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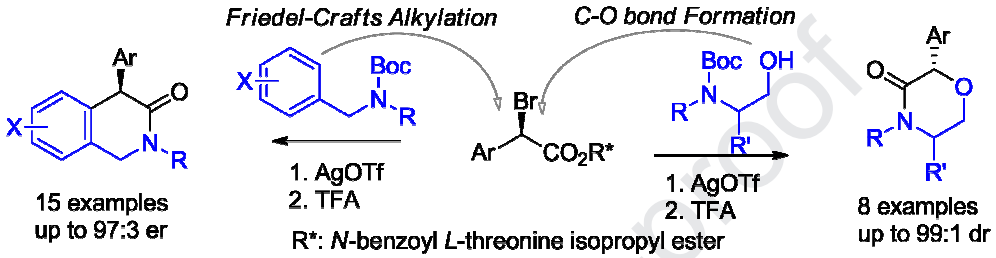

Asymmetric Synthesis of 4-Aryl Dihydroisoquinolin-3-ones and 2-Aryl Morpholin-3-ones using AgOTf-activated α-Bromo Arylacetate

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Abstract: A novel asymmetric synthetic strategy to prepare 4-aryl-dihydroisoquinolinones has been developed through a highly regioselective Friedel-Crafts alkylation of benzylamine derivatives with (*αR*)-α-bromo arylacetates and subsequent facile lactamization. In addition, an efficient asymmetric synthesis of 2-aryl morpholinones is demonstrated with 2-aminoethanol derivatives using the same convenient substitution-lactamization protocol.

1. Introduction

Tetrahydroisoquinolines constitute a broad class of frameworks in biologically active materials.[1] In particular, 4-aryl substituted tetrahydroisoquinolines attract substantial attention due to their potent neuropharmacological activities.[1c,1d] Some notable examples of this class of compounds include nomifensine, dichlofensine, latifine and cherylline.[2] Despite their enantioselective pharmacological activities, the studies on the asymmetric synthesis of 4-aryl tetrahydroisoquinolines have been sparsely reported in the literature.[3] The asymmetric synthetic methods used include the stereoselective protonation of lactam enolates,[3a,3b] Friedel–Crafts alkylation[3c,3d] and Suzuki coupling of aryl boronic acid.[3e] Although these methods are generally reliable, the efficient stereocontrol of the *gem*-diarylmethine C(4)-stereogenic center remains challenging in asymmetric synthesis. In this paper, we present the highly regioselective arene C-H bond functionalization of benzylamine derivatives with configurationally labile α-bromo arylacetates for the asymmetric synthesis of 4-aryl-1,4-dihydroisoquinolin-3(2*H*)-ones, which could be easily reduced to provide the corresponding 4-aryl-tetrahydroisoquinoline. In addition, we have investigated the reactions of arene nucleophiles bearing a competing alcohol nucleophile and the related reactions of α-bromo phenylacetate with 2-aminoethanol-derived nucleophiles were presented for the asymmetric synthesis of 2-aryl-morpholin-3-one derivatives.

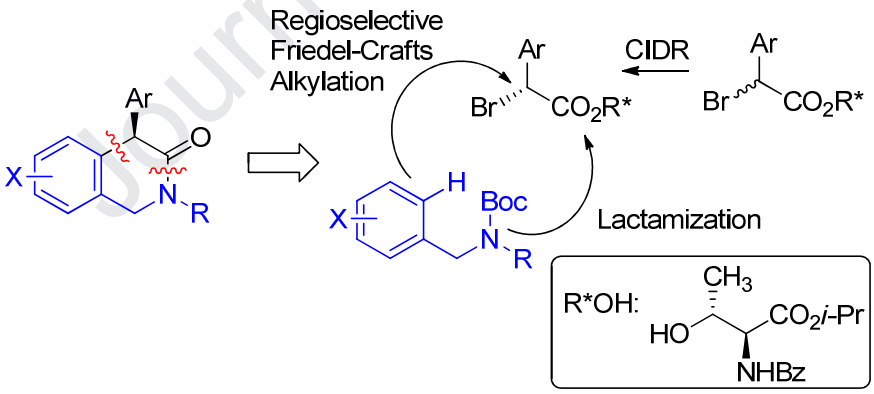


Figure 1. Retrosynthetic analysis for asymmetric preparation of 4-aryl-dihydroisoquinolinones.

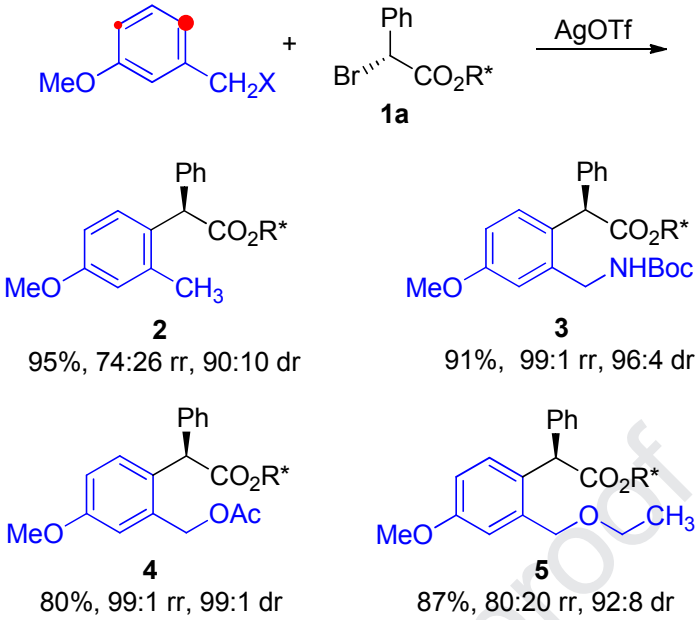
Our new strategy to construct the enantioenriched 4-aryl substituted dihydroisoquinolinone is based on the regioselective Friedel-Crafts alkylation at the *ortho*-position of benzylamine derivatives with α-bromo arylacetates, followed by lactamization after deprotection as shown in Figure 1. We previously reported that highly diastereoenriched (*αR*)-α-bromo arylacetates (>99:1 dr) were obtained as a solid through crystallization induced dynamic resolution (CIDR) using *N*-benzoyl-L-threonine isopropyl ester and then developed as generally useful optically pure

electrophiles in various substitution reactions.[4a-d] For the substitution to be of asymmetric synthetic value, the substitution should occur fast with respect to the epimerization of (*αR*)-α-bromo arylacetate under the reaction conditions. Therefore, the use of highly reactive benzylamine derivatives bearing electron donating substituents on the arene group is necessary for the efficient preparation of highly enantioenriched dihydroisoquinolinones.[4c] In addition, due to the existence of a potentially unstable diaryl substituted stereocenter of products, the use of mild reaction conditions is needed for both the alkylation and the lactamization reactions.[4e]

A major challenge involved in the Friedel-Crafts alkylation of the benzylamine derivative is the control of the regioselectivity for the reaction at one of multiple arene C–H bonds. When two electron-donating substituents are already present, they may have cooperating or conflicting directing effects on the third substitution. For the desired lactamization depicted in Figure 1, highly regioselective C-H functionalization at the *ortho*-position to the aminomethyl substituent is required to minimize waste production and enhance synthetic efficiency. Installing a carbonyl protecting group on the aminomethyl substituent could be one solution for directing the alkylation at *ortho*-position. Based on our previous studies investigating the reactions of α-bromo arylacetates, we envisaged that the efficient asymmetric synthesis of 4-aryl-dihydroisoquinolinone would be possible through the regioselective Friedel-Crafts alkylation of *meta*-electron donating group substituted *N*-Boc-benzylamines in the presence of AgOTf and with subsequent *N*-Boc deprotection and lactamization under mild conditions.

