*/*z*: [M-BOC + H]$^+$ calcd for $C_{14}H_{14}F_6NO_3$, 358.0879; found, 358.0898.

*(2S,4S)-tert-Butyl 4-(3,5-Bis(trifluoromethyl)phenoxy)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**26**).* To a stirred solution of **25** (425 mg, 0.93 mmol) in THF (10 mL) was added $LiBH_4$ (95 mg, 4.37 mmol) at 0 °C and stirred at room temperature for 48 h. After completion of the reaction, the mixture was quenched with ice water at 0 °C and the organic parts were extracted with ethyl acetate, washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, and filtered and the filtrate was concentrated under reduced pressure. The crude material was purified over silica gel (100−200 mesh) column chromatography using a mixture of 40% ethylacetate in hexane to get **26** in 94% yield (377 mg) as a colorless sticky liquid. $[\alpha]_D^{25}$ −4.7 (*c* 0.6, $CHCl_3$); IR (neat): $\overline{\nu}$ 1679 (−NCO−) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 7.64−7.61 (m, 3H), 5.27 (brs, 1H), 4.71 (brs, 1H), 3.80−3.64 (m, 3H), 3.31 (brs, 1H), 2.32−2.26 (m, 1H), 2.21−2.17 (m, 1H), 1.41 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −63.02 (s, 6F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C

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J. Org. Chem. 2021, 86, 5213−5226

157.5, 133.1 (q, $^2J_{C-F}$ = 33.33 Hz), 123.0 (q, $^1J_{C-F}$ = 271.14 Hz), 115.4, 114.9 (q, $^3J_{C-F}$ = 3.90 Hz), 81.2, 76.1, 67.8, 59.4, 52.6, 33.9, 28.4; Chiral HPLC using CHIRALPAK IG, (hexane/EtOH/IPA: 80:20:0.1), flow rate 1.0 mL/min, t_R = 3.87 min; LC−MS (ESI): 430.2 $[M + H]^+$; HRMS (ESI-TOF) m/z: $[M\text{-BOC} + H]^+$ calcd for $C_{13}H_{14}F_6NO_2$, 330.0929; found, 330.0913.

*(2S,4S)-tert-Butyl-4-(3,5-bis(trifluoromethyl)phenoxy)-2-((tosyloxy)methyl)pyrrolidine-1-carboxylate (**27**).* Compound **27** was prepared from **26** (680 mg, 1.58 mmol) following the literature procedure[22] in 89% yield (820 mg) as a colorless liquid purified by flash chromatography of silica gel column and eluted with hexane/EtOAc, 4/1. $[\alpha]_D^{25}$ −26.6 (*c* 0.6, $CHCl_3$); IR (neat): $\bar{\nu}$ 1698 (−NCO^{t}Bu) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.75 (d, *J* = 8.04 Hz, 2H), 7.48 (s, 1H), 7.31 (d, *J* = 6.6 Hz, 2H), 7.17−7.10 (m, 2H), 4.92 (brs, 1H), 4.29 (brs, 1H), 4.17 (brs, 1H), 3.99−3.94 (m, 1H), 3.76−3.73 (m, 1H), 3.52 (d, *J* = 12.36 Hz, 1H), 2.40 (s, 3H), 2.31 (brs, 2H), 1.42 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −62.99 (s, 6F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 161.9, 157.3 and 157.2 (rotamers), 156.7, 153.8, 145.5 and 145.1 (rotamers), 141.1 and 140.8 (rotamers), 133.5, 133.05 (q, $^2J_{C-F}$ = 33.5 Hz), 131.6, 129.9, 129.8, 129.03, 128.12, 125.14, 122.9 (q, $^1J_{C-F}$ = 271.0 Hz), 115.93 and 115.69 (rotamers), 115.37 and 114.93 (rotamers), 80.9, 78.8, 76.17 and 75.65 (rotamers), 69.57 and 69.37 (rotamers), 69.18, 67.4, 57.21 and 56.96 (rotamers), 55.1, 52.8, 52.3, 51.9, 51.1, 38.0, 33.70 and 32.89 (rotamers), 31.2, 29.7, 28.3, 21.50 and 21.20 (rotamers); Chiral HPLC using CHIRALPAK IG, EtOH, flow rate 0.5 mL/min, t_R = 7.71 min; LC−MS (ESI): 584.2 $[M + H]^+$; HRMS (ESI-TOF) m/z: $[M\text{-BOC} + H]^+$ calcd for $C_{20}H_{20}F_6NO_4S$, 484.1018; found, 484.1012.

