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Dynamic Kinetic Resolution-Based Asymmetric Transfer Hydrogenation of 2-Benzoylmorpholinones and Its Use in Concise Stereoselective Synthesis of All Four Stereoisomers of the Antidepressant Reboxetine

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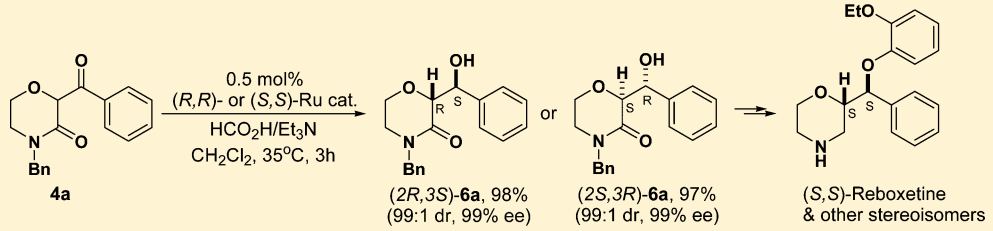
Supporting Information



ABSTRACT: Dynamic kinetic resolution-driven, asymmetric transfer hydrogenation reaction of 2-benzoylmorpholin-3-ones (**4**) proceeds efficiently to give the corresponding (2*R*,3*S*)- or (2*S*,3*R*)-2-(hydroxyphenylmethyl)morpholin-3-ones (**6**) with an excellent level of diastereo- and enantioselectivity and simultaneous control of two contiguous stereogenic centers in a single step. This process is employed to prepare all four stereoisomers of the antidepressant reboxetine.

INTRODUCTION

C-Substituted morpholine substructures are found in a variety of natural products as well as biologically and pharmaceutically important substances.[1] For example, selective norepinephrine reuptake inhibitors, such as reboxetine (**1**, **A**), edivoxetine (**B**), and viloxazine (**C**), possess the 2-substituted morpholine ring skeleton (Figure 1). In addition, the 2-morpholine structural

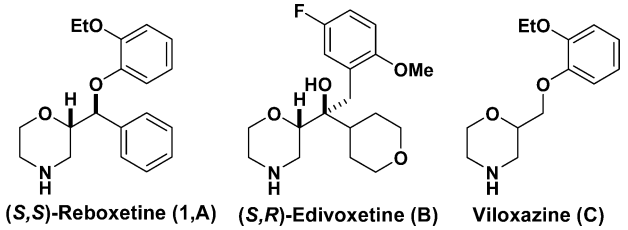


Figure 1. Selective norepinephrine reuptake inhibitors possessing the 2-substituted morpholine structure.

scaffold is found in other pharmaceutically active compounds, such as the NK 1-receptor antagonist aprepitant, antifungal agent amorofine, and selective GABA β-antagonist SCH-50911.[2]

However, despite the importance of these chiral, C-substituted morpholine-containing substances, only a limited number of methods have been developed for their nonracemic synthesis. Because morpholines are often prepared from amino alcohols or amino acids, access to enantiomerically enriched chiral members of this group is often achieved by using routes that start from chiral amino alcohols, amino acids, or other chiral pool sources.[1] However, only a limited number of nonracemic chiral amino alcohols and amino acids are available in the chiral pool. Moreover, the need to carry out synthetic sequences to generate specific members of these starting material families adds to the length of pathways for the preparation of enantiomerically pure 2-substituted morpholines. Therefore, the development of direct and efficient methods to synthesize chiral 2-substituted morpholines, which do not rely on the use of chiral amino alcohols or amino acids and which utilize well-known chiral catalysts, is a significant goal of organic chemists interested in devising efficient routes to biologically important substances containing the 2-substituted morpholine skeleton.

In the studies described below, we have developed a new, highly efficient, and stereoselective method for the synthesis of (*R*,*S*)- and (*S*,*R*)-2-(hydroxyphenylmethyl)morpholin-3-ones (**6**) starting with the corresponding racemic *N*-benzyl-2-benzoylmorpholin-3-ones (**4**). The process, which enables simultaneous stereochemical control of two contiguous stereogenic centers in a single step, involves dynamic kinetic resolution (DKR)-driven chiral transition metal-catalyzed asymmetric transfer hydrogenation (ATH).

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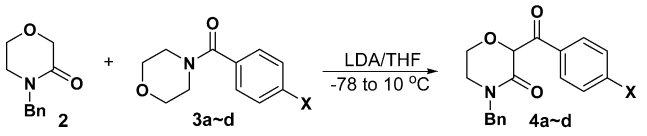
Asymmetric transfer hydrogenation (ATH), using hydrogen sources other than molecular hydrogen, has proven to be one of the most powerful general procedures for asymmetric reduction of ketone, which yields the corresponding chiral alcohol.[3] Major reasons for this lie in the operational simplicity and excellent selectivity of the ATH process, the availability of varied hydrogen sources, and ability to use readily accessible and less sensitive catalysts. In this context, transition metal-catalyzed asymmetric transfer hydrogenation of configurationally labile carbonyl compounds via DKR has emerged as an efficient and powerful technique for controlling the stereochemistry at two contiguous stereogenic centers formed in the process. Examples of this application include ATH of α-substituted β-keto esters,[4] β-keto amides,[5] β-keto sulfones,[6] 2-substituted cycloalkanones,[7] 1,3-diketones,[8] 1,2-diketones,[9] α-keto esters,[10] and α-keto phosphonates.[11] Recently, stereoselective ATH-DKR of cyclic sufamidate imine to the corresponding sulfamidate was also reported.[12] However, there were no previous examples of ATH-DKR of cyclic α-oxy-β-keto-amides (2-benzoylmorpholine-3-ones) using chiral Ru- or Rh-catalysts.[4,5,13]

RESULTS AND DISCUSSION

The racemic *N*-benzyl-2-aroylmorpholin-3-ones (**4**), used in this effort, were easily prepared by employing condensation reactions of *N*-benzyl-3-morpholinone (**2**) with *N*-aroylmorpholines (**3**) promoted by LDA (Scheme 1).

Scheme 1. Synthesis of *N*-Benzyl-2-aroylmorpholin-3-ones (4)



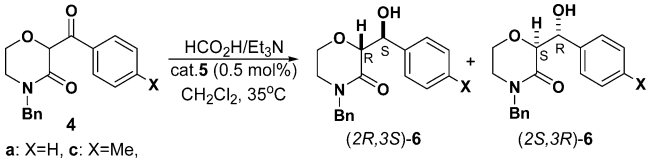
a: X=H, 93%; **c**: X=Me, 81%
b: X=Cl, 93%; **d**: X=OMe, 75%

In preliminary studies, *N*-benzyl-2-benzoylmorpholin-3-one (**4a**) was subjected to ATH reactions using various known chiral transition metal catalysts **5a**–**e** (0.5 mol %) and a mixture of formic acid and triethylamine (F/T = 5:2) as the hydrogen source (Table 1).

ATH reactions of **4a** in CH_2Cl_2 using the rhodium **5a** or iridium catalyst **5b** do not proceed to completion in 24 h at 35 °C (entries 1, 2, Table 1). However, when Noyori's (*R*,*R*)-RuCl(TsDPEN)(*p*-cymene) ((*R*,*R*)-**5c**) catalyst is employed,[3f] ATH reaction of **4a** takes place completely in 24 h to give (2*R*,3*S*)-**6a** as major product with high levels of diastereo- and enantioselectivity (95:5 dr, 87% ee, entry 3, Table 1). Similar observations were made in a study of the ATH reaction of **4a** using Ru-catalyst **5d**,[5] which has an electron-deficient pentafluorophenyl sulfonyl group on the chiral ligand. In this case, (2*R*,3*S*)-**6a** was generated as the major product in 24 h with a high dr (96:4) but a decreased ee (84%) (entry 4, Table 1). The results of a further effort revealed that ATH reaction of **4a** using the catalyst (*R*,*R*)-RuCl(TsDPEN)(mesitylene) ((*R*,*R*)-**5e**),[3g,4a] which possesses an η^6-arene = mesitylene ligand, produces (2*R*,3*S*)-**6a** in the highest yield (>99%), dr (99:1), and ee (99%) (entry 5, Table 1). (Results of solvent effect studies are given in the Supporting Information.)