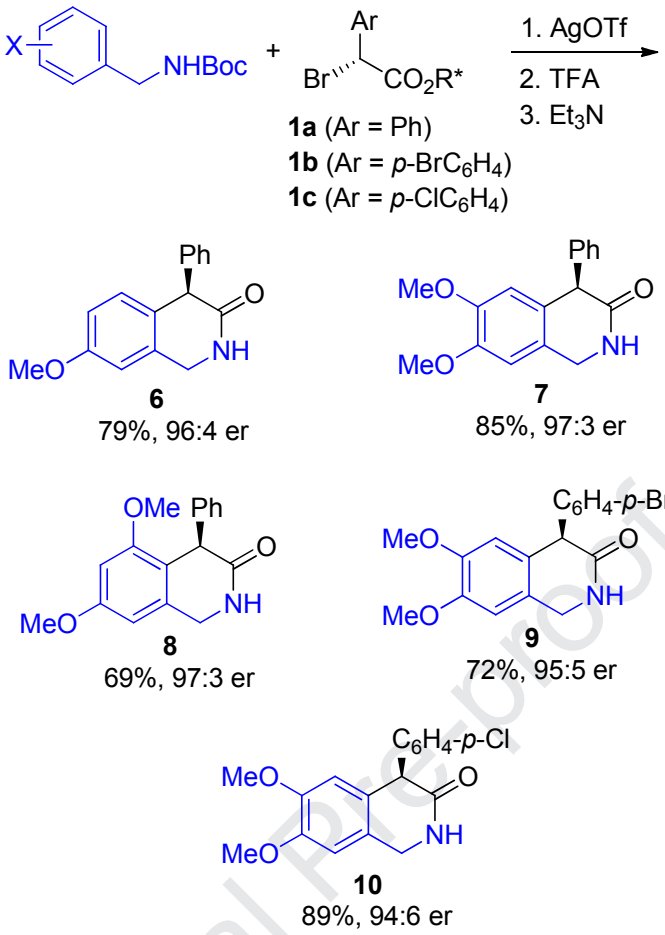
2. Results and Discussion

In our initial model studies with 3-methylanisole, which has two activating substituents, the Friedel-Crafts alkylation with (*R*)-α-bromo phenylacetate (**1a**) in the presence of AgOTf (1.0 equiv) in $CHCl_3$ successfully afforded the desired product **2** in 95% yield with 90:10 dr (diastereomeric ratio) after 3 h. However, as shown in Scheme 1, the reaction produced two regioisomers in a regioisomeric ratio (rr) of 74:26.[5] The structure of major regioisomer **2** was confirmed after the conversion to *N*-benzyl-2-(4-methoxy-2-methylphenyl)-2-phenylacetamide by the comparison of H-NMR with the authentic compound.[3e] A strongly activating methoxy substituent is the major director over a weakly activating methyl substituent. Under the same conditions, the reaction of 4-methylanisole does not afford the substitution product. The results indicate that the presence of a strong electron-donating group at the *meta*-position of benzylamine is necessary for our strategy to build a dihydroisoquinolinone scaffold and the inherent low regioselectivity can be a potent problem hindering the development of practical synthetic methods.



Scheme 1. Regioselective Friedel-Crafts alkylation with (*αR*)-α-bromo phenylacetate

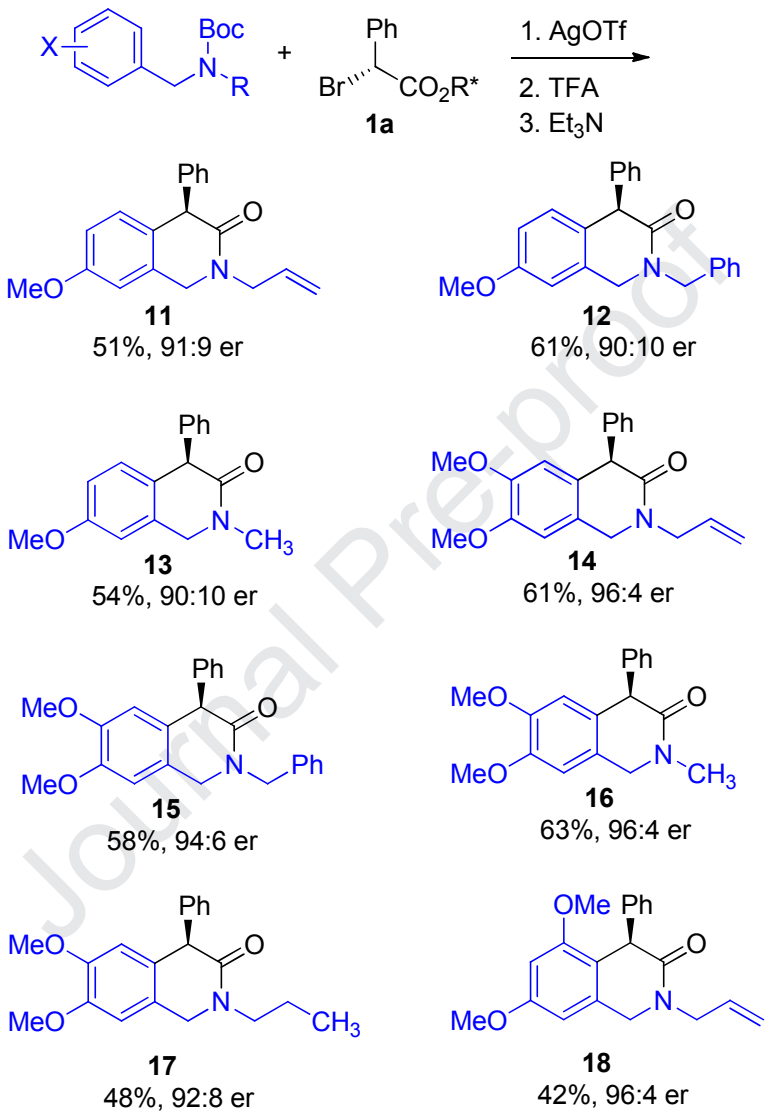
Encouraged by recent reports of the highly *ortho*-selective C-H functionalization of benzylamine derivatives by employing a directing group,[6] we next examined whether incorporating the *N*-Boc aminomethyl group into the arene nucleophile can affect the regioselectivity. When *N*-Boc 3-methoxybenzylamine was treated with (*αR*)-**1a** and AgOTf for 3 h, we observed that the *ortho*-alkylated regioisomer **3** was exclusively isolated in 91% yield with a higher dr of 96:4, as was desired. Further, we investigated whether installing the *O*-Ac hydroxyl group helped in directing reactions toward an *ortho*-substituted product. Interesting high regioselectivity was also observed in the reaction of *O*-acetyl 3-methoxybenzylalcohol under the same conditions to afford **4** exclusively with 99:1 dr. In order to understand the possible role of the carbonyl groups in *N*-Boc and *O*-Ac protection, we conducted the reaction of 3-methoxybenzyl ethyl ether with no carbonyl group under the same conditions and obtained the substitution product **5** with a regioisomeric ratio (rr) of 80:20 with 92:8 dr. Although the origin of the high regioselectivity in the syntheses of **3** and **4** currently remains unclear, the coordination of the *N*-Boc or *O*-Ac directing group to the silver ion may be crucial in bringing the Lewis acid catalyst in proximity to the *ortho* C-H bond to activate, therefore, ensuring high levels of regioselectivity and stereoselectivity.[6]