*(2S,4S)-tert-Butyl-4-(3,5-bis(trifluoromethyl)phenoxy)-2-((1-oxoisoquinolin-2(1H)-yl)methyl)pyrrolidine-1-carboxylate (**28**).* Compound **28** was prepared from **27** (1.5 g, 2.57 mmol) following the abovementioned protocol used for compound **15** in 24% yield (340 mg) as a white solid purified by flash chromatography and eluted with hexane/EtOAc, 3/2. $[\alpha]_D^{25}$ −2.2 (*c* 0.6, $CHCl_3$); IR (neat): $\bar{\nu}$ 1657 (−NCO−), 1694 (−NCO^{t}Bu) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 at 100 °C): δ_H 8.20 (d, *J* = 8.0 Hz, 1H), 7.74−7.44 (m, 6H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.28−5.25 (m, 1H), 4.46−4.41 (m, 1H), 4.29−4.19 (m, 2H), 3.95−3.90 (m, 1H), 3.46 (d, *J* = 12.0 Hz, 1H), 2.50−2.40 (m, 1H), 2.16−1.12 (m, 1H), 1.27 (s, 9H); ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −62.88 (s, 3F), −62.95 (s, 3F); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 162.7, 157.0, 153.8, 136.79 and 136.54 (rotamers), 132.3, 131.8, 127.3, 126.4, 126.3, 125.7, 125.3, 122.2 (q, $^1J_{C-F}$ = 271.14 Hz), 114.9, 114.3, 105.73 and 105.40 (rotamers), 80.1, 55.4, 51.9, 49.8, 34.3, 29.1, 27.81 and 27.49 (rotamers); LC−MS (ESI): 556.8 $[M + H]^+$; HRMS (ESI-TOF) m/z: $[M\text{-BOC} + H]^+$ calcd for $C_{22}H_{19}F_6N_2O_2$, 457.1351; found, 457.1356.

*2-(((2S,4S)-4-(3,5-Bis(trifluoromethyl)phenoxy)pyrrolidin-2-yl)methyl)isoquinolin-1(2H)-one (**5**).* Compound **5** was prepared from **28** (330 mg, 0.59 mmol) following the abovementioned protocol used for compound **1** in 78% yield (210 mg) as a white solid: $[\alpha]_D^{25}$ +42 (*c* 1, $CHCl_3$); IR (neat): $\bar{\nu}$ 1650 (−NCO−), cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H 8.20 (d, *J* = 7.96 Hz, 1H), 7.70−7.66 (m, 1H), 7.64−7.60 (m, 2H), 7.50−7.46 (m, 4H), 6.57 (d, *J* = 7.36 Hz, 1H), 5.12 (brs, 1H), 4.11 (dd, *J* = 13.12 and 4.68 Hz, 1H), 3.97−3.91 (m, 1H), 3.52 (brs, 1H), 3.12 (dd, *J* = 12.12 and 4.28 Hz, 1H), 2.98 (d, *J* = 11.80 Hz, 1H), 2.67 (brs, 1H), 2.37−2.30 (m, 1H), 1.63 (d, *J* = 10.56 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ_F −63.00 (s, 6F). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 162.6, 158.1, 137.1, 132.8 (q, $^2J_{C-F}$ = 33.30 Hz), 132.4, 132.3, 127.7, 126.8, 126.0, 125.9, 123.0 (q, $^1J_{C-F}$ = 273.51 Hz), 115.4, 114.3 (q, $^3J_{C-F}$ = 3.44 Hz), 105.9, 78.8, 57.5, 53.9, 52.7, 36.3; Chiral HPLC using CHIRALPAK IC, EtOH, flow rate 0.5 mL/min, t_R = 8.49 min; LC−MS (ESI): 457.2 $[M + H]^+$; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{19}F_6N_2O_2$, 457.1351; found, 457.1322.