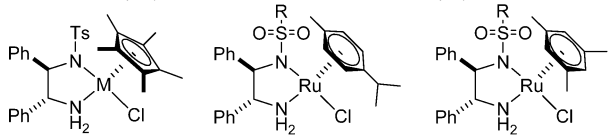
The results of a recent study have shown that the F/T ratio has a significant effect on both the rates and enantioselectivities of ATH reactions of ketones.[14] In the current effort, we

Table 1. ATH-DKR of *N*-Benzyl-2-benzoylmorpholin-3-ones (4)[a]



a: X=H, **c**: X=Me,
b: X=Cl, **d**: X=OMe

entry	4	cat. 5	(F/T) ratio	time (h)	conv (%)[b]	dr[c]	ee (%)[d]
1	**4a**	(*R*,*R*)-**5a**	5:2	24	11	–	–
2	**4a**	(*R*,*R*)-**5b**	5:2	24	12	–	–
3	**4a**	(*R*,*R*)-**5c**	5:2	24	>99	95/5	87
4	**4a**	(*R*,*R*)-**5d**	5:2	24	>99	96/4	84
5	**4a**	(*R*,*R*)-**5e**	5:2	24	>99(96)[e]	99/1	99
6	**4a**	(*R*,*R*)-**5e**	1:1	12	>99	98/2	98
7	**4a**	(*R*,*R*)-**5e**	0.2:1[f]	3	>99(98)[e]	99/1	99
8	**4b**	(*R*,*R*)-**5e**	0.2:1[f]	3	>99(90)[e]	96/4	95
9	**4c**	(*R*,*R*)-**5e**	0.2:1[f]	3	>99(96)[e]	99/1	99
10	**4d**	(*R*,*R*)-**5e**	0.2:1[f]	3	>99(98)[e]	99/1	99
11	**4a**	(*S*,*S*)-**5e**	5:2	24	>99(97)[e]	99/1	99[g]



(*R*,*R*)-**5a**: M=Rh
(*R*,*R*)-**5b**: M=Ir
(*R*,*R*)-**5c**: R= *p*-CH_3Ph
(*R*,*R*)-**5d**: R= F_5Ph
(*R*,*R*)-**5e**: R= *p*-CH_3Ph

[a]**4** (1 mmol), **5** (0.5 mol %), F/T (1 mL), CH_2Cl_2 (10 mL), at 35 °C. [b]Determined by ^{1}H NMR. [c](*R*,*S*/*S*,*R*)-**6a**/(*R*,*R*/*S*,*S*)-**6a**, determined by chiral HPLC of the crude reaction mixture. [d]Determined by chiral HPLC. [e]Isolated yields in parentheses. [f]Neat solution of F/T (0.1 M). [g]%ee of (2*S*,3*R*)-**6a**.

observed that the F/T ratio dramatically affects the time required for completion of the ATH reaction of **4a** catalyzed by **5e** (F/T = 5:2, 1:1 and 0.2:1; respective completion time = 24, 12, and 3 h) without deterioration of the dr and ee (entries 5–7, Table 1).

The scope of the ATH reaction was explored using the para-substituted benzoylmorpholin-3-ones **4b**–**d** with the optimized conditions described above. The results of this effort show that ATH reactions of the electron-donating group substituted substrates **4c** and **4d** generate the corresponding alcohols (2*R*,3*S*)-**6c** and (2*R*,3*S*)-**6d** with excellent dr and ee (99:1 dr, 99% ee, entries 9 and 10, Table 1) but that, in contrast, the reaction of the electron-withdrawing group substituted morpholin-3-one **4b** produces (2*R*,3*S*)-**6b** with slightly decreased dr and ee (96:4 dr, 95% ee, entry 8, Table 1).

In a further exploratory study, we found that ATH reaction of **4a** with the enantiomeric catalyst (*S*,*S*)-**5e** produces the enantiomeric alcohol (2*S*,3*R*)-**6a** as the major product with excellent levels of stereoselectivity (99:1 dr, 99% ee). This observation indicates that the source of dynamic kinetic resolution in this process is the configurational lability of the hydrogen at C-2 of **4a**, which results in rapid racemization of the substrate under the ATH reaction conditions (Scheme 2).

As a consequence, the absolute stereochemistry of the major reduction product depends on the chirality of the Ru-catalysts used in a manner such that (2*R*)-**4a** is preferentially reduced with (*R*,*R*)-**5e** to afford alcohol (2*R*,3*S*)-**6a**, and (2*S*)-**4a** is preferentially reduced with (*S*,*S*)-**5e** to give alcohol (2*S*,3*R*)-**6a**.

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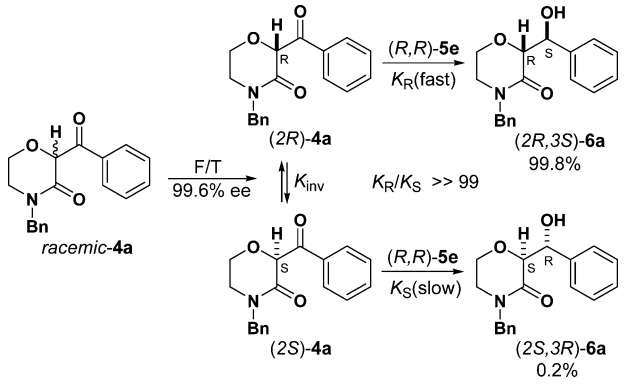
Scheme 2. Dynamic Kinetic Resolution in ATH of *rac*-4a



Moreover, single recrystallizations of the products (2*R*,3*S*)-**6a** and (2*S*,3*R*)-**6a** arising from the respective reactions promoted by (*R*,*R*)-**5e** and (*S*,*S*)-**5e** produce the corresponding optically pure substances (dr and ee >99%). The absolute stereochemistry of (2*S*,3*R*)-**6a** was determined by using X-ray crystallographic analysis (deposited, CCDC 898360, see Supporting Information).

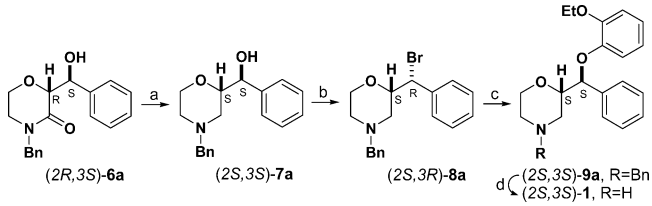
The resulting optically pure morpholine alcohols, (2*R*,3*S*)-**6a** and (2*S*,3*R*)-**6a**, could potentially serve as valuable late stage intermediates in routes for the preparation of biologically important substances possessing the 2-substituted morpholine ring system and, in particular, those that are selective norepinephrine and dual serotonine/norepinephrine reuptake inhibitors.[15] Reboxetine (**1**) is a potent selective norepinephrine reuptake inhibitor, currently marketed in over 60 countries for the treatment of depression under the trade names Edronax, Prolift, Vestra, Norebox, and Integrex.[16] While reboxetine is commercially sold as a racemic mixture of (2*S*,3*S*)- and (2*R*,3*R*)-enantiomers, recent studies have shown that the (2*S*,3*S*)-isomer, named as (*S*,*S*)-reboxetine, is significantly more active and selective for the norepinephrine transporter (NET) than is the racemate.[17,18] In addition, (*S*,*S*)-reboxetine succinate is currently undergoing advanced clinical evaluation as a drug for the treatment of neurophatic pain, fibromyalgia, and other indications.[19]

One early pathway developed for (*S*,*S*)-reboxetine synthesis relied on the use of a *S*-(+)-mandelic acid-promoted, chiral resolution of racemic reboxetine.[20] Other strategies uncovered for the synthesis of (*S*,*S*)-reboxetine are based on the use of optically active starting materials[17] or Sharpless epoxidation/dihydroxylation steps.[18] However, most of these methods require the utilization of stoichiometric amounts of expensive chiral starting materials or long (9−10 steps) reaction sequences.[17−19,21,22] Only recently, a highly efficient, stereoselective synthesis of (*S*,*S*)-reboxetine, which employs a key BINAP-based, Ru-catalyst promoted asymmetric hydrogenation (10−50 atm) step was described.[13]

To demonstrate the usefulness of the ATH-DKR reaction of 2-benzoylmorpholinones, herein we describe a concise synthesis of (*S*,*S*)-reboxetine (**1**) starting with the optically pure alcohol (2*R*,3*S*)-**6a** (Scheme 3).