Scheme 2. Substitution-lactamization protocol for asymmetric synthesis of 4-aryl-dihydroisoquinolinones

Following simple *N*-Boc deprotection with trifluoroacetic acid (TFA), intramolecular lactamization to remove the chiral auxiliary was successfully completed within 1 h in the presence of Et_3N to ultimately afford (*R*)-dihydroisoquinolinone **6** in 89% yield with 96:4 er.[7] We next examined a simple procedure that does not involve purification of the substitution product **3** and instead uses the crude material in the following lactamization step. After the reaction mixture was rapidly filtered through silica gel, subjecting the crude mixture to the deprotection and cyclization afforded dihydroisoquinolinone **6** in a comparable overall yield of 79% as shown in Scheme 2. Using the optimized substitution-lactamization protocol, the reactions of two 3-methoxybenzylamine derivatives with two different α-bromo arylacetates **1b** and **1c** were carried out to examine the effect of changing the substituents on the two aromatic rings of reactants. The reactions of (α*R*)-**1a** with *N*-Boc-3,4-dimethoxybenzylamine and *N*-Boc-3,5-dimethoxybenzylamine produced dihydroisoquinolinones **7** and **8**, respectively, with a slightly higher er of 97:3. In addition, dihydroisoquinolinones **9** and **10** were obtained with 95:5 er and 94:6 er from the reactions of *N*-

Boc-3,4-dimethoxybenzylamine with 4-bromoaryl substituted α-bromoacetate **1b** and 4-chloroaryl substituted α-bromoacetate **1c**, respectively. The results indicate that the variations of the substituents of the two aryl groups of reactants did not significantly influence the er of 4-aryl-dihydroisoquinolinones.



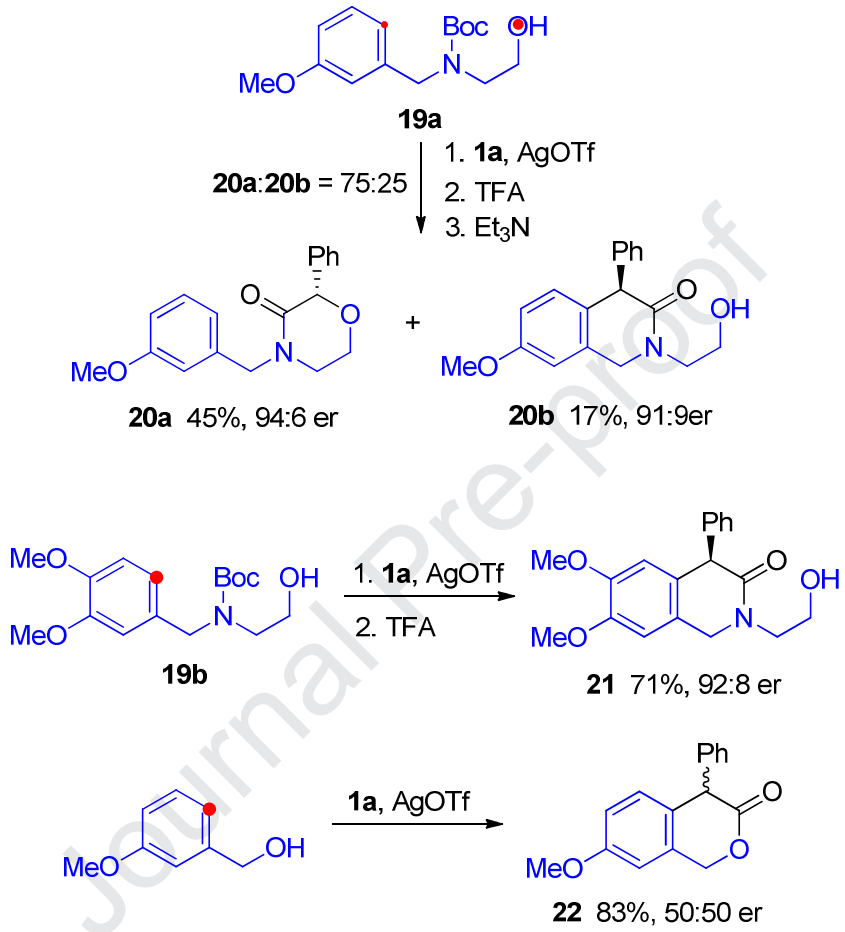
Scheme 3. Asymmetric Synthesis of *N*-alkyl substituted 4-aryl-dihydroisoquinolinones.

The scope of the substitution-lactamization protocol was further extended to the synthesis of various *N*-substituted dihydroisoquinolinones as shown in Scheme 3. The reactions of (α*R*)-**1a** with *N*-allyl, *N*-benzyl or *N*-methyl substituted *N*-Boc 3-methoxybenzylamine gave dihydroisoquinolinones **11**, **12** and **13**, respectively, in 61-51% yields with ers of 91:9 and 90:10. The reactions were somewhat slower most likely due to the steric effect of the *N*-alkyl groups than the reactions of nucleophiles bearing no *N*-substituent shown in Scheme 2 and consequently showed

lower yields and ers of **11**-**13** under the same conditions. The diminished ers indicate that the substitution was not sufficiently fast in terms of the epimerization, and the competitive epimerization of (α*R*)-**1a** led to a slight reduction of enantioselectivities. When *N*-substituted nucleophiles are activated with two methoxy groups, the same protocol provided improved ers of products. The reactions of (α*R*)-**1a** with *N*-allyl, *N*-benzyl, *N*-methyl or *N*-*n*-propyl substituted *N*-Boc-3,4-dimethoxybenzylamine gave dihydroisoquinolinones **14**, **15**, **16** and **17** with 96:4 er, 94:6 er, 96:4 er and 92:8 er, respectively. The protocol was readily extended to *N*-allyl substituted *N*-Boc-3,5-dimethoxybenzylamine to give dihydroisoquinolinone **18** in 48% yield with 96:4 er. This synthetic strategy enables the convenient preparation of highly enantioenriched *N*-alkyl substituted 4-phenyl-dihydroisoquinolinones.