General Procedure: Michael Addition Reaction of Carbonyls and Nitroolefins. To a stirred solution of catalyst **1** (10 mol %, 0.1 equiv) in water (2 mL) were added carbonyl compound (5.0 mmol, 5 equiv) and TFA (2 mol %, 0.02 equiv). Then, the reaction mixture was stirred at room temperature for 5 min, followed by the addition of nitroolefins (1.0 mmol, 1 equiv) and the resulting mixture was stirred at the same temperature for appropriate time. After completion of the reaction (monitored by GCMS), the mixture was diluted with saturated solution of NH_4Cl (10 mL) and the organic parts were extracted with dichloromethane (10−15 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed in vacuum. The crude product was purified by silica gel flash chromatography to give the corresponding Michael adducts. Relative and absolute configurations of the products were determined by comparing the ^1H NMR and specific rotation values with those reported in the literature. Enantiomeric excess was determined by chiral HPLC.

*(S)-2-((R)-2-Nitro-1-phenyl-ethyl)-cyclohexanone (**31a**).*[22] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 3/2). White solid (200 mg, 81% yield); $[\alpha]_D^{25}$ −27.76 (*c* 0.99, $CHCl_3$), [lit. $[\alpha]_D^{25}$ −27.0 (*c* 1, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.31−7.29 (m, 3H), 7.16 (d, *J* = 7.28 Hz, 2H), 4.92 (dd, *J* = 12.56 Hz and 4.44 Hz, 1H), 4.65−4.60 (m, 1H), 3.78−3.73 (m, 1H), 2.71−2.65 (m, 1H), 2.49−2.46 (m, 1H), 2.42−2.34 (m, 1H), 2.07 (brs, 1H), 1.75−1.66 (m, 3H), 1.25−1.22 (m, 2H); HPLC analysis: 98% ee, Chiral HPLC using CHIRALPAK 1A, EtOH, flow rate 0.5 mL/min, t_R = 8.54 min (minor) and 9.32 min (major).

*(S)-2-((R)-1-Naphthalen-2-yl-2-nitro-ethyl)-cyclohexanone (**31b**).*[22] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 4/1). White solid (207 mg, 70% yield); $[\alpha]_D^{25}$ −37.11 (*c* 0.54, $CHCl_3$), [lit. $[\alpha]_D^{25}$ −36.2 (*c* 1, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.82−7.77 (m, 3H), 7.62 (brs, 1H), 7.48−7.46 (m, 2H), 7.29 (brs, 1H), 5.01 (dd, *J* = 12.56 and 3.64 Hz, 1H), 4.75−4.70 (m, 1H), 3.94−3.93 (m, 1H), 2.80−2.77 (m, 1H), 2.51−2.48 (m, 1H), 2.44−2.40 (m, 1H), 2.06 (brs, 1H), 1.73−1.63 (m, 3H), 1.30−1.24 (m, 2H); HPLC analysis: 98% ee, CHIRALPAK 1A, (hexane/EtOH/IPA: 80/20/0.1) flow rate 1 mL/min, t_R = 9.35 min (minor) and 11.10 min (major).