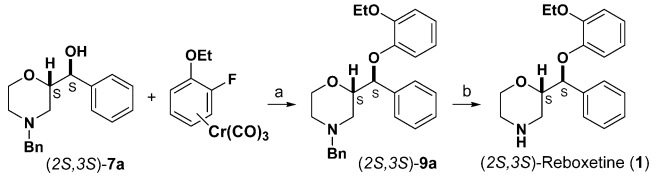
The sequence used for this purpose utilizes a yield improving modification of the one previously described for the transformation of racemic (*R*,*S*/*S*,*R*)-**6a** to racemic (*R*,*R*/*S*,*S*)-reboxetine (**1**).[15] First, reduction of the lactam moiety in (2*R*,3*S*)-**6a** with BH_3·THF smoothly produces the morpholine benzyl alcohol (2*S*,3*S*)-**7a** in excellent yield (97%). This alcohol

Scheme 3. Synthesis of (*S*,*S*)-Reboxetine (1)[a]



[a](a) BH_3·THF, THF, 60 °C 2 h, then MeOH, 97%; (b) Ph_3PBr_2, CH_2Cl_2, 50 °C, 95%; (c) 2-EtO-phenol, KOBu-*t*, *t*-BuOH/THF (3:1), 80 °C, 24 h, 91%; (d) α-chloroethyl chloroformate, $(i\text{-Pr})_2$NEt, CH_2Cl_2, 50 °C, 4 h, then MeOH, reflux, 2 h, 86%.

Scheme 4. Synthesis of (*S*,*S*)-Reboxetine (1)[a]



[a](a) i. NaH, DMF, rt, 2 h; ii. I_2, THF, 0 °C to rt, 1 h, 88%; (b) see Scheme 3.

is then converted to the corresponding morpholine bromide (2*S*,3*R*)-**8a** using Ph_3PBr_2, a process that takes place with inversion of configuration. Bromide displacement of (2*S*,3*R*)-**8a** with 2-ethoxyphenol in the presence of KOBu-*t* provides the N-benzyl-protected (*S*,*S*)-reboxetine (2*S*,3*S*)-**9a**. It should be noted that the use of *t*-BuOH/THF (3:1) as a solvent for this process causes an improvement in the yield reported earlier (80%) when *t*-BuOH alone is used as solvent to 91%. This enhancement is likely a result of the improved solubility of bromide (2*S*,3*R*)-**8a** in *t*-BuOH/THF. Treatment of (2*S*,3*S*)-**9a** with α-chloroethyl chloroformate followed by methanolysis of the intermediate α-chloroethyl carbamate promotes selective removal of the *N*-benzyl group and generates (*S*,*S*)-reboxetine (**1**) in a four-step route from optically pure alcohol (2*R*,3*S*)-**6a** in 72% overall yield and without deterioration of optical purity (Scheme 3). (*R*,*R*)-Reboxetine (**1**) was also prepared from optically pure (2*S*,3*R*)-**6a** (67% overall yield) using essentially the same procedure as employed for the production of (*S*,*S*)-reboxetine (see Experimental Section).

In an alternative synthetic route, the 2-ethoxyphenyl group in the target is directly incorporated into the morpholine benzyl alcohol (2*S*,3*S*)-**7a** with retention of stereochemistry at the benzylic alcohol position (Scheme 4). Thus, reaction of morpholine benzyl alcohol (2*S*,3*S*)-**7a** with the tricarbonylchromium complex of 1-ethoxy-2-fluorobenzene[17] in the presence of NaH, followed by subsequent oxidative dechromination with iodine, provides *N*-benzyl-protected (*S*,*S*)-reboxetine (2*S*,3*S*)-**9a**.

While great attention has been given to the synthesis and pharmaceutical evaluation of (2*S*,3*S*)-reboxetine, much less is known about the preparation and biological properties of its (2*S*,3*R*)- and (2*R*,3*S*)-diastereomers.[23,24] Therefore, the development of convenient routes for stereoselective synthesis of (*R*,*S*)- and (*S*,*R*)-reboxetine could benefit research programs focusing on norepinephrine transporter (NET) modulators. We observed that (2*S*,3*R*)-reboxetine can be conveniently prepared from the same intermediate (2*S*,3*S*)-**7a** used in the (2*S*,3*S*)-reboxetine synthetic pathway (Scheme 5).

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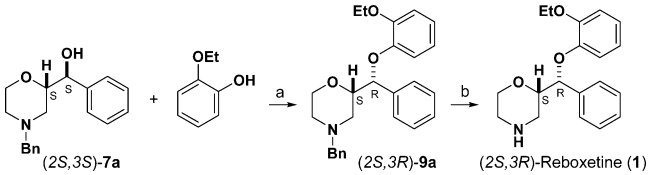
Scheme 5. Synthesis of (2*S*,3*R*)-Reboxetine[a]



[a](a) DIAD, PPh_3, THF, 0 °C to rt, 24 h, 72%; (b) see d of Scheme 3, 75%.

Thus, reaction of (2*S*,3*S*)-**7a** with 2-ethoxyphenol under Mitsunobu conditions affords (2*S*,3*R*)-**9a** with inversion of stereochemistry at benzylic position. Subsequent *N*-debenzylation of (2*S*,3*R*)-**9a** produces (2*S*,3*R*)-reboxetine (99% ee, 54% yield over two steps). (2*R*,3*S*)-Reboxetine was also prepared (99% ee, 45% overall yield) starting with optically pure (2*R*,3*R*)-**7a** using essentially the same procedure (see Experimental Section).

In summary, we have successfully achieved the first example of dynamic kinetic resolution-driven chiral Ru-catalyzed asymmetric transfer hydrogenation reactions of readily available racemic 2-benzoylmorpholin-3-ones (**4**) that give the corresponding (*R*,*S*)- and (*S*,*R*)-2-(hydroxyphenylmethyl)-morpholin-3-ones (**6**). In this process, stereochemistry at two contiguous stereogenic centers is controlled simultaneously with excellent levels of diastereo- and enantioselectivity. In addition, this study has resulted in the development of efficient, highly stereoselective routes for the preparation of all four stereoisomers [(*S*,*S*)-, (*R*,*R*)-, (*S*,*R*)-, (*R*,*S*)] of reboxetine from the common intermediates, (2*R*,3*S*)-**6a** and (2*S*,3*R*)-**6a**, which are produced by chiral Ru-catalyzed ATH-DKR of racemic *N*-benzyl-2-benzoyl-3-morpholinone (**4a**).

EXPERIMENTAL SECTION

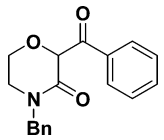
General Methods. Dichloromethane, ether, THF were dried and purified using a solvent purification system. Flash column chromatography was carried out on silica gel (38−75 μm). Analytical thin layer chromatography (TLC) was performed on silica gel 60 F_{254} plates. Preparative thin layer chromatography (PLC) was performed on silica gel 60 F_{254} 2 mm plates. Visualization of the developed chromatogram was accomplished with UV light and by staining with ethanolic phosphomolybdic acid (PMA) solution or ninhydrin solution followed by heating.

Nuclear magnetic resonance (NMR) spectra were recorded using a 500 MHz NMR instrument (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) or a 300 MHz NMR instrument (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz). ^{1}H NMR data are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constants (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High performance liquid chromatography (HPLC) was carried out on a HPLC system equipped with a Chiralpak IB, Chiralpak IC, or Chiralpak AD-H column. HR-MS were measured with electron impact (EI) ionization via double focusing mass analyzer (magnetic and electric fields) or electrospray ionization (ESI) via time of flight (TOF) analyzer.

The formic acid/triethylamine mixtures (molar ratio = 5:2 or 1:1) are commercially available. The formic acid/triethylamine mixture (molar ratio = 0.2:1) was prepared by slow addition of formic acid to triethylamine with stirring at rt according to the literature procedure.[14] *N*-Benzoylmorpholine derivatives[27] (**3a**−**d**) were prepared from the condensation reaction of the corresponding benzoyl chloride and excess morpholine in CH_2Cl_2 (90−97%). Chiral catalysts (*R*,*R*)-**5c**, (*R*,*R*)-**5d**, and (*R*,*R*)-**5e** are commercially available. (*R*,*R*)-**5a**[25] and (*R*,*R*)-**5b**[26] were prepared according to the literature procedures.