In a recent study, we reported that alcohols can be used as a nucleophile for the substitution of α-bromo arylacetates in the presence of Lewis acid.[4d] With the substitution-lactamization protocol investigated for 3-methoxybenzylamine derivatives, we were curious to know the competing reactivity of alcohol nucleophiles towards C–O bond forming reactions. As shown in in Scheme 4, compounds bearing two competing nucleophiles *i.e.* arene and alcohol were examined. The substitution-lactamization with *N*-Boc-*N*-(3-methoxybenzyl)-2-aminoethanol (**19a**) gave two products **20a** and **20b** in a ratio of 75:25. Morpholinone **20a** was produced in 45% yield with 94:6 er, while dihydroisoquinolinone **20b** was produced in 17% yield with 91:9 er. The electrophile, α-bromo phenylacetate, was preferentially attacked by the alcohol nucleophile and underwent subsequent lactamization after removing Boc protection to give 2-phenyl-morpholin-3-one **20a** as a major product. The observed chemoselectivity between two different reactive functional groups in a nucleophile is based on the innate reactivities of two competing nucleophiles. In this case, the presence of the additional electron-donating methoxy group on the arene was sufficient to ensure the differentiation of two nucleophiles, and therefore switch chemoselectivity. The reaction of *N*-Boc-*N*-(3,4-dimethoxybenzyl)-2-aminoethanol (**19b**) gave dihydroisoquinolinone **21** exclusively in 71% yield with 92:8 er. In addition, the reaction of 3-methoxybenzylalcohol was carried out to examine the competing reactivities between the arene and benzylic alcohol. Under the same conditions, the reaction produced racemic 4-phenyl-isochromanone **22** in 83% yield through the Friedel-Crafts reaction and spontaneous cyclization to give the lactone.[8] Due to the poor nucleophility of benzylic alcohol,[9] the substitution occurred preferentially with the arene nucleophile. By sharp contrast, the reaction of (α*R*)-**1a** with *N*-Boc-*N*-benzyl-2-aminoethanol (**19c**) exclusively produced morpholin-3-one **23** in 76% yield with 96:4 er as shown in Scheme 5. The substitution with the aliphatic alcohol is substantially faster than that with arene nucleophile bearing no strongly activating substituents. The

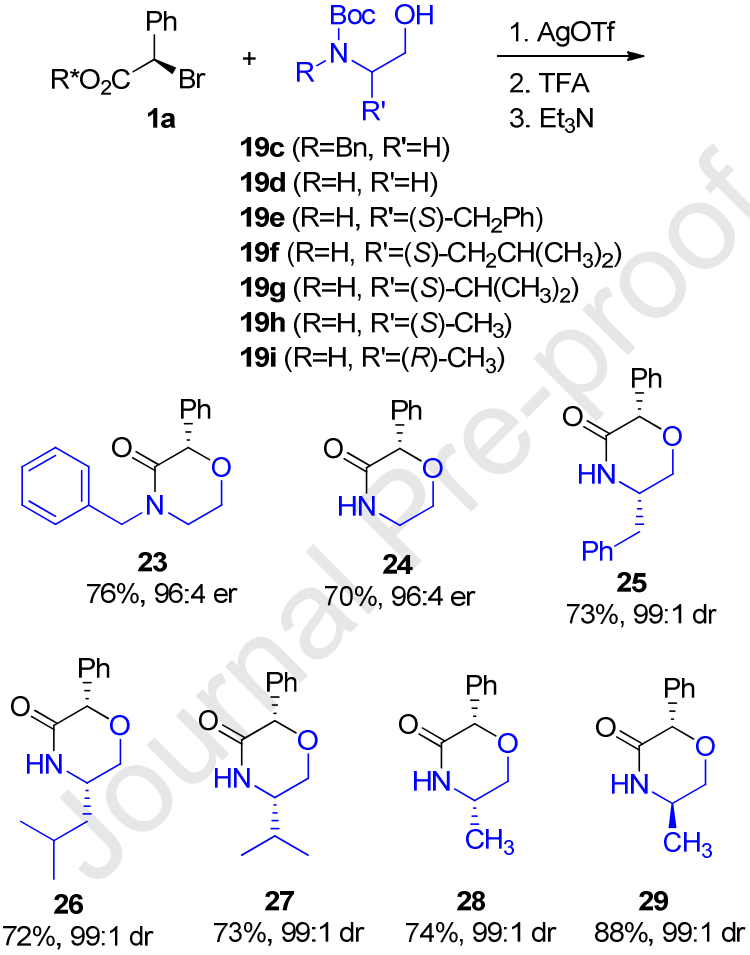
results shown in Scheme 4 and 5 indicate that the substitution of α-bromo arylacetate with the nucleophile bearing two competing nucleophilic functional groups offers strategies for the asymmetric synthesis of two different chiral lactams, dihydroisoquinolinone and morpholinone, switching chemoselectivity within the similar precursors.



Scheme 4. Chemoselective reactions of two competing nucleophiles

The related asymmetric synthesis of 2-phenyl morpholin-3-one was achieved using the substitution-lactamization of (α*R*)-**1a** with *N*-Boc-2-aminoethanol (**19d**) to give **24** in 70% yield with 96:4 er as shown in Scheme 5. Given the prevalence and importance of highly substituted morpholinones,[10] we applied the synthetic protocol to the asymmetric preparation of 2,5-disubstituted morpholinones using 2-alkyl-2-aminoethanols **19e-i** as nucleophiles. The substitutions of (α*R*)-**1a** with L-phenylalanine, L-leucine, L-valine or L-alanine-derived *N*-Boc-2-aminoethanol (**19e**, **19f**, **19g** or **19h**) and subsequent lactamization respectively afforded *cis*-2,5-disubstituted morpholinones **25**, **26**, **27** and **28** in good yields with 99:1 dr. Compared to the substitution for the preparation of **24**, a much higher stereoselectivity of 99:1 dr was observed in the substitution with *N*-

Boc-2-(*S*)-alkyl-2-aminoethanols **19e-h** under the same reaction conditions. No stereo-differentiation was observed in the reaction with D-alanine-derived *N*-Boc-2-(*R*)-methyl-2-aminoethanol (**19i**). Using the same protocol, *trans*-5-methyl-2-phenyl-morpholin-3-one **29** was obtained in 88% yield with 99:1 dr. The relative configurations of **28** and **29** were confirmed by the comparison of H-NMR with the authentic compound after the reduction to the corresponding morpholines.[11]