*(S)-2-((R)-2-Nitro-1-(3,4,5-trimethoxyphenyl)ethyl)-cyclohexanone (**31c**).* Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 3/1). White solid (320 mg, 95% yield); $[\alpha]_D^{25}$ −22.51 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.34 (brs, 2H), 4.89 (dd, *J* = 12.40 and 3.96 Hz, 1H), 4.66−4.60 (m, 1H), 3.83−3.81 (m, 9H), 3.68−3.65 (m, 1H), 2.63−2.61 (m, 1H), 2.49−2.45 (m, 1H), 2.42−2.37 (m, 1H), 2.07 (brs, 1H), 1.79−1.76 (m, 2H), 1.70−1.62 (m, 1H), 1.31−1.24 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ_C 211.8, 153.4, 137.4, 133.4, 105.1, 78.7, 60.8, 56.1, 52.7, 44.2, 42.7, 33.2, 28.5, 25.0; HPLC analysis: 99% ee, Chiral HPLC using CHIRACEL OJ-H, (hexane/EtOH/IP amine: 80/20/0.1), flow rate 1.0 mL/min, t_R = 19.39 min (minor) and 21.80 min (major); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{23}NO_6Na$, 360.1423; found, 360.1418.

*(S)-2-((R)-1-(Benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)-cyclohexanone (**31d**).*[26] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 7/3). Off-white solid (218 mg, 75%); $[\alpha]_D^{25}$ −27.7 (*c* 0.4, $CHCl_3$), [lit. $[\alpha]_D^{25}$ −28.2 (*c* 0.92, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$): δ_H 6.73 (d, *J* = 7.88 Hz, 1H), 6.63−6.60 (m, 2H), 5.94 (s, 2H), 4.89 (dd, *J* = 12.36 and 4.44 Hz, 1H), 4.57−4.51 (m, 1H), 3.70−3.67 (m, 1H), 2.60−2.56 (m, 1H), 2.48−2.45 (m, 1H), 2.40−2.31 (m, 1H), 2.09−2.06 (m, 1H), 1.85−1.77 (m, 2H), 1.70−1.66 (m, 1H), 1.31−1.19 (m, 2H); HPLC analysis: 99.30% ee, Chiral HPLC using CHIRALPAK 1A, (hexane/EtOH/IPA: 80/20/0.1), flow rate 1.0 mL/min, t_R = 13.02 min (minor) and 15.87 min (major).

*(S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (**31e**).*[26] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 7/3). Off-white semisolid (236 mg, 84% yield); $[\alpha]_D^{25}$ −23.31 (*c* 0.54, $CHCl_3$), [lit. $[\alpha]_D^{25}$ −23.4 (*c* 1.1, $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.29 (d, *J* = 8.32 Hz, 2H), 7.11 (d, *J* = 8.36 Hz, 2H), 4.92 (dd, *J* = 12.60 and 4.56 Hz, 1H), 4.62−4.57 (m, 1H), 3.78−3.72 (m, 1H), 2.67−2.60 (m, 1H), 2.49−2.40 (m, 1H), 2.39−2.36 (m, 1H), 2.11−2.06 (m, 1H), 1.81−1.58 (m, 4H), 1.24−1.20 (m, 1H); HPLC analysis: 97% ee, Chiral HPLC using CHIRALPAK

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J. Org. Chem. 2021, 86, 5213−5226

1A, EtOH, flow rate 0.5 mL/min, t_R = 10.45 min (minor) and 13.41 min (major).

(S)-2-[(R)-1-(3,5-Dichloro-phenyl)-2-nitro-ethyl]-cyclohexanone ***(31f)***.[22] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 4/1). Colorless liquid (264 mg, 84% yield); $[\alpha]_D^{25}$ −26.2 (*c* 0.42, $CHCl_3$), [lit. $[\alpha]_D^{25}$ −25.4 (*c* 0.36, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.27 (brs, 1H), 7.07 (brs, 2H), 4.92 (dd, *J* = 12.92 and 4.32 Hz, 1H), 4.62−4.56 (m, 1H), 3.75−3.71 (m, 1H), 2.65−2.60 (m, 1H), 2.49−2.46 (m, 1H), 2.39−2.35 (m, 1H), 2.10 (brs, 1H), 1.85−1.81 (m, 1H), 1.75−1.62 (m, 3H), 1.27−1.24 (m, 1H); HPLC analysis: 92% ee, Chiral HPLC using CHIRALPAK IF-3, EtOH, flow rate 0.3 mL/min, t_R = 13.04 min (minor) and 13.94 min (major).