*1. General Procedure for the Synthesis of 2-Benzoyl-4-benzylmorpholin-3-one (**4**).* A solution of LDA (2.0 M, 13.75 mL, 27.5 mmol) in THF (60 mL) was cooled to −78 °C and treated with 4-benzylmorpholin-3-one[15] (**2**, 4.78 g, 25 mmol) in THF (20 mL) and stirred for 30 min at that temperature to give a pale yellow solution. *N*-Benzoylmorpholine (**3**, 5.5 g, 28.7 mmol) in THF (20 mL) was added dropwise to the above solution. The reaction was allowed to slowly warm to 10 °C and then quenched by addition of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with EtOAc (70 mL × 2), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexane/EtOAc 8:1 to 5:1) to give 2-benzoyl-4-benzylmorpholin-3-one (**4a**, 6.9 g, 93%) as pale yellow oil.

*1.1. 2-Benzoyl-4-benzylmorpholin-3-one (**4a**).*



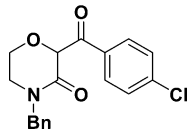
Yield: 93% (6.9 g), pale yellow oil. Keto and enol mixture; enol form:keto form = 1:0.4−0.9 by ^{1}H NMR analysis.

Enol form: ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.17 (s, 1H), 7.99 (d, 2H, *J* = 7.6 Hz), 7.32−7.44 (m, 8H), 4.74 (s, 2H), 4.05 (t, 2H, *J* = 4.9 Hz), 3.43 (t, 2H, *J* = 4.9 Hz).

Keto form: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.1 (d, 2H, *J* = 7.5 Hz), 7.62 (t, 1H, *J* = 7.4 Hz), 7.51 (t, 2H, *J* = 7.8 Hz), 7.32−7.44 (m, 5H), 5.64 (s, 1H), 4.87 (d, 1H, *J* = 14.6 Hz), 4.54 (d, 1H, *J* = 14.6 Hz), 4.16−4.21 (m, 1H), 3.94−3.90 (m, 1H), 3.42−3.34 (m, 2H).

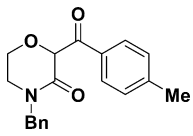
^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 165.8, 164.2, 153.7, 136.1, 135.9, 135.2, 133.9, 133.5, 129.7, 129.5, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 128.0, 127.9, 125.2, 77.9, 64.0, 62.2, 49.9, 49.6, 45.8, 45.5. HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1208.

*1.2. 2-(4-Chlorobenzoyl)-4-benzylmorpholin-3-one (**4b**).*



Yield: 93% (2 g), pale yellow solid, mp: 107.7−109.6 °C. Predominantly exist as enol form by ^{1}H NMR analysis. Enol form: ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.13 (s, 1H), 7.94 (d, 2H, *J* = 8.8 Hz), 7.40−7.33 (m, 7H), 4.74 (s, 2H), 4.07 (t, 2H, *J* = 4.9 Hz), 3.46 (t, 2H, *J* = 5.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 152.3, 135.9, 135.2, 131.9, 129.8, 128.9, 128.1, 128.1, 127.9, 125.3, 64.0, 49.6, 45.6. HRMS (EI): *m*/*z* calcd for $C_{18}H_{16}ClNO_3$ 329.0819, found 329.0812.

*1.3. 2-(4-Methylbenzoyl)-4-benzylmorpholin-3-one (**4c**).*



Yield: 81% (2 g). Keto and enol mixture; enol form:keto form = 1:0.1−0.2 by ^{1}H NMR analysis.

Enol form: ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.11 (s, 1H), 7.86 (d, 2H, *J* = 8.3 Hz), 7.39−7.32 (m, 5H), 7.23(d, 2H, *J* = 8.2 Hz), 4.74 (s, 2H), 4.06 (t, 2H, *J* = 5.0 Hz), 3.45 (t, 2H, *J* = 5.0 Hz), 2.40 (s, 3H).

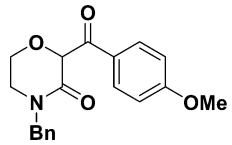
Keto form: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, 2H, *J* = 8.2 Hz), 7.41−7.30 (m, 7H), 5.63 (s, 1H), 4.86 (d, 1H, *J* = 14.8 Hz), 4.56 (d, 1H, *J* = 14.7 Hz), 4.20−4.18 (m, 1H), 3.94−3.91 (m, 1H), 3.43−3.41 (m, 1H), 3.38−3.37 (m, 1H), 2.45 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 165.7, 164.2, 153.9, 144.8, 139.6, 136.1, 135.9, 132.7, 130.6, 129.7, 129.3, 128.9, 128.8, 128.6, 128.3, 128.3, 128.1, 127.8, 124.8, 77.7, 63.9, 62.1, 49.8, 49.5, 45.8, 45.5,

dx.doi.org/10.1021/jo401102d | J. Org. Chem. 2013, 78, 8396−8404

21.8, 21.5. HRMS (EI): m/z calcd for $C_{19}H_{19}NO_3$ 309.1365, found 309.1357.

*1.4. 2-(4-Methoxybenzoyl)-4-benzylmorpholin-3-one (**4d**).*



Yield: 75% (2 g). Keto and enol mixture; enol form:keto form = 1:0.4−0.5 by ^{1}H NMR analysis.

Enol form: ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.18 (s, 1H), 8.08 (d, 2H, J = 9.0 Hz), 7.40−7.32 (m, 5H), 6.98(d, 2H, J = 8.9 Hz), 4.74 (s, 2H), 4.07 (t, 2H, J = 4.8 Hz), 3.87(s, 3H). 3.45 (t, 2H, J = 4.7 Hz).

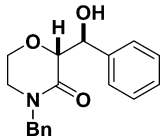
Keto form: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09−8.05 (m, 1H), 7.96(d, 1H, J = 9.1 Hz), 7.40−7.32(m, 5H), 7.00−6.96(m, 1H), 6.94(d, 1H, J = 9.0 Hz), 5.62 (s, 1H), 4.86 (d, 1H, J = 14.6 Hz), 4.55 (d, 1H, J = 14.6 Hz), 4.23−4.19 (m, 1H), 3.95−3.91 (m, 1H), 3.91 (s, 3H), 3.46−3.41 (m, 1H), 3.38−3.35 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 165.8, 164.4, 164.1, 160.4, 153.7, 136.1, 135.8, 132.2, 132.0, 130.0, 128.8, 128.8, 128.3, 128.2, 128.1, 127.8, 126.0, 124.4, 113.8, 113.7, 113.3, 63.9, 62.0, 55.5, 55.3, 49.8, 49.4, 45.8, 45.5. HRMS (EI): m/z calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1308.

*2. General Procedure for the ATH-DKR Reaction of 2-Benzoyl-4-benzylmorpholin-3-one (**4**).* With F/T = 5:2: To 2-benzoyl-4-benzylmorpholin-3-one (**4a**, 3.48 g, 11.8 mmol) in CH_2Cl_2 (60 mL) were added sequentially (*R*,*R*)-**5e** catalyst (37 mg, 0.06 mmol, 0.005 equiv) and HCO_2H/Et_3N (5:2) (7 mL), and the mixture was stirred for 24 h at 35 °C. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$, H_2O, and brine. The solution was dried over $MgSO_4$ and concentrated under reduced pressure to afford crystalline solid. The product was fractionated on a short path column of SiO_2 to remove colored impurity to give white crystals (3.35 g, 96%, dr = 99:1, 99% ee). Recrystallization in EtOAc/*n*-hexane produced optically pure product (3.0 g, >99% ee and dr). Yield: 96%, dr = 99:1, 99% ee.

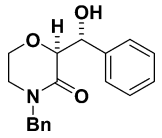
With F/T = 0.2:1: To 2-benzoyl-4-benzylmorpholin-3-one (**4a**, 150 mg, 0.51 mmol) in HCO_2H/Et_3N (0.2:1) mixture (2.4 mL) was added (*R*,*R*)-**5e** catalyst (1.6 mg, 2.5 μmol 0.005 equiv), and the mixture was stirred for 3 h at 40 °C. The reaction mixture was diluted with EtOAc (10 mL) and water (10 mL). Next the organic layer was separated, and aqueous layer was extracted again with EtOAc (5 mL × 2). The combined organic layer was washed with saturated aqueous $NaHCO_3$, H_2O, and brine. The solution was dried over $MgSO_4$ and concentrated under reduced pressure to afford crystalline solid. The product was fractionated on a short path column of SiO_2 to remove colored impurity to give white crystals (149 mg, 98.4%, dr = 99:1, 99.6% ee). Recrystallization in EtOAc/*n*-hexane produced optically pure product (>99% ee and dr).