Scheme 5. Substitution-lactamization for the synthesis of 2-aryl-morpholinones

3. Conclusions

We report a novel asymmetric synthetic method for two chiral lactams, 4-aryl-dihydroisoquinolinones and 2-aryl-morpholinones, which has been rarely reported in the literature. The synthetic strategy for 4-aryl-dihydroisoquinolinones has been developed through the Friedel-Crafts alkylation of *N*-Boc-benzylamine derivatives with α-bromo arylacetates and subsequent facile lactamization. The highly regioselective and fast alkylation at the *ortho*-C-H bond of 3-methoxybenzylamine derivatives and the convenient lactamization under mild reaction conditions

are crucial factors to achieve the observed excellent product yields and stereoselectivities. In addition, the convenient substitution-lactamization protocol was also useful for the preparation of highly enantioenriched 2-aryl-morpholinones with *N*-Boc-2-aminoethanol derivatives. Notably, to our knowledge, we have presented the first general asymmetric synthetic method for 2-aryl-morpholin-3-ones. Furthermore, we simply demonstrate that the substitution of α-bromo arylacetate with the nucleophile bearing two competing nucleophilic functional groups, *i.e.* arene and alcohol, can offer strategies for the asymmetric synthesis of the two different lactams, switching chemoselectivity within the similar precursors. Considering the importance of the dihydroisoquinolinones and morpholinones in various ranges of biologically active substances, this operationally simple methodology should be useful for a number of applications in a variety of fields.

4. Experimental

General Methods: All reactions were performed in oven-dried glassware under nitrogen atmosphere. All chemicals were obtained from commercial sources and were used as received. Analytical thin layer chromatography (TLC) was performed on silica gel plates with QF-254 indicator and TLC visualization was carried out with UV-light. Flash column chromatography was performed with 230–400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were acquired on Bruker (400 MHz ^{1}H, 100.6 MHz ^{13}C) spectrometer using chloroform-*d* ($CDCl_3$) as the internal standard. Chemical shifts (δ) are reported in ppm relative to chloroform-*d* (7.26 ppm ^{1}H, 77.07 ppm ^{13}C). Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet) and br (broad). Coupling constants (*J*) are reported in Hz.

I. General Procedure for the asymmetric preparation of dihydroisoquinolinones 6-21: To a solution of L-threonine-derived α-bromo ester **1a-c** (1.0 equiv, >99:1 dr) at room temperature were added AgOTf (1.2 equiv) and benzylamine nucleophile (10 equiv). After the mixture was stirred at rt for 3 h in the least possible amount of solvent, $CHCl_3$, the resulting mixture was filtered through silica gel, and concentrated under reduced pressure. The crude material was stirred in 50% trifluoroacetic acid/CH_2Cl_2 at room temperature for 1 h, washed with saturated $NaHCO_3$ solution, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. After the mixture was treated with Et_3N (2 equiv) in CH_2Cl_2 for 1 h and concentrated under reduced pressure, the chromatographic separation of the mixture on silica gel afforded a highly enantioenriched dihydroisoquinolinone (**6-21**). The ers of products were determined by CSP-HPLC.

7-Methoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (6): 79% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.29-7.22 (m, 4H), 7.17-7.15 (m, 2H), 7.03-7.01 (m, 1H), 6.84-6.82 (m, 1H), 6.74-6.73 (m, 1H), 4.75

(s, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 4.31 (dd, *J* = 16.0 and 4.0 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.2, 158.7, 139.0, 132.8, 129.9, 128.7, 128.0, 127.3, 127.2, 113.8, 110.6, 55.4, 51.7, 45.2. The spectral data were identical to those of the authentic material reported previously.[12a] HPLC: 96:4 er, t_R (*R*)-major enantiomer, 18.4 min; t_R (*S*)-minor enantiomer, 23.8 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

6,7-Dimethoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (7) 85% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.91 (br, 1H), 7.29-7.16 (m, 5H), 6.78 (s, 1H), 6.55 (s, 1H), 4.69 (s, 1H), 4.50 (d, *J* = 16.0 Hz, 1H), 4.31 (dd, *J* = 16.0 and 4.0 Hz, 1H), 3.89 (s, 3H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.0, 148.7, 148.2, 139.3, 128.7, 128.0, 127.2, 127.0, 123.5, 111.1, 108.2, 56.0, 55.0, 51.8, 44.8; HRMS: calcd. for $C_{17}H_{18}NO_3$ [M^++1] 284.1287; found 284.1285; Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 21.7 min; t_R (*S*)-minor enantiomer, 16.5 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

5,7-Dimethoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (8) 69% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.66 (br, 1H), 7.25-7.15 (m, 5H), 6.38 (d, *J* = 2.4 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 5.02 (s, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 4.24 (dd, *J* = 16.0 and 4.4 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.6, 160.0, 157.7, 138.8, 133.8, 128.5, 127.6, 126.9, 116.4, 101.3, 97.6, 55.6, 55.5, 46.1, 45.3; HRMS: calcd. for $C_{17}H_{18}NO_3$ [M^++1] 284.1287; found 284.1289; Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 76.0 min; t_R (*S*)-minor enantiomer, 57.8 min (Chiralcel OD column; 40% 2-propanol in hexane; 0.5 mL/min).

6,7-Dimethoxy-4-(4-bromophenyl)-1,4-dihydroisoquinolin-3-one (9) 72% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40 (d, *J* = 8.8 Hz, 1H), 7.21 (br, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.70 (s, 1H), 6.51 (s, 1H), 4.66 (s, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 4.35 (dd, *J* = 16.0 and 3.6 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1, 148.9, 148.4, 138.2, 131.8, 129.8, 126.3, 123.2, 121.4, 111.1, 108.2, 56.1, 56.0, 51.1, 44.9; HRMS: calcd. for $C_{17}H_{17}BrNO_3$ [M^++1] 362.0392; found 362.0389; Chiral HPLC: 95:5 er, t_R (*R*)-major enantiomer, 19.4 min; t_R (*S*)-minor enantiomer, 17.1 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

6,7-Dimethoxy-4-(4-chlorophenyl)-1,4-dihydroisoquinolin-3-one (10) 89% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.59 (br, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.69 (s, 1H), 6.51 (s, 1H), 4.67 (s, 1H), 4.50 (d, *J* = 15.6 Hz, 1H), 4.34 (dd, *J* = 15.6 and 3.6 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.5, 148.9, 148.4, 137.7, 133.2, 129.5, 128.8, 126.3, 123.3, 111.1, 108.3, 56.1, 56.0, 51.0, 44.8; HRMS: calcd. for $C_{17}H_{17}ClNO_3$ [M^++1] 318.0897; found 318.0899; Chiral HPLC: 94:6 er, t_R (*R*)-major enantiomer, 17.5 min; t_R (*S*)-minor enantiomer, 15.0 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

2-Allyl-7-methoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (11) 51% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.26-7.05 (m, 6H), 6.87-6.84 (m, 1H), 6.76-6.75 (m, 1H), 5.78-5.68 (m, 1H), 5.16-5.06 (m, 2H), 4.85 (s, 1H), 4.48 (d, *J* = 16.0 Hz, 1H), 4.23-4.17 (m, 2H), 4.03 (dd, *J* = 15.6 and 6.0 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.1, 158.7, 138.9, 133.1, 132.4, 129.6, 128.6, 127.8, 127.7, 127.1, 117.7, 113.8, 110.6, 55.4, 52.3, 49.8, 49.4; HRMS: calcd. for $C_{19}H_{20}NO_2$ [M^++1] 294.1494; found 294.1494; Chiral HPLC: 91:9 er, t_R (*R*)-major enantiomer, 17.8 min; t_R (*S*)-minor enantiomer, 23.6 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