(S)-2-((R)-1-(4-Morpholinophenyl)-2-nitroethyl)cyclohexanone ***(31g)***. White solid (278 mg, 84% yield); $[\alpha]_D^{25}$ −24.19 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.05 (d, *J* = 8.56 Hz, 2H), 6.83 (d, *J* = 8.56 Hz, 2H), 4.88 (dd, *J* = 12.24 and 4.56 Hz, 1H), 4.60−4.55 (m, 1H), 3.84−3.82 (m, 4H), 3.70−3.65 (m, 1H), 3.14−3.12 (m, 4H), 2.66−2.60 (m, 1H), 2.48−2.43 (m, 1H), 2.40−2.33 (m, 1H), 2.07−2.03 (m, 1H), 1.76−1.56 (m, 4H), 1.28−1.26 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C 212.1, 150.5, 128.9, 128.5, 115.6, 79.0, 66.8, 52.6, 48.9, 43.1, 42.6, 33.1, 28.5, 24.9; HPLC analysis: 98% ee, Chiral HPLC using CHIRALPAK IA, EtOH, flow rate 0.5 mL/min, t_R = 14.49 min (minor) and 17.60 min (major); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_4$, 333.1815; found, 333.1845.

(S)-2-((R)-2-Nitro-1-pyridin-3-yl-ethyl)-cyclohexanone ***(31h)***.[22] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 3/2). Light-brown solid (188 mg, 76% yield); $[\alpha]_D^{25}$ −9.6 (*c* 1.04, $CHCl_3$); [lit. $[\alpha]_D^{25}$ −22 (*c* 0.48, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.53−8.47 (m, 2H), 7.53 (d, *J* = 7.72 Hz, 1H), 7.28 (brs, 1H), 4.94 (dd, *J* = 12.80 and 4.60 Hz, 1H), 4.71−4.66 (m, 1H), 3.84−3.78 (m, 1H), 2.75−2.69 (m, 1H), 2.50−2.34 (m, 2H), 2.11−2.07 (m, 1H), 1.84−1.60 (m, 3H), 1.31−1.21 (m, 2H); HPLC analysis: 100% ee, Chiral HPLC using CHIRALPAK 1A, (hexane/EtOH/IPA: 80/20/0.1), flow rate 1.0 mL/min, t_R = 18.08.

(S)-2-((R)-1-(1-Methyl-1H-indol-3-yl)-2-nitroethyl)cyclohexanone ***(31i)***. Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 4/1). Light-brown semisolid (258 mg, 86% yield); $[\alpha]_D^{25}$ −11 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54 (d, *J* = 7.88 Hz, 1H), 7.30−7.27 (m, 1H), 7.22−7.20 (m, 1H), 7.13−7.09 (m, 1H), 6.90 (brs, 1H), 4.90−4.79 (m, 2H), 4.12−4.02 (m, 1H), 3.73 (s, 3H), 2.94−2.90 (m, 1H), 2.49−2.38 (m, 2H), 2.03 (brs, 1H), 1.93−1.90 (m, 1H), 1.78−1.65 (m, 2H), 1.34−1.23 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C 212.4, 137.1, 127.8, 126.7, 121.8, 119.3, 118.6, 110.4, 109.6, 78.5, 52.3, 42.7, 35.9, 33.3, 32.7, 28.5, 25.1; HPLC analysis: 93% ee, Chiral HPLC using CHIRALPAK IA, (hexane/EtOH/IP amine: 80/20/0.1), flow rate 1.0 mL/min, t_R = 6.81 min (minor) and 10.75 min (major); Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.92; H, 6.77; N, 9.27.