*2.1. (2R,3S)-4-Benzyl-2-(hydroxyphenylmethyl)morpholin-3-one [(2R,3S)-**6a**].*



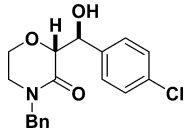
Yield: 96−98% (3.35 g); mp: 117.3−118.2 °C; dr = 99:1; 99% ee: Chiralpak IB, 10% 2-propanol/*n*-hexane, 1.5 mL/min, 254 nm, t_R(minor) = 8.9 min, t_R(major) = 10.2 min; $[\alpha]_D^{18}$ = +95.6 (c 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.48 (m, 2H), 7.39−7.34 (m, 3H), 7.29−7.26 (m, 3H), 7.00−6.98 (m, 2H), 5.24 (dd, 1H, J = 9.7 Hz, J = 3.4 Hz), 4.79 (d, 1H, J = 14.7 Hz), 4.57 (d, 1H, J = 3.4 Hz), 4.35 (d, 1H, J = 14.9 Hz), 4.32 (d, 1H, J = 9.8 Hz), 3.98 (ddd, 1H, J = 1.6, 4.2, 11.9 Hz), 3.76 (dt, 1H, J = 3.1, 11.2 Hz), 3.25 (dt, 1H, J = 4.3, 12.0 Hz), 2.95 (d, 1H, J = 12.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 140.6, 135.5, 128.8, 128.1, 128.0, 127.7, 127.6, 126.8, 79.7, 73.6, 63.1, 49.8, 45.7; HRMS (EI): m/z calcd for $C_{18}H_{19}NO_3$ 297.1365, found 297.1365.

*2.2. (2S,3R)-4-Benzyl-2-(hydroxyphenylmethyl)morpholin-3-one [(2S,3R)-**6a**].*



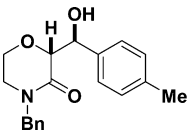
To 2-benzoyl-4-benzylmorpholin-3-one (**4a**, 3.3 g, 11.2 mmol) in CH_2Cl_2 (60 mL) were added sequentially (*S*,*S*)-**5e** catalyst (35 mg, 0.056 mmol) and HCO_2H/Et_3N (5:2) (7 mL), and the mixture was stirred for 24 h at 35 °C. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$, H_2O, and brine. The solution was dried over $MgSO_4$ and concentrated under reduced pressure to afford crystalline solid. The product was fractionated on a short path column of SiO_2 to remove colored impurity to give white crystals (3.24 g, 97%, dr = 99:1, 99.0% ee). Recrystallization at EtOAc/*n*-hexane produced optically pure product (>99% ee and dr). mp: 117.3−118.2 °C; Chiralpak IB, 10% 2-propanol/*n*-hexane, 1.5 mL/min, 254 nm, t_R(major) = 8.7 min, t_R(minor) = 10.7 min; $[\alpha]_D^{19}$ = −96.8 (c 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, 2H, J = 7.1 Hz), 7.39−7.32 (m, 3H), 7.30−7.27 (m, 3H), 7.02−6.99 (m, 2H), 5.25 (dd, 1H, J = 9.6 Hz, J = 3.2 Hz), 4.78 (d, 1H, J = 14.8 Hz), 4.57 (d, 1H, J = 3.1 Hz), 4.37−4.34 (m, 2H), 4.00−3.96 (m, 1H), 3.75 (dt, 1H, J = 3.0, 11.6 Hz), 3.26 (dt, 1H, J = 4.1, 12.1 Hz), 2.97−2.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 140.6, 135.5, 128.8, 128.1, 127.9, 127.7, 127.6, 126.8, 79.7, 73.6, 63.0, 49.8, 45.7; HRMS (EI): m/z calcd for $C_{18}H_{19}NO_3$ 297.1365, found 297.1364.

*2.3. (2R,3S)-4-Benzyl-2-[hydroxy-(4-chlorophenyl)methyl]-morpholin-3-one [(2R,3S)-**6b**].*



Yield: 95% (170 mg) at F/T = 5:2, 90% at F/T = 0.2:1; mp: 125.8−127.6 °C; dr = 96:4; 95.3% ee (Chiralpak IB, 10% 2-propanol/*n*-hexane, 1.0 mL/min, 254 nm, t_R(minor) = 13.8 min, t_R(major) = 16.5 min); $[\alpha]_D^{31}$ = +62.6 (c 0.3, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 8.3 Hz), 7.32−7.29 (m, 5H), 6.92−6.91 (m, 2H), 5.15 (d, 1H, J = 5.6 Hz), 4.85 (d, 1H, J = 14.7 Hz), 4.58 (d, 1H, J = 9.3 Hz), 4.55 (d, 1H, J = 3.5 Hz), 4.23 (d, 1H, J = 14.7 Hz), 3.96 (dd, 1H, J = 3.1 Hz, J = 11.9 Hz), 3.78 (dt, 1H, J = 3.0 Hz, J = 11.5 Hz), 3.23 (dt, 1H, J = 4.2 Hz, J = 12.0 Hz), 2.94 (d, 1H, J = 12.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 139.1, 135.3, 133.4, 128.9, 128.3, 128.2, 127.9, 127.9, 79.3, 73.0, 63.1, 49.9, 45.7; HRMS (EI): m/z calcd for $C_{18}H_{18}NO_3Cl$ 331.0975, found 331.0972.

*2.4. (2R,3S)-4-Benzyl-2-(hydroxy-p-tolylmethyl)morpholin-3-one [(2R,3S)-**6c**].*

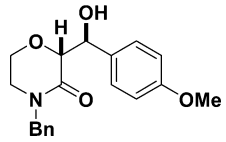


Yield: 96% (160 mg); mp: 113.4−115.2 °C; dr = 99:1; 98.9% ee; Chiralpak IB, 20% 2-propanol/*n*-hexane, 1.5 mL/min, 254

dx.doi.org/10.1021/jo401102d | J. Org. Chem. 2013, 78, 8396−8404

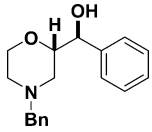
nm, t_R(minor) = 4.9 min, t_R(major) = 5.4 min; $[\alpha]_D^{31}$ = +92.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, 2H, *J* = 7.9 Hz), 7.29−7.27 (m, 3H), 7.18 (d, 2H, *J* = 7.9 Hz), 7.02 (m, 2H), 5.22 (dd, 1H, *J* = 9.5 Hz, *J* = 3.0 Hz), 4.81 (d, 1H, *J* = 14.8 Hz), 4.55 (d, 1H, *J* = 3.2 Hz), 4.36 (d, 1H, *J* = 14.8 Hz), 4.15 (d, 1H, *J* = 9.6 Hz), 4.00−3.97 (m, 1H), 3.76 (dt, 1H, *J* = 3.1 Hz, *J* = 11.2 Hz), 3.28 (dt, 1H, *J* = 4.4 Hz, *J* = 12.2 Hz), 2.96 (d, 1H, *J* = 12.3 Hz), 2.40(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 137.7, 137.2, 135.6, 128.9, 128.8, 128.0, 127.8, 126.7, 79.8, 73.5, 63.1, 49.9, 45.8, 21.3; HRMS (EI): *m*/*z* calcd for $C_{19}H_{21}NO_3$ 311.1521, found 311.1516.

*2.5. (2R,3S)-4-Benzyl-2-[hydroxy-(4-methoxyphenyl)methyl]-morpholin-3-one [(2R,3S)-**6d**].*



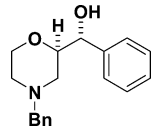
Yield: 98% (170 mg); mp: 128.4−129.1 °C; dr = >99:1; 99.3% ee (Chiralpak IB, 20% 2-propanol/*n*-hexane, 1.5 mL/min, 254 nm, t_R(minor) = 6.5 min, t_R(major) = 7.3 min); $[\alpha]_D^{31}$ = +75.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, 2H, *J* = 8.7 Hz), 7.29−7.27 (m, 3H), 6.99−6.98 (m, 2H), 6.90 (d, 2H, *J* = 8.7 Hz), 5.17 (dd, 1H, *J* = 9.6 Hz, *J* = 3.2 Hz), 4.82 (d, 1H, *J* = 14.8 Hz), 4.54 (d, 1H, *J* = 3.3 Hz), 4.32 (d, 1H, *J* = 14.7 Hz), 4.31 (d, 1H, *J* = 9.4 Hz), 4.00−3.97 (m, 1H), 3.85(s, 3H), 3.77 (dt, 1H, *J* = 3.0 Hz, *J* = 11.5 Hz), 3.25 (dt, 1H, *J* = 4.2 Hz, *J* = 12.1 Hz), 2.95 (d, 1H, *J* = 12.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 159.2, 135.6, 132.7, 128.8, 128.0, 128.0, 127.8, 113.5, 79.7, 73.3, 63.1, 55.3, 49.8, 45.8; HRMS (EI): *m*/*z* calcd for $C_{19}H_{21}NO_4$ 327.1471, found 327.1466.