2-Benzyl-7-methoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (12): 61% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.19-7.08 (m, 10H), 7.03-7.00 (m, 1H), 6.88-6.80 (m, 1H), 6.62 (s, 1H), 4.94 (s, 1H), 4.76 (d, *J* = 2.8 Hz, 1H), 4.45 (d, *J* = 16.0 Hz, 1H), 4.17 (d, *J* = 16.0 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.4, 158.7, 139.1, 136.7, 132.9, 129.6, 128.7, 128.6, 127.9, 127.8, 127.5, 127.4, 127.2, 113.9, 110.5, 55.4, 52.3, 50.2, 50.0. The spectral data were identical to those of the authentic material reported previously.[3d] Chiral HPLC: 90:10 er, t_R (*R*)-major enantiomer, 25.1 min; t_R (*S*)-minor enantiomer, 36.4 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

7-Methoxy-2-methyl-4-phenyl-1,4-dihydroisoquinolin-3-one (13) 54% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.27-7.11 (m, 5H), 7.04-7.02 (m, 1H), 6.86-6.76 (m, 1H), 6.75 (s, 1H), 4.81 (s, 1H), 4.61 (d, *J* = 16.0 Hz, 1H), 4.26 (d, *J* = 16.0 Hz, 1H), 3.82 (s, 3H), 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.2, 158.6, 139.4, 132.6, 129.6, 128.6, 127.9, 127.7, 127.1, 113.9, 110.4, 55.4, 52.6, 51.9, 34.9; HRMS: calcd. for $C_{17}H_{18}NO_2$ [M^++1] 268.1338; found 268.1339; Chiral HPLC: 90:10 er, t_R (*R*)-major enantiomer, 22.1 min; t_R (*S*)-minor enantiomer, 25.3 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

2-Allyl-6,7-dimethoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (14) 61% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.29-7.14 (m, 5H), 6.72 (s, 1H), 6.60 (s, 1H), 5.78-5.69 (m, 1H), 5.16-5.07 (m, 2H), 4.81 (s, 1H), 4.49 (d, *J* = 15.6 Hz, 1H), 4.24-4.17 (m, 2H), 4.01 (dd, *J* = 15.6 and 6.0 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.7, 148.9, 148.2, 139.1, 132.5, 128.6, 127.8, 127.4, 127.2, 123.7, 117.6, 111.0, 108.2, 56.1, 56.0, 52.5, 49.5, 49.4; HRMS: calcd. for $C_{20}H_{22}NO_3$ [M^++1] 324.1600; found 324.1604; Chiral HPLC: 96:4 er, t_R (*R*)-major enantiomer, 21.0 min; t_R (*S*)-minor enantiomer, 18.4 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

2-Benzyl-6,7-dimethoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (15) 58% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.30-7.12 (m, 10H), 6.62 (s, 1H), 6.60 (s, 1H), 4.89 (s, 1H), 4.75 (d, *J* = 15.2 Hz, 1H), 4.65 (d, *J* = 15.2 Hz, 1H), 4.43 (d, *J* = 15.6 Hz, 1H), 4.16 (d, *J* = 15.6 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.0, 148.9, 148.2, 139.2, 136.7, 128.7, 127.9, 127.8, 127.5, 127.2, 123.5, 110.9, 108.1, 56.0, 52.5, 50.2, 49.6; HRMS: calcd. for $C_{24}H_{24}NO_3$ [M^++1] 374.1756;

found 374.1755; Chiral HPLC: 94:6 er, t_R (*R*)-major enantiomer, 36.1 min; t_R (*S*)-minor enantiomer, 28.1 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

6,7-Dimethoxy-2-methyl-4-phenyl-1,4-dihydroisoquinolin-3-one (16): 63% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.29-7.14 (m, 5H), 6.72 (s, 1H), 6.57 (s, 1H), 4.77 (s, 1H), 4.62 (d, *J* = 15.6 Hz, 1H), 4.26 (d, *J* = 15.6 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.8, 148.9, 148.2, 139.5, 128.6, 127.9, 127.4, 127.1, 123.3, 110.9, 108.0, 56.1, 56,0, 52.3, 52.1, 34.9. The spectral data were identical to those of the authentic material reported previously.[12c] Chiral HPLC: 96:4 er, t_R (*R*)-major enantiomer, 21.4 min; t_R (*S*)-minor enantiomer, 19.7 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

6,7-Dimethoxy-4-phenyl-2-propyl-1,4-dihydroisoquinolin-3-one (17) 48% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.28-7.13 (m, 5H), 6.74 (s, 1H), 6.61 (s, 1H), 4.79 (s, 1H), 4.53 (d, *J* = 15.6 Hz, 1H), 4.20 (d, *J* = 15.6 Hz, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.55-3.48 (m, 1H), 3.40-3.33 (m, 1H), 1.62-1.52 (m, 2H), 0.83 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.8, 148.9, 148.2, 139.0, 128.6, 127.7, 127.6, 127.1, 124.0, 111.0, 108.2, 56.1, 56.0, 52.7, 50.2, 48.9, 20.5, 11.1; HRMS: calcd. for $C_{20}H_{24}NO_3$ [M^++1] 326.1756; found 326.1756; Chiral HPLC: 92:8 er, t_R (*R*)-major enantiomer, 16.0 min; t_R (*S*)-minor enantiomer, 13.8 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

2-Allyl-5,7-dimethoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (18) 42% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.30-7.14 (m, 5H), 6.72 (s, 1H), 6.60 (s, 1H), 5.79-5.69 (m, 1H), 5.17-5.07 (m, 2H), 4.82 (s, 1H), 4.49 (d, *J* = 15.6 Hz, 1H), 4.24-4.19 (m, 2H), 4.01 (dd, *J* = 15.6 and 6.0 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.7, 148.9, 148.2, 139.1, 132.5, 128.6, 127.8, 127.4, 127.2, 123.7, 117.6, 111.0, 108.2, 56.1, 56.0, 52.5, 49.5, 49.4; HRMS: calcd. for $C_{20}H_{22}NO_3$ [M^++1] 324.1600; found 324.1603; Chiral HPLC: 96:4 er, t_R (*R*)-major enantiomer, 18.7 min; t_R (*S*)-minor enantiomer, 16.8 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

2-(2-Hydroxyethyl)-7-methoxy-4-phenyl-1,4-dihydroisoquinolin-3-one (20b) 17% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.29-7.13 (m, 5H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.87-8.85 (m, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 4.85 (s, 1H), 4.67 (d, *J* = 16.0 Hz, 1H), 4.39 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 3.83-3.59 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1, 158.7, 138.8, 132.8, 129.6, 128.7, 127.8, 127.4, 127.2, 113.9, 110.5, 61.8, 55.4, 52.4, 52.2, 51.2; HRMS: calcd. for $C_{18}H_{20}NO_3$ [M^++1] 298.1443; found 298.1441; Chiral HPLC: 91:9 er, t_R (*R*)-major enantiomer, 18.1 min; t_R (*S*)-minor enantiomer, 23.9 min (Chiralpak AD-H column; 40% 2-propanol in hexane; 0.5 mL/min).