(S)-2-((R)-2-Nitro-1-thiophen-3-yl-ethyl)-cyclohexanone ***(31j)***.[22] White solid (237 mg, 94% yield);$[\alpha]_D^{25}$ −17.2 (*c* 1.01, $CHCl_3$); [lit $[\alpha]_D^{25}$ −28.2 (*c* 0.42, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 4.92 and 2.96 Hz, 1H), 7.0 (s, 1H), 6.92 (dd, *J* = 4.96 and 1.16 Hz, 1H), 4.83 (dd, *J* = 12.32 and 4.88 Hz, 1H), 4.62 (dd, *J* = 12.32 and 9.28 Hz, 1H), 3.99−3.93 (m, 1H), 2.69−2.62 (m, 1H), 2.47−2.32 (m, 2H), 2.10−2.06 (m, 1H), 1.83−1.66 (m, 4H), 1.30−1.21 (m, 1H); HPLC analysis: 97% ee, Chiral HPLC using CHIRALPAK 1A, EtOH, flow rate 0.5 mL/min, t_R = 10.36 min (minor) and 11.49 min (major).

(S)-2-((S)-1-Cyclopropyl-2-nitro-ethyl)-cyclohexanone ***(31k)***.[22] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 3/1). Colorless liquid (160 mg, 76% yield);$[\alpha]_D^{25}$ −33.17 (*c* 0.52, $CHCl_3$); [lit. $[\alpha]_D^{25}$ −17.81 (*c* 0.5, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 4.69 (dd, *J* = 11.68 and 6.12 Hz, 1H), 4.50 (dd, *J* = 11.68 and 4.84 Hz, 1H), 2.70−2.64 (m, 1H), 2.42−2.33 (m, 3H), 2.12−2.09 (m, 1H), 1.95−1.92 (m, 1H), 1.75−1.66 (m, 3H), 1.48 (brs, 1H), 0.79−0.73 (m, 1H), 0.54 (d, *J* = 7.64 Hz, 2H), 0.23−0.16 (m, 2H); GCMS $(M\text{-}NO_2)^+$ = 164.25; HPLC analysis: 98% ee, Chiral HPLC using CHIRALPAK 1A, EtOH, flow rate 0.5 mL/min, t_R = 8.27 (minor) and 9.44 min (major).

(R)-3-((R)-2-Nitro-1-phenyl-ethyl)-tetrahydro-pyran-4-one ***(33a)***.[22] White solid (161 mg, 65% yield); $[\alpha]_D^{25}$ −29 (*c* 1.0, $CHCl_3$) [lit. $[\alpha]_D^{25}$ −34 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.28 (m, 3H), 7.18−7.16 (m, 2H), 4.92 (dd, *J* = 12.68 and 4.44 Hz, 1H), 4.62 (dd, *J* = 12.52 and 10.12 Hz, 1H), 4.14−4.12 (m, 1H), 3.82−3.67 (m, 3H), 3.26 (dd, *J* = 11.32 and 8.92 Hz, 1H), 2.88−2.87 (m, 1H), 2.58−2.54 (m, 2H); HPLC analysis: 98% ee, Chiral HPLC using CHIRALPAK 1A, EtOH, flow rate 1.0 mL/min, t_R = 14.06 (minor) and 23.66 min (major).

(S)-3-((R)-2-Nitro-1-phenyl-ethyl)-tetrahydro-thiopyran-4-one ***(33b)***.[22] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 3/2). White solid (159 mg, 60% yield); $[\alpha]_D^{25}$ −22.6 (*c* 0.52, $CHCl_3$) [lit. $[\alpha]_D^{25}$ −26.9 (*c* 1.0, $CHCl_3$)]; 7.36−7.25 (m, 3H), 7.19−7.18 (m, 2H),4.73 (dd, *J* = 12.56 and 4.52 Hz, 1H), 4.62 (dd, *J* = 12.64 and 9.84 Hz, 1H), 4.0−3.94 (m, 1H), 3.07−2.96 (m, 3H), 2.93−2.75 (m, 2H), 2.63−2.58 (m, 1H), 2.48−2.44 (m, 1H); HPLC analysis: 91% ee, Chiral HPLC using CHIRALPAK 1A, EtOH, flow rate: 0.5 mL/min, t_R = 11.0 (minor) and 28.22 min (major).

(R)-tert-Butyl 3-((R)-2-Nitro-1-phenylethyl)-4-oxopiperidine-1-carboxylate ***(33c)***. White solid (222 mg, 64% yield); $[\alpha]_D^{25}$ +11.46 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.35−7.28 (m, 3H), 7.19−7.17 (m, 2H), 4.92 (dd, *J* = 12.44 and 4.64 Hz, 1H), 4.67−4.59 (m, 1H), 4.20−4.09 (m, 1H), 3.79 (brs, 2H), 3.25−3.19 (m, 1H), 2.77−2.67 (m, 2H), 2.55−2.38 (m, 2H), 1.38 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ_C 208.3, 154.0, 129.2, 129.0, 128.2, 128.1, 128.0, 80.7, 78.8, 44.2, 41.8, 41.7, 40.8, 28.2; HPLC analysis: 76% ee, Chiral HPLC using CHIRALPAK 1G, (hexane/DCM/EtOH: 80/10/10), flow rate: 1.0 mL/min, t_R= 6.68 (major) and 7.23 min (minor); Anal. Calcd. for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.01; H, 7.01; N, 8.01.

(R)-5-Nitro-4-phenyl-pentan-2-one ***(33d)***.[22] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 4/1). White solid (101 mg, 49% yield); $[\alpha]_D^{25}$ −4.4 (*c* 0.42, $CHCl_3$) [lit. $[\alpha]_D^{25}$ −0.70 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.34−7.30 (m, 2H), 7.28 (brs, 1H), 7.21−7.19 (m, 2H), 4.71−4.66 (m, 1H), 4.62−4.57 (m, 1H), 4.03−3.98 (m, 1H), 2.91 (d, *J* = 7.00 Hz, 2H), 2.11 (s, 3H); HPLC analysis: 55% ee, Chiral HPLC using CHIRACEL OJ-H (hexane/EtOH/IPA: 60/40/0.1), flow rate 1.0 mL/min, t_R= 12.69 (minor) and 17.33 min (major).

(3S,4R)-3-Methyl-5-nitro-4-phenylpentan-2-one ***(33e)***.[22] White solid (77 mg, 35% yield); $[\alpha]_D^{25}$ −13.6 (*c* 0.3, $CHCl_3$) [lit. $[\alpha]_D^{25}$ −11.04 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.34−7.24 (m, 3H), 7.15 (d, *J* = 7.48 Hz, 2H), 4.69−4.59 (m, 2H), 3.69−3.63 (m, 1H), 2.99−2.95 (m, 1H), 2.22 (s, 3H), 0.97 (d, *J* = 7.12 Hz, 3H); HPLC analysis: 89% ee, Chiral HPLC using CHIRALPAK IG (hexane/EtOH/IPA): 80/20/0.1, flow rate 1.0 mL/min, t_R = 12.10 (minor) and 20.16 min (major).

(S)-2,2-Dimethyl-4-nitro-3-phenylbutanal ***(33f)***.[26,27] Purified by flash chromatography on silica gel (eluted with hexane/EtOAc, 3/1). Colorless liquid (59 mg, 27%); $[\alpha]_D^{25}$ +1.2 (*c* 1, $CHCl_3$) [lit. $[\alpha]_D^{25}$ −4.9 (*c* 1.0, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 9.52 (s, 1H), 7.35−7.28 (m, 3H), 7.19−7.7.18 (m, 2H), 4.83 (dd, *J* = 13.04 and 11.28 Hz, 1H), 4.68 (dd, *J* = 13.04 and 4.2 Hz, 1H), 3.77 (dd, *J* = 11.28 and 4.2 Hz, 1H), 1.13 (s, 3H), 1.00 (s, 3H). HPLC analysis: 69% ee, Chiral HPLC using CHIRACEL OD-H (hexane/IPA: 80/20), flow rate 1.0 mL/min, t_R= 16.53 (minor) and 23.38 min (major).

(3R,3aS,7aR)-3-(Naphthalen-2-yl)octahydro-1H-indole ***(34a)*** *and (3R,3aS,7aS)-3-(Naphthalen-2-yl)octahydro-1H-indole* ***(34b)***.[22,28] To a stirred solution of **31b** (200 mg, 0.67 mmol) in methanol (10 mL) was added 20% $Pd(OH)_2$ on carbon and the mixture was stirred under a hydrogen atmosphere at room temperature for 16 h in a Parr shaker at 50 psi pressure. After completion of the reaction, the mixture was filtered through Celite bed and the filtrate was concentrated in vacuo. The crude product was purified by preparative HPLC to afford (3*R*,3a*S*,7a*R*)-3-(naphthalen-2-yl)octahydro-1*H*-indole **34a** (80 mg, 47%) as a light-brown semisolid and (3*R*,3a*S*,7a*S*)-3-(naphthalen-2-yl)octahydro-1*H*-indole **34b** (51 mg, 30%) as an off-white solid.

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J. Org. Chem. 2021, 86, 5213−5226

*(3R,3aS,7aR)-3-(Naphthalen-2-yl)octahydro-1H-indole (**34a**).*[22,28] Light-brown semisolid (80 mg, 47%); *trans* isomer $[\alpha]_D^{25}$ −35.03 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.79−7.76 (m, 3H), 7.64 (brs, 1H), 7.46−7.36 (m, 3H), 3.51 (t, *J* = 10.4 Hz, 1H), 3.17−3.12 (m, 1H), 3.04−2.97 (m, 1H), 2.61−2.55 (m, 1H), 2.11−2.09 (m, 1H), 1.82−1.70 (m, 4H), 1.51−1.43 (m, 1H), 1.31−1.26 (m, 2H), 1.17−1.07 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, MeOD): δ_C 139.9, 134.1, 133.0, 128.4, 127.6, 127.5, 126.2, 126.1, 125.6, 125.5, 64.7, 53.8, 52.2, 50.8, 31.1, 28.5, 25.7, 25.0; LC−MS (ESI): 252.2 $[M + H]^+$.

*(3R,3aS,7aS)-3-(Naphthalen-2-yl)octahydro-1H-indole (**34b**).*[22,28] Off-white solid (51 mg, 30%); *cis* isomer, $[\alpha]_D^{25}$ −35.2 (*c* 0.29, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ; 7.84−7.78 (m, 3H), 7.70 (brs, 1H), 7.46−7.42 (m, 3H), 3.85−3.75 (m, 1H), 3.61−3.32 (m, 2H), 2.57−2.53 (m, 1H), 2.06 (s, 2H), 1.85−1.82 (m, 1H), 1.67−1.50 (m, 5H), 1.30−1.28 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, MeOD): δ_C 138.2, 135.1, 134.4, 130.1, 128.8, 128.2, 127.6, 127.2, 126.3, 73.6, 62.3, 60.5, 51.0, 46.6, 45.4, 26.7, 24.4, 24.2, 21.0; LC−MS (ESI): 252.2 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00124.

Copies of ^1H, ^{13}C NMR, and ^{19}F spectra; chiral HPLC chromatogram of compounds; and images of the reaction mixture (PDF)

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Notes

The authors declare no competing financial interest.

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