*3. Borane Reduction of Morphlin-3-one to Morpholine. 3.1. Synthesis of (2S,3S)-(4-Benzylmorpholin-2-yl)phenylmethanol [(2S,3S)-**7**].*



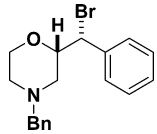
To a solution of (2*R*,3*S*)-4-benzyl-2-(hydroxyphenylmethyl)-morpholin-3-one (**6a**, 2.93 g, 9.8 mmol) in anhydrous THF (50 mL) under nitrogen at room temperature was slowly added BH_3·THF (1 M in THF, 39 mL, 39 mmol). The solution was stirred at 60 °C for 3 h. After cooling to 0 °C, dry MeOH (20 mL) was slowly added to quench excess borane reagent. Aqueous HCl solution (1 M, 20 mL) was added, and the reaction mixture was heated to 60 °C for 1 h. The organic solvents were evaporated under reduced pressure, and the concentrated solution was poured onto aqueous K_2CO_3 solution (1 M, 100 mL) and extracted with diethyl ether (100 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatograph (SiO_2, hexane/EtOAc 3:1 to 2:1) to give (2*S*,3*S*)-(4-benzylmorpholin-2-yl)phenylmethanol (2.67 g, 97%) as white solid. Mp: 70.1−71.5 °C; $[\alpha]_D^{18}$ = −3.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.25 (m, 10H), 4.60 (d, 1H, *J* = 7.4 Hz), 3.97 (dt, 1H, *J* = 2.8, 11.3 Hz), 3.72−3.67 (m, 2H), 3.57 (d, 1H, *J* = 13.0 Hz), 3.32 (d, 1H, *J* = 13.0 Hz), 3.19 (brs, 1H), 2.60 (d, 1H, *J* = 11.5 Hz), 2.49 (d, 1H, *J* = 11.3 Hz), 2.17 (dt, 1H, *J* = 3.2 Hz, *J* = 11.1 Hz), 2.11 (t, 1H, *J* = 10.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1, 137.6, 129.3, 128.5, 128.4, 128.2, 127.3, 127.1, 79.5, 75.6, 66.7, 63.4, 55.2, 52.4; HRMS (EI): *m*/*z* calcd for $C_{18}H_{21}NO_2$ 283.1572, found 283.1573.

*3.2. (2R,3R)-(4-Benzylmorpholin-2-yl)phenylmethanol [(2R,3R)-**7**].*



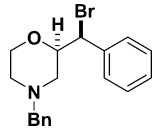
Yield: 95.7% (2.0 g); mp: 70.9−72.7 °C; $[\alpha]_D^{18}$ = +3.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.25 (m, 10H), 4.61 (d, 1H, *J* = 7.4 Hz), 3.97 (dt, 1H, *J* = 2.6, 11.3 Hz), 3.72−3.67 (m, 2H), 3.56 (d, 1H, *J* = 12.9 Hz), 3.33 (d, 1H, *J* = 13.0 Hz), 3.21 (brs, 1H), 2.60 (d, 1H, *J* = 11.4 Hz), 2.48 (d, 1H, *J* = 11.4 Hz), 2.18 (dt, 1H, *J* = 3.1, 11.1 Hz), 2.11 (dd, 1H, *J* = 9.8, 10.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 137.3 129.3, 128.5, 128.3, 128.1, 127.3, 127.1, 79.4, 75.5, 66.5, 63.3, 55.1, 52.3; HRMS (EI): *m*/*z* calcd for $C_{18}H_{21}NO_2$ 283.1572, found 283.1574.

*4. Conversion of Alcohol to Bromide. 4.1. Synthesis of (2S,3R)-4-Benzyl-2-(bromophenylmethyl)morpholine [(2S,3R)-**8**].*



To a solution of (2*S*,3*S*)-(4-benzylmorpholin-2-yl)-phenylmethanol (2 g, 7.1 mmol) in anhydrous CH_2Cl_2 (70 mL) under nitrogen was added PPh_3·Br_2 (6 g, 14.2 mmol). The reaction mixture was stirred for 6 h under reflux. The reaction mixture was cooled to room temperature and washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (SiO_2, hexane/EtOAc 10:1) to give (2*S*,3*R*)-4-benzyl-2-(bromophenylmethyl)morpholine (2.3 g, 95%) as a white solid. Mp: 69.3−71.5 °C; $[\alpha]_D^{26}$ = −90.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.28 (m, 10H), 4.94 (d, 1H, *J* = 8.0 Hz), 4.11 (dt, 1H, *J* = 2.1 Hz, *J* = 9.3 Hz), 3.83 (dt, 1H, *J* = 2.5, 11.3 Hz), 3.65 (d, 1H, *J* = 13.0 Hz), 3.61 (dd, 1H, *J* = 2.3 Hz, *J* = 11.1 Hz), 3.49 (d, 1H, *J* = 13.0 Hz) 3.29 (d, 1H, *J* = 11.2 Hz), 2.60−2.58 (m, 1H), 2.19−2.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 137.7, 129.2, 128.7, 128.6, 128.5, 128.4, 127.4, 78.1, 67.1, 63.3, 56.9, 54.0, 52.5; HRMS (EI): *m*/*z* calcd for $C_{18}H_{20}BrNO$ 345.0728, found 345.0729.

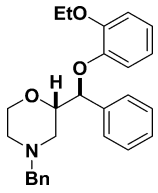
*4.2. (2R,3S)-4-Benzyl-2-(bromophenylmethyl)morpholine [(2R,3S)-**8**].*



Yield: 85.7% (1.2 g); mp: 69.9−72.2 °C; $[\alpha]_D^{28}$ = +89.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, 2H, *J* = 7.3 Hz), 7.38−7.28 (m, 8H), 4.94 (d, 1H, *J* = 8.0 Hz), 4.12−4.08 (m, 1H), 3.83 (dt, 1H, *J* = 2.6, 11.3 Hz), 3.67−3.59 (m, 2H), 3.48 (d, 1H, *J* = 13.0 Hz) 3.28 (d, 1H, *J* = 11.3 Hz), 2.58 (dd, 1H, *J* = 1.2, 11.5 Hz), 2.19−2.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 137.7, 129.2, 128.7, 128.6, 128.5, 128.5, 127.4, 78.1, 67.1, 63.3, 56.9, 54.0, 52.5; HRMS (EI): *m*/*z* calcd for $C_{18}H_{20}BrNO$ 345.0728, found 345.0729.

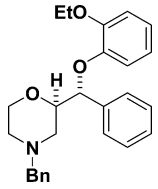
dx.doi.org/10.1021/jo401102d | *J. Org. Chem.* 2013, 78, 8396−8404

*5. Synthesis of N-Benzylreboxetine. 5.1. Synthesis of (2S,3S)-4-Benzyl-2-[(2-ethoxyphenoxy)phenylmethyl]morpholine [(2S,3S)-**9**].*