6,7-Dimethoxy-2-(2-Hydroxyethyl)-4-phenyl-1,4-dihydroisoquinolin-3-one (21) 71% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.30-7.14 (m, 5H), 6.72 (s, 1H), 6.58 (s, 1H), 4.80 (s, 1H), 4.68 (d, *J* = 15.6

Hz, 1H), 4.38 (dd, *J* = 15.6 Hz, 1H), 3.90 (s, 3H), 3.82-3.55 (m, 4H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.7, 149.0, 148.3, 139.0, 128.7, 127.8, 127.3, 127.2, 123.4, 110.9, 108.1, 61.6, 56.1, 56.0, 52.4, 52.0, 51.1; HRMS: calcd. for $C_{19}H_{22}NO_4$ [M^++1] 328.1549; found 328.1549; Chiral HPLC: 92:8 er, t_R (*R*)-major enantiomer, 21.0 min; t_R (*S*)-minor enantiomer, 19.2 min (Chiralpak AD-H column; 40% 2-propanol in hexane; 0.5 mL/min).

II. General Procedure for the asymmetric preparation of morpholinones 20a and 23-29: To a solution of L-threonine-derived α-bromo ester **1a-c** (1.0 equiv, >99:1 dr) at room temperature were added AgOTf (1.2 equiv) and 2-aminoethanol nucleophile (10 equiv). After the mixture was stirred at rt for 10 h in the least possible amount of solvent, $CHCl_3$, the resulting mixture was filtered through silica gel, and concentrated under reduced pressure. The crude material was stirred in 50% trifluoroacetic acid/CH_2Cl_2 at room temperature for 1 h, washed with saturated $NaHCO_3$ solution, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. After the mixture was treated with Et_3N (2 equiv) in CH_2Cl_2 (or ethanol) for 1 h and concentrated under reduced pressure, the chromatographic separation of the mixture on silica gel afforded a highly enantioenriched morpholinone (**20a** and **23-29**). The ers of **20a**, **23**, and **24** were determined by CSP-HPLC. The drs of **25-29** were determined by the ^{1}H NMR integration of the hydrogens of the two diastereomers.

4-(3-Methoxybenzyl)-2-phenyl-morpholin-3-one (20a) 45% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.49-7.24 (m, 6H), 6.89-6.84 (m, 3H), 5.26 (s, 1H), 4.70 (d, *J* = 14.4 Hz, 1H), 4.59 (d, *J* = 14.4 Hz, 1H), 4.01-3.97 (m, 1H), 3.89-3.86 (m, 1H), 3.79 (s, 3H), 3.50-3.47 (m, 1H), 3.34-3.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.6, 160.0, 137.9, 137.5, 129.8, 128.5, 128.4, 127.9, 120.6, 113.6, 113.4, 79.6, 61.8, 55.3, 49.9, 46.1; HRMS: calcd. for $C_{18}H_{20}NO_3$ [M^++1] 298.1443; found 298.1440; Chiral HPLC: 94:6 er, t_R (*R*)-major enantiomer, 53.1 min; t_R (*S*)-minor enantiomer, 65.6 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

4-Benzyl-2-phenyl-morpholin-3-one (23) 76% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.49-7.29 (m, 10H), 5.26 (s, 1H), 4.67 (s, 3H), 4.00-3.97 (m, 1H), 3.88-3.82 (m, 1H), 3.52-3.46 (m, 1H), 3.33-3.28 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 167.6, 137.4, 136.3, 128.8, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.6, 79.7, 61.8, 50.0, 46.1. The spectral data were identical to those of the authentic material reported previously.[10b] Chiral HPLC: 96:4 er, t_R (*R*)-major enantiomer, 40.0 min; t_R (*S*)-minor enantiomer, 63.1 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

2-phenyl-morpholin-3-one (24) 70% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.47-7.34 (m, 5H), 7.06 (br, 1H), 5.26 (s, 1H), 5.17 (s, 1H), 4.04-4.00 (m, 1H), 3.90-3.84 (m, 1H), 3.64-3.59 (m, 1H), 3.46-3.42 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 170.1, 136.9, 128.5, 128.0, 79.7, 61.7, 42.1. The spectral data were identical to those of the authentic material reported previously.[4b] Chiral HPLC: 96:4 er, t_R (*R*)-

major enantiomer, 11.0 min; t_R (*S*)-minor enantiomer, 10.3 min (Chiralpak AD-H column; 10% 2-propanol in hexane; 0.5 mL/min).

***cis*-5-Benzyl-2-phenyl-3-morpholinone (25)** 73% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.48-7.18 (m, 10H), 6.45 (br, 1H), 5.18 (s, 1H), 3.89-3.85 (m, 1H), 3.78-3.75 (m, 2H), 2.99-2.94 (m, 1H), 2.89-2.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.4, 136.5, 136.3, 129.3, 129.0, 128.6, 128.0, 127.2, 79.4, 64.6, 53.5, 40.2; HRMS: calcd. for $C_{17}H_{18}NO_2$ [M^++1] 268.1338; found 268.1336.

***cis*-5-(2-Methylpropyl)-2-phenyl-3-morpholinone (26)** 72% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.48-7.33 (m, 5H), 6.50 (br, 1H), 5.20 (s, 1H), 3.88-3.84 (m, 1H), 3.68-3.65 (m, 2H), 1.71-1.64 (m, 1H), 1.59-1.52 (m, 1H), 1.46-1.39 (m, 1H), 0.96-0.93 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.5, 136.6, 128.5, 128.4, 127.9, 79.1, 65.2, 50.4, 42.7, 24.3, 22.9, 22.2; HRMS: calcd. for $C_{14}H_{20}NO_2$ [M^++1] 234.1494; found 234.1495.

***cis*-5-Isopropyl-2-phenyl-3-morpholinone (27)** 73% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.47-7.31 (m, 5H), 6.54 (br, 1H), 5.18 (s, 1H), 3.84-3.82 (m, 2H), 3.30-3.27 (m, 1H), 1.92-1.87 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.8, 136.5, 128.5, 128.4, 128.0, 79.0, 63.0, 57.9, 31.2, 18.7, 18.5; HRMS: calcd. for $C_{13}H_{18}NO_2$ [M^++1] 220.1338; found 220.1335.

***cis*-5-Methyl-2-phenyl-3-morpholinone (28)** 74% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.49-7.34 (m, 5H), 6.83 (br, 1H), 5.19 (s, 1H), 3.87-3.82 (m, 1H), 3.76-3.75 (m, 1H), 3.60-3.56 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.6, 136.6, 128.5, 128.4, 128.0, 78.7, 66.1, 48.0, 19.4; HRMS: calcd. for $C_{11}H_{14}NO_2$ [M^++1] 192.1025; found 192.1025.