To a solution of 2-ethoxyphenol (1.32 g, 9.54 mmol) in anhydrous *t*-BuOH (10 mL) was added dropwise potassium *tert*-butoxide solution (1 M in *t*-BuOH, 9.6 mL, 9.6 mmol), and the mixture was stirred for 10 min at room temperature. In another round-bottomed flask, (2*S*,3*R*)-4-benzyl-2-(bromophenylmethyl)morpholine (1.65 g, 4.77 mmol) was dissolved in anhydrous *t*-BuOH (30 mL) and THF (10 mL). This solution was added dropwise to the potassium 2-ethoxyphenoxide solution, and the mixture was heated to reflux for 24 h. The reaction mixture was cooled to room temperature, and most of solvent was evaporated under reduced pressure. H_2O (50 mL) and EtOAc (50 mL) was added, and the aqueous layer was extracted again with EtOAc (30 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatograph (SiO_2, hexane/EtOAc 5:1 to 3:1) to give (2*S*,3*S*)-4-benzyl-2-[(2-ethoxyphenoxy)phenylmethyl]morpholine (1.75 g, 91%) as a sticky oil: $[\alpha]_D^{29}$ = +23.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.41 (d, 2H, *J* = 7.1 Hz), 7.35−7.26 (m, 8H), 6.87 (d, 2H, *J* = 4.0 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 6.76−6.72 (m, 1H), 5.22 (d, 1H, *J* = 5.7 Hz), 4.10−4.03 (m, 3H), 3.97 (dt, 1H, *J* = 2.4, 11.3 Hz), 3.72 (dt, 1H, *J* = 2.4, 11.1 Hz), 3.55 (d, 1H, *J* = 13.0 Hz), 3.38 (d, 1H, *J* = 13.0 Hz), 2.63 (t, 2H, *J* = 12.8 Hz), 2.20−2.12 (m, 2H), 1.43 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 148.2, 138.3, 137.9, 129.2, 128.3, 128.2, 128.0, 127.5, 127.2, 122.3, 121.0, 118.6, 114.5, 82.9, 78.5, 66.9, 64.8, 63.5, 55.1, 52.8, 15.1; HRMS (EI): *m*/*z* calcd for $C_{26}H_{29}NO_3$ 403.2147, found 403.2145.

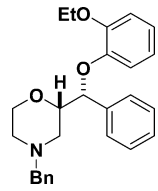
*5.2. (2R,3R)-4-Benzyl-2-[(2-ethoxyphenoxy)phenylmethyl]-morpholine [(2R,3R)-**9**].*



Yield: 90.5%, 920 mg; $[\alpha]_D^{29}$ = −21.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, 2H, *J* = 7.1 Hz), 7.33−7.25 (m, 8H), 6.86 (d, 2H, *J* = 4.0 Hz), 6.80 (d, 1H, *J* = 7.9 Hz), 6.75−6.72 (m, 1H), 5.21 (d, 1H, *J* = 5.7 Hz), 4.08−4.04 (m, 3H), 3.96 (d, 1H, *J* = 11.4 Hz), 3.71 (dt, 1H, *J* = 2.3, 11.2 Hz), 3.54 (d, 1H, *J* = 13.0 Hz), 3.37 (d, 1H, *J* = 13.0 Hz), 2.62 (t, 2H, *J* = 11.8 Hz), 2.20−2.11 (m, 2H), 1.42 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.1, 148.2, 138.3, 137.9, 129.2, 128.3, 128.2, 128.0, 127.6, 127.2, 122.3, 121.0, 118.5, 114.7, 82.9, 78.5, 66.9, 64.9, 63.5, 55.2, 52.8, 15.2; HRMS (EI): *m*/*z* calcd for $C_{26}H_{29}NO_3$ 403.2147, found 403.2149.

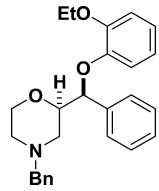
*5.3. Synthesis of (2S,3S)-**9** from (2S,3S)-**7** and the Tricarbonylchromium Complex of 1-Ethoxy-2-fluorobenzene.* To a suspension of NaH (60% oil dispersion, 66 mg, 1.65 mmol, washed once with *n*-hexane) in 1 mL of DMF was added dropwise (2*S*,3*S*)-(4-benzylmorpholin-2-yl)phenylmethanol (312 mg, 1.1 mmol) in 3 mL of DMF at room temperature under nitrogen atmosphere. η^6-(1-Ethoxy-2-fluorobenzene)tricarbonylchromium[17] (456 mg, 1.65 mmol) in DMF (3 mL) was added to the mixture and stirred for 2 h at room temperature. The reaction mixture was cooled to 0 °C, and a solution of I_2 (1.68 g, 6.6 mmol) in 5 mL of THF was added dropwise over 30 min. The reaction mixture was stirred for an additional 30 min at room temperature, and then 10% $Na_2S_2O_3$ (50 mL) solution was added. The mixture was extracted with EtOAc (30 mL × 3), and combined organic layers were washed with H_2O (30 mL × 2), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatograph (SiO_2, hexane/EtOAc 5:1 to 3:1) to give (2*S*,3*S*)-4-benzyl-2-[(2-ethoxyphenoxy)phenylmethyl]morpholine (390 mg, 88%) as a sticky oil. The spectroscopic (^{1}H and ^{13}C NMR) and optical data of this compound were exactly same as those of the compound prepared from the above method (section 5.1).

*5.4. Synthesis of (2S,3R)-4-Benzyl-2-[(2-ethoxyphenoxy)-phenylmethyl]morpholine [(2S,3R)-**9**].* To a solution of (2*S*,3*S*)-(4-benzylmorpholin-2-yl)phenylmethanol (600 mg, 2.12 mmol), Ph_3P (1.12 g, 4.24 mmol), and 2-ethoxyphenol (590 mg, 4.24 mmol) in 20 mL of THF at 0 °C was added diisopropyl azodicarboxylate (860 mg, 4.24 mmol). The reaction mixture was allowed to reach room temperature and stirred for 24 h. The reaction mixture was evaporated under reduced pressure and purified by flash chromatography on silica gel (hexane/EtOAc 7:1 to 5:1) to give (2*S*,3*R*)-4-benzyl-2-[(2-ethoxyphenoxy)phenylmethyl]morpholine (615 mg, 72%) as a sticky oil.



Yield: 72%; $[\alpha]_D^{29}$ = −22.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, 2H, *J* = 7.3 Hz), 7.37−7.20 (m, 8H), 6.87−6.86 (m, 2H), 6.73−6.69 (m, 2H), 5.07 (d, 1H, *J* = 6.8 Hz), 4.06−3.98 (m, 3H), 3.85 (d, 1H, *J* = 11.3 Hz), 3.67 (d, 1H, *J* = 13.1 Hz), 3.62 (dt, 1H, *J* = 2.4, 11.3 Hz), 3.47 (d, 1H, *J* = 13.1 Hz), 3.30 (d, 1H, *J* = 11.4 Hz), 2.64 (d, 1H, *J* = 11.3 Hz), 2.33 (t, 1H, *J* = 11.1 Hz), 2.19 (dt, 1H, *J* = 3.2, 11.3 Hz), 1.41 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 148.0, 139.2, 138.0, 129.2, 128.4, 128.3, 128.0, 127.6, 127.2, 122.1, 121.0, 117.8, 114.5, 82.7, 78.9, 67.2, 64.8, 63.6, 55.7, 52.9, 15.2; HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{29}NO_3Na$ 426.2045, found 426.2031. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}NO_3$ 404.2226, found 404.2227.

*5.5. (2R,3S)-4-Benzyl-2-[(2-ethoxyphenoxy)phenylmethyl]-morpholine [(2R,3S)-**9**].*



Yield: 70.2% (340 mg); $[\alpha]_D^{29}$ = +22.9 (*c* 0.5, $CHCl_3$);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, 2H, *J* = 7.3 Hz), 7.36−7.25 (m, 8H), 6.86−6.85 (m, 2H), 6.73−6.69 (m, 2H), 5.07 (d, 1H, *J* = 6.8 Hz), 4.06−3.97 (m, 3H), 3.87−3.84 (m, 1H), 3.68−3.65 (d, 1H, *J* = 13.2 Hz), 3.65−3.59 (dt, 1H, *J* = 2.3, 11.2 Hz), 3.47 (d, 1H, *J* = 13.1 Hz), 3.30 (d, 1H, *J* = 11.3 Hz), 2.63 (d, 1H, *J* = 11.6 Hz), 2.33 (t, 1H, *J* = 11.0 Hz), 2.19 (dt, 1H, *J* = 3.2, 11.4 Hz), 1.41 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 148.0, 139.2, 138.0, 129.3, 128.4, 128.3, 128.0, 127.6, 127.2, 122.1, 121.0, 117.8, 114.5, 82.7, 79.0, 67.2, 64.8, 63.6, 55.7, 52.9, 15.2; HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{29}NO_3Na$ 426.2045, found 426.2047. HRMS

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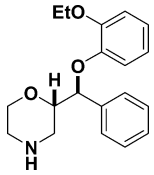
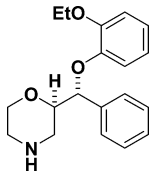
(ESI-TOF): m/z $[M + H]^+$ calcd for $C_{26}H_{30}NO_3$ 404.2226, found 404.2226.

6. Synthesis of Reboxetine: Selective N-Debenzylation. 6.1. Synthesis of (2S,3S)-Reboxetine [(2S,3S)-1].



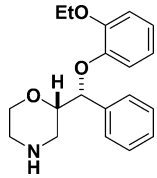
To a solution of (2*S*,3*S*)-4-benzyl-2-[(2-ethoxyphenoxy)-phenylmethyl]morpholine (150 mg, 0.37 mmol) and *i*-Pr_2NEt (260 μL, 1.5 mmol) in anhydrous 1,2-dichloroethane (10 mL) was added dropwise α-chloroethyl chloroformate (161 μL, 1.5 mmol), and the mixture was stirred for 10 min at room temperature. The reaction mixture was refluxed for 4 h, and the solvent was evaporated under reduced pressure. MeOH (20 mL) was added, and the solution was heated to reflux for 2 h. MeOH was evaporated under reduced pressure. The residue was dissolved in EtOAc (10 mL), washed with 1 N NaOH solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (2 mm thickness) (SiO_2, CH_2Cl_2/MeOH 9:1, two times elution) to give (2*S*,3*S*)-reboxetine (100 mg, 86%) as colorless oil: >99.9% ee (Chiralpak IC, Hex/EtOH/DEA = 90/10/0.1, 1.0 mL/min, 254 nm, t_R(minor) = 8.2 min, t_R(major) = 9.8 min); $[\alpha]_D^{28}$ = +12.3 (c 0.3, MeOH); $[\alpha]_D^{28}$ = +22.5 (*c* 0.75, $CHCl_3$); lit.[17] $[\alpha]_D^{20}$ = +13.0 (*c* 1.03, MeOH), 99% ee, lit.[22] $[\alpha]_D^{25}$ = +12.59 (*c* 1.1, MeOH), lit.[13] $[\alpha]_D^{21}$ = +11.8 (*c* 1.01, MeOH), 99.4% ee; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, 2H, J = 7.2 Hz), 7.35−7.26 (m, 3H), 6.86 (d, 2H, J = 4.0 Hz), 6.81 (d, 1H, J = 7.9 Hz), 6.75−6.71 (m, 1H), 5.14 (d, 1H, J = 5.8 Hz), 4.12−4.05 (m, 2H), 4.04−3.94 (m, 2H), 3.70 (dt, 1H, J = 3.0 Hz, J = 11.2 Hz), 2.92−2.82 (m, 2H), 2.77−2.69 (m, 2H), 2.29 (brs, 1H), 1.46 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 148.1, 138.0, 128.3, 128.1, 127.5, 122.4, 121.0, 118.4, 114.5, 83.3, 79.2, 68.0, 64.8, 47.4, 45.7, 15.1; HRMS (EI): m/z calcd for $C_{19}H_{23}NO_3$ 313.1678, found 313.1676.

6.2. (2R,3R)-Reboxetine [(2R,3R)-1].



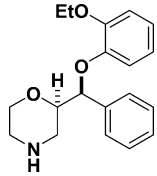
To a solution of (2*R*,3*R*)-4-benzyl-2-[(2-ethoxyphenoxy)-phenylmethyl]morpholine (150 mg, 0.37 mmol) and diisopropylamine (polymer-bound, Aldrich, 2.0−3.5 mmol/g) (370 mg, 0.74 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise 1-chloroethyl chloroformate (201 μL, 1.85 mmol), and the mixture was stirred for 10 min at room temperature. The reaction mixture refluxed for 4 h with vigorous stirring, and the reaction mixture was filtered and the resin washed with CH_2Cl_2. The combined organic phases were evaporated under reduced pressure. MeOH (20 mL) was added, and the solution was heated to reflux for 2 h. MeOH was evaporated under reduced pressure. The residue was dissolved in EtOAc (10 mL) and washed with 1 N NaOH solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC (2 mm thickness) (SiO_2, CH_2Cl_2/MeOH 9:1, 2 times elution) to give (2*R*,3*R*)-reboxetine (105 mg, 90%) as colorless oil. Yield: 90%; >99.9% ee; Chiralpak IC, Hex/EtOH/DEA = 90/10/0.1, 1.0 mL/min, 254 nm, t_R(major) = 8.2 min, t_R(minor) = 9.8 min; $[\alpha]_D^{29}$ = −13.9 (*c* 0.3, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, 2H, J = 7.2 Hz), 7.35−7.20 (m, 3H), 6.89−6.85 (m, 2H), 6.80 (d, 1H, J = 7.6 Hz), 6.76−6.71(m, 1H), 5.14 (d, 1H, J = 5.7 Hz), 4.13−4.05 (m, 2H), 4.03−3.97 (m, 2H), 3.71 (dt, 1H, J = 3.5 Hz, J = 11.5 Hz), 2.93−2.85 (m, 2H), 2.80−2.72 (m, 3H), 1.46 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 148.0, 138.0, 128.4, 128.2, 127.5, 122.4, 121.0, 118.4, 114.4, 83.2, 78.9, 67.7, 64.8, 47.2, 45.5, 15.1; HRMS (EI): m/z calcd for $C_{19}H_{23}NO_3$ 313.1678, found 313.1676.

6.3. (2S,3R)-Reboxetine [(2S,3R)-1].



Yield: 74.5%; >99.9% ee (Chiralpak IB, Hex/EtOH/DEA = 80/20/0.1, 1.0 mL/min, 254 nm, t_R(major) = 7.5 min, t_R(minor) = 8.2 min); $[\alpha]_D^{29}$ = −16.9 (c 0.2, CH_2Cl_2), $[\alpha]_D^{29}$ = −32.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 7.3 Hz), 7.34 (t, 2H, J = 7.4 Hz), 7.30−7.29 (m, 1H), 6.88−6.86 (m, 2H), 6.72−6.69 (m, 2H), 5.10(d, 1H, J = 6.5 Hz), 4.12−4.07 (m, 2H), 3.91 (d, 1H, J = 11.4 Hz), 3.86−3.82 (m, 1H). 3.58 (dt, 1H, J = 2.7 Hz, J = 11.2 Hz), 3.35 (d, 1H, J = 11.8 Hz), 3.02−2.92 (m, 2H), 2.85(d, 1H, J = 12.5 Hz), 2.17(brs, 1H), 1.48 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 147.7, 138.8, 128.2, 127.8, 127.2, 122.0, 121.0, 117.3, 114.1, 82.8, 79.6, 68.1, 64.6, 47.3, 45.8, 15.1; HRMS (EI): m/z calcd for $C_{19}H_{23}NO_3$ 313.1678, found 313.1676.

6.4. (2R,3S)-Reboxetine [(2R,3S)-1].



Yield: 64.7%; >99.9% ee (Chiralpak IB, Hex/EtOH/DEA = 80/20/0.1, 1.0 mL/min, 254 nm, t_R(minor) = 7.5 min, t_R(major) = 8.2 min); $[\alpha]_D^{29}$ = +16.1 (*c* 0.5, CH_2Cl_2), $[\alpha]_D^{29}$ = +33.3 (*c* 0.3, $CHCl_3$), lit.[24] $[\alpha]_D^{28}$ = +16.0 (*c* 0.68, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 2H, J = 7.3 Hz), 7.34 (t, 2H, J = 7.4 Hz), 7.30−7.29 (m, 1H), 6.88−6.86 (m, 2H), 6.73−6.69 (m, 2H), 5.09(d, 1H, J = 6.1 Hz), 4.12−4.07 (m, 2H), 3.91 (d, 1H, J = 11.3 Hz), 3.85−3.82 (m, 1H). 3.57 (dt, 1H, J = 2.5 Hz, J = 11.2 Hz), 3.35 (d, 1H, J = 12.3 Hz), 3.02−2.92 (m, 2H), 2.85(d, 1H, J = 12.3 Hz), 2.22(brs, 1H), 1.48 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 147.7, 138.8, 128.2, 127.9, 127.2, 122.0, 120.9, 117.3, 114.1, 82.8, 79.6, 68.1, 64.6, 47.3, 45.7, 15.1; HRMS (EI): m/z calcd for $C_{19}H_{23}NO_3$ 313.1678, found 313.1678.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, chiral HPLC chromatograms of all chiral compounds, and X-ray crystallography data

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for (2*S*,3*R*)-**6a** in CIF format (CCDC 898360). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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