***trans*-5-Methyl-2-phenyl-3-morpholinone (29)** 88% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.46-7.33 (m, 5H), 6.83 (br, 1H), 5.08 (s, 1H), 4.05-4.02 (m, 1H), 3.90-3.85 (m, 1H), 3.51-3.45 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 169.8, 137.0, 128.6, 128.5, 128.0, 79.5, 68.9, 48.2, 18.1; HRMS: calcd. for $C_{11}H_{14}NO_2$ [M^++1] 192.1025; found 192.1029.

III. General Procedure for the asymmetric preparation of 2,2-diarylacetates 2, **4**, and **5:** To a solution of L-threonine-derived α-bromo ester **1a** (1.0 equiv, >99:1 dr) at room temperature were added a nucleophile (10 equiv) and AgOTf (1.2 equiv). After the mixture was stirred at rt for 3 h in the least possible amount of solvent, $CHCl_3$, the resulting mixture was washed with saturated $NaHCO_3$ solution, dried with anhydrous $MgSO_4$, concentrated and purified by column chromatography to afford a diarylacetate (**2**, **4** and **5**). The drs were determined by the ^{1}H NMR integration of the hydrogens of the two diastereomers.

***N*-Benzoyl-*O*-[*α*-(4-methoxy-2-methylphenyl)phenylacetyl]-L-threonine Isopropyl Ester (2)** Obtained as an inseparable mixture (74:26) with two regioisomers in 95% yield; ^{1}H NMR ($CDCl_3$,

400 MHz) 7.60-7.12 (m, 10H), 6.90-6.41 (m, 4H), 5.60-5.32 (m, 1H), 5.26 (s, minor), 5.14 (s, 1H, major), 5.01-4.81 (m, 2H), 3.74 (s, minor), 3.73 (s, 3H, major), 2.32 (s, minor), 2.24 (s, 3H, major), 1.35-1.17 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.6, 169.3, 167.5, 158.7, 138.2, 137.8, 133.5, 131.9, 129.4, 129.1, 129.0, 128.8, 128.6, 127.2, 127.1, 116.4, 111.2, 71.6, 70.0, 56.0, 55.1, 53.2, 21.8, 21.6, 20.1, 17.5; HRMS: calcd. for $C_{30}H_{34}NO_6$ [M^++1] 504.2386; found 504.2388. To a solution of diarylacetate **2** in THF (0.5 M) was added a solution of $LiAlH_4$ (1.0 M in THF, 3 equiv) at 0˚C. After the reaction mixture was stirred at room temperature for 2 h, the reaction was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Chromatographic separation on silica gel afforded 2-(4-methoxy-2-methylphenyl)-2-phenylethanol in 65% yield. ^{1}H-NMR (CDCl3, 400MHz) δ 7.29-7.02 (m, 6H), 6.77-6.68 (m, 2H), 4.60 (t, *J* = 7.2 Hz, minor), 4.30 (t, *J* = 7.2 Hz, 1H, major), 4.11-4.07 (m, 2H), 3.76 (s, 3H, major), 3.75 (s, minor), 2.31 (s, minor), 2.21 (s, 1H, major). The er of major regioisomer were determined by chiral stationary phase-HPLC analysis. Chiral HPLC: 90:10 er, t_R (*R*)-major enantiomer, 23.8 min; t_R (*S*)-minor enantiomer, 37.4 min (Chiralcel OJ-H column; 40% 2-propanol in hexane; 0.5 mL/min).

***N*-Benzoyl-*O*-[α-(2-acetoxymethyl-4-methoxyphenyl)phenylacetyl]-L-threonine Isopropyl Ester (4)** 80% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.65-7.19 (m, 11H), 6.94-6.83 (m, 2H), 6.63 (d, *J* = 9.2 Hz, 1H), 5.60-5.58 (m, 1H), 5.29 (s, 1H), 5.11-5.05 (m, 2H), 4.94-4.88 (m, 2H), 3.76 (s, 3H), 1.92 (s, 3H), 1.35 (d, *J* = 6.4 Hz, 1H), 1.20 (d, *J* = 6.0 Hz, 1H), 1.13 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.3, 170.7, 169.2, 167.6, 158.8, 138.4, 135.4, 133.5, 131.9, 130.4, 129.2, 128.62, 128.59, 129.55, 127.3, 127.2, 116.1, 114.0, 71.7, 70.0, 64.1, 55.9, 55.3, 52.0, 21.7, 21.5, 20.7, 17.5; HRMS: calcd. for $C_{32}H_{36}NO_8$ [M^++1] 562.2441; found 562.2438.

***N*-Benzoyl-*O*-[α-(2-ethoxymethyl-4-methoxyphenyl)phenylacetyl]-L-threonine Isopropyl Ester (5)** Obtained as an inseparable mixture (80:20) with two regioisomers in 87% yield; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.61-7.22 (m, 11H), 6.97-6.54 (m, 3H), 5.59-5.55 (m, 1H), 5.41 (s, 1H, major), 5.30 (s, minor), 5.05-4.88 (m, 2H), 5.45 (s, 2H), 3.77 (s, minor), 3.73 (s, 3H, major), 3.55-3.44 (m, 2H), 1.34-1.16 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.5, 169.3, 167.5, 158.7, 138.6, 137.8, 133.5, 131.9, 130.4, 129.4, 129.1, 128.7, 128.6, 128.5, 127.2, 115.4, 113.1, 71.5, 71.1, 70.0, 65.7, 56.2, 55.2, 52.0, 21.8, 21.6, 17.5, 15.1; HRMS: calcd. for $C_{32}H_{38}NO_7$ [M^++1] 548.2648; found 548.2649.

References and Notes

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5. The regioisomeric ratio (rr) of **2** was determined by H-NMR of the reaction mixture and the dr of **2** was determined after reductive removal of the chiral auxiliary by chiral stationary phase-HPLC analysis of the corresponding alcohols. (see *experimental section* for details)

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7. The absolute configurations of dihydroisoquinolinones were assigned to be (*R*) by the chiral

stationary phase HPLC analysis of previously reported dihydroisoquinolinones **6** and **12**.[12a,3d] The complete inversion of stereochemistry indicates the occurrence of an S_N2-type reaction as previously observed in the various substitution of (*αR*)-α-bromo arylacetates.[4,3d]

8. We observed a wide range of er values of **22** from the reactions of 3-methoxy benzylalcohol. In all cases, the er value was lowered and eventually racemic product was obtained.
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Supporting Information. The copies of NMR spectra and HPLC chromatograms are provided in supporting information.

- Novel asymmetric synthetic method for two chiral lactams
- Friedel-Crafts alkylation of *N*-Boc-benzylamine derivatives
- Highly *ortho*-selective C-H functionalization of benzylamine derivatives
- Competing reactivities between the arene and benzylic alcohol

Declaration of interests

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

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: