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ARTICLE

Friedel-Crafts Alkylation with α-Bromo Arylacetates for the Preparation of Enantioenriched 2,2-Diarylethanols

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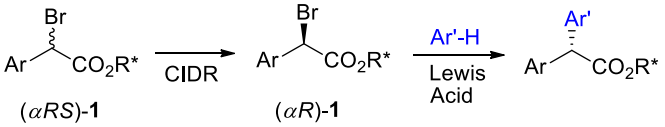
Highly enantioenriched 2,2-diarylethanols can be efficiently synthesized through the Friedel-Crafts alkylation of (hetero)arenes with configurationally labile α-bromo arylacetates. The substitution of highly diastereoenriched α-bromo arylacetates occurs in the presence of AgOTf, and the subsequent reduction affords diverse 2,2-diarylethanols with high yields and enantioselectivities up to 99:1 er. In addition, the application of this asymmetric synthetic methodology to the preparation of highly enantioenriched dihydrobenzofuran and indoline derivatives is demonstrated.

Introduction

Diarylmethine stereogenic centers are ubiquitous in many important bioactive molecules,[1] and the synthesis of optical active *gem*-diarylalkyl derivatives has been investigated in numerous studies.[2] Asymmetric Friedel-Crafts alkylation has recently been developed[3] and provide a simple and attractive method for the formation of optically active *gem*-diarylalkyl derivatives from various electrophiles.[4] Some particularly effective examples have included the Friedel–Crafts alkylation of (hetero)arenes with secondary alcohols,[4a-c] electron-deficient olefins,[4d-g] aldimines,[4h-j] and optically pure epoxides.[4k-o] Inspired by these works, we began to envision whether α-bromoacetates could be utilized as an electrophile in the Friedel–Crafts alkylation of arenes. While many methods for stereoselective substitution (S_N2) of α-bromoacetates with diverse nucleophiles have been developed by the dynamic resolution of configurationally labile α-bromoacetates, the subject of stereoselective reactions with arene nucleophiles has yet to be successfully explored.[5,6,7] The Friedel–Crafts reaction of arene nucleophiles with a secondary alkyl halide for generating a tertiary carbon center remains an unusual disconnection in asymmetric organic synthesis. In this paper, we describe a novel method for the asymmetric synthesis of 2,2-diarylethanols using the Friedel–Crafts alkylation of (hetero)arenes with highly diastereoenriched α-bromo arylacetates. The practical utility of this method is demonstrated through the preparation of highly enantioenriched dihydrobenzofuran and indoline derivatives.

We recently reported the *N*-benzoyl *L*-threonine isopropyl ester-mediated crystallization induced dynamic resolution (CIDR) of configurationally labile α-bromo arylacetates.[8] Highly diastereoenriched α-bromo arylacetate (α*R*)-**1** was obtained as a solid with a diastereomeric ratio (dr) of >99:1 and efficiently used for the asymmetric synthesis of α-substituted arylacetates under various reaction conditions. These results led us to examine the possibility that α-bromo arylacetate (α*R*)-**1** might be activated by Lewis acid and used as a chiral electrophile for the Friedel-Crafts reaction of (hetero)arene (Ar'-H) as shown in Figure 1. The stereoselective Friedel–Crafts reaction of (hetero)arene with chiral alkyl halide is a powerful way to introduce new chiral functionalities into the (hetero)arene. Given the ready availability of optically pure α-bromo arylacetates by CIDR, this simple substitution could be rather useful for the asymmetric synthesis of *gem*-diarylalkyl derivatives using a wide variety of easily available (hetero)arenes under mild conditions.



(R* = *N*-benzoyl *L*-threonine isopropyl ester)

Figure 1. The CIDR of α-bromo arylacetates and stereospecific Friedel-Crafts alkylations

Results and discussion

In order to obtain highly diastereoenriched product from the Friedel-Crafts alkylation described in Figure 1, it is important that the substitution occurs fast with respect to the epimerization, so that the epimerization of α-bromo arylacetate is minimized upon exposure to Lewis acid. We thus chose 1,2,5-trimethylpyrrole as a strong heteroarene nucleophile for our initial experiment with α-bromo phenylacetate (α*R*)-**1a**. As shown in Table 1, entry 1, no substitution of (α*R*)-**1a** with 1,2,5-trimethylpyrrole occurred without Lewis acid catalyst. We next attempted the same reaction in the presence of some selected Lewis acids. Using

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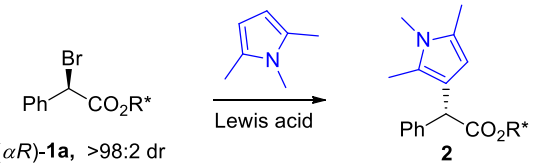
aluminum chloride ($AlCl_3$), which is the most frequently used Lewis acid in Friedel–Crafts reactions, the reaction in $CHCl_3$ for 24 h gave **2** with 56:44 dr and 30% conversion (entry 2) and the unreacted **1a** was recovered with significant epimerization (ca. 50:50 dr). Therefore, a mild activation of the C-Br bond of the α-bromoacetate is required as the strongly acidic catalysts may promote the epimerization of (αR)-**1a**. When milder conventional catalysts such as $FeCl_3$ and $SnCl_4$ were employed in place of $AlCl_3$, the reactions successfully produce **2** with substantially higher drs of 75:25 and 98:2, respectively, albeit with low conversions of 44% and 58% after 24 h (entries 3 and 4, respectively). In order to promote the reactivity of (αR)-**1a**, it is advisable to use a mild and strongly halophilic Lewis acid such as silver salts to facilitate bromide abstraction and AgBr precipitation.[9] Using Ag_2O as a Lewis acid produced the substitution product **2** with 68% conversion and 95:5 dr (entry 5). Silver trifluoroacetate (AgO_2CCF_3) and silver triflate (AgOTf) gave the substitution with high conversions and drs as shown in entries 6 and 7, respectively. AgOTf was found to be the most efficient Lewis acid for catalyzing the stereoselective substitution reaction of (αR)-**1a** with 1,2,5-trimethylpyrrole to proceed to completion within 5 min. and ultimately produced (αR)-**2** of 99:1 dr with complete inversion of the stereochemistry.[10] None of other solvents explored gave better selectivities than $CHCl_3$ and the reactions in DMF and CH_3CN are very slow.

Table 1. Alkylation of 1,2,5-trimethylpyrrole with (αR)-**1a.**



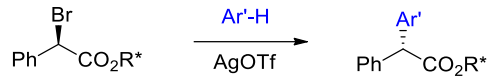
(αR)-**1a**, >98:2 dr **2**

Entry[a]	Conditions	Conversion[b]	Dr of **2**[b]
1	no catalyst	-	-
2	$AlCl_3$	30	56:44
3	$FeCl_3$	44	75:25
4	$SnCl_4$	58	98:2
5	Ag_2O	68	95:5
6	AgO_2CCF_3	99	97:3
7	AgOTf	99	99:1
8	AgOTf (0.5 h); Nuc[c]	99	80:20
9	AgOTf (1 h); Nuc[c]	99	63:37
10	AgOTf with **1a** of 52:48 dr	99	51:49
11	AgOTf with **1a** of 75:25 dr	99	75:25

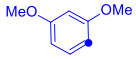
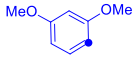
(a) All the reactions were carried out with 5.0 equiv of pyrrole and 1.0 equiv of Lewis acid in $CHCl_3$ (0.2 M) at rt for 24 h. (b) The conversions after 24 h and the dr values were determined by ^{1}H NMR of the reaction mixture. (c) Stepwise addition of AgOTf and nucleophile after the time shown in parentheses.

In the AgOTf-catalyzed nucleophilic substitution of (αR)-**1a** with 1,2,5-trimethylpyrrole nucleophiles, the substitution rate may be sufficiently fast relative to the epimerization of (αR)-**1a**, thereby giving the highly diastereoenriched product (αR)-**2** of 99:1 dr with no loss of optical purity (entry 7).[11] In order to clarify the information about the configurational lability of (αR)-**1a** in the presence of AgOTf, we carried out the reactions of stepwise addition of AgOTf and the nucleophile as shown in entries 8 and 9, respectively. When (αR)-**1a** was treated with AgOTf for 0.5 h or 1 h prior to the addition of 1,2,5-trimethylpyrrole, the product **2** was obtained with 80:20 dr and 63:37 dr, respectively. The results clearly indicate that (αR)-**1a** underwent an epimerization process in the presence of AgOTf prior to the addition of the nucleophile. In addition, the nucleophilic substitutions of **1a** of 52:48 and 75:25 drs produced **2** with 51:49 and 75:25 dr values, respectively (entries 9 and 10, respectively). The observed dependency of the product ratios on the dr of **1a** implies that no dynamic kinetic resolution of configurationally labile **1a** is operating in the nucleophilic substitution.

Table 2. Alkylations of selected (hetero)arenes with (αR)-**1a**.



(αR)-**1a**, >98:2 dr (αR)-**3-6**

Entry	Ar'-H	Conditions[a]	Product	Time to Completion[b]	Dr[c]
1		A	**3**	0.1 h	98:2
2		A	**4**	0.5 h	93:7
3		A	**5**	1 h	80:20
4		A	**6** (86:14)	3 h	60:40
5		B	**4**	0.1 h	99:1
6		B	**5**	0.5 h	98:2
7		B	**6** (92:8)	2 h	77:23
8		C	**6** (90:10)	24 h	86:14

(a) Conditions A: The reactions were carried out with 5.0 equiv of arene in $CHCl_3$ (0.2 M) at room temp.; Conditions B: neat (20 equiv of arene) at room temp.; Conditions C: neat at 0°C. (b) The time to completion was determined by ^{1}H NMR of the reaction mixture. (c) The dr values were determined by ^{1}H NMR of the reaction mixture and confirmed by chiral HPLC analysis after the removal of auxiliary.

In order to investigate the influence of nucleophilicity of (hetero)arenes on stereoselectivity in the substitutions of (αR)-**1a**, a series of (hetero)arene nucleophiles with varying nucleophilicities was selected and is presented in Table 2. The four nucleophiles that are, less reactive than 1,2,5-trimethylpyrrole, are selected to represent a range in reactivity spanning from the most reactive, 1-methylindole, to the least

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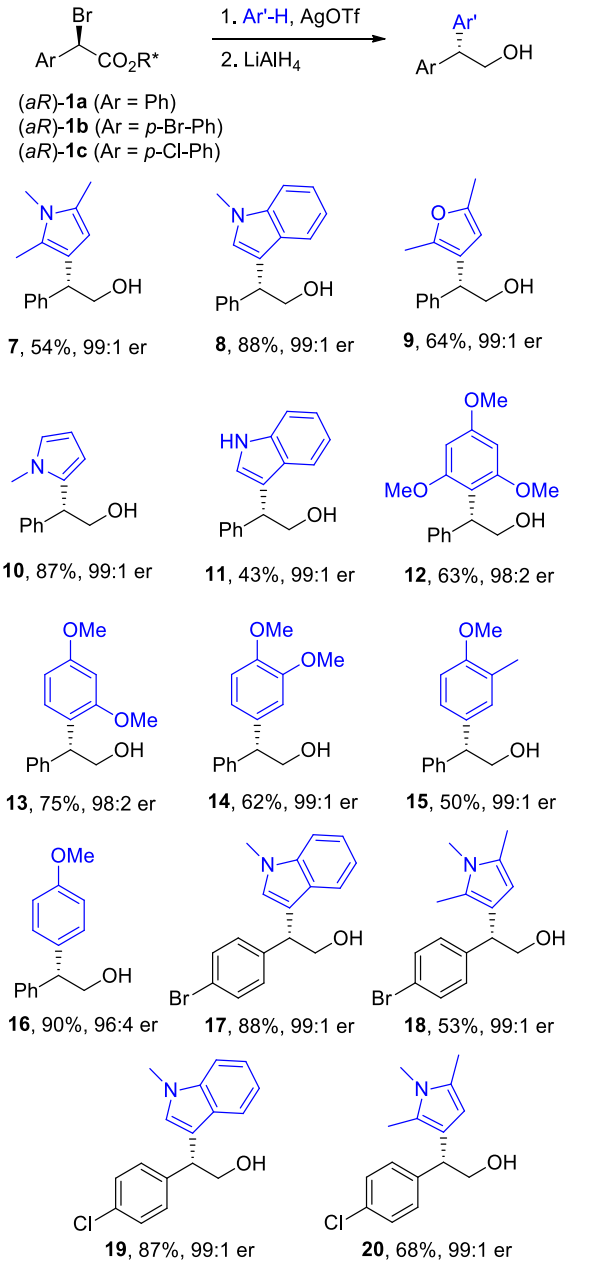
reactive, toluene.[12] When (*αR*)-**1a** was treated with 1-methylindole in $CHCl_3$ (0.2 M) at room temp. in the presence of AgOTf, the fast substitution successfully gave Friedel-Crafts alkylation product (*αR*)-**3** with 98:2 dr (Table 2, entry 1). However, when 2,5-dimethylfuran was used as the nucleophile in the presence of AgOTf, the substitution produced (*αR*)-**4** with 93:7 dr (Table 1, entry 2). The markedly diminished dr of **4** indicates that the substitution with 2,5-dimethylfuran is not sufficiently fast relative to the rate of epimerization of (*αR*)-**1a**. Additionally, in the slower substitution reaction with 1,3-dimethoxybenzene (1 h for completion), the epimerization of (*αR*)-**1a** is more likely to proceed under acidic conditions, which results in a much lower dr value of 80:20 (entry 3). As shown in entry 4, the reaction with the least reactive toluene proceeded most slowly (3 h for completion) and gave *para*-substituted product with 60:40 dr along with ortho-substituted product (86:14 regioisomeric ratio). Consistent with the previously reported nucleophilicity scale,[12] the competitive epimerization gave an erosion of product dr values in every case of reduced nucleophilicity (entries 2-4). In addition, when we carried out a competition experiment to compare the rates of substitution of 2,5-dimethylfuran, 1,3-dimethoxybenzene and toluene, the reaction gave a mixture of **4**, **5**, and **6** in a ratio of 9:5:1, respectively. From these results, it can clearly be seen that the stereoselectivity significantly depends on the reactivity of the (hetero)arene nucleophiles.[13]

In order to increase the rate of substitution with respect to the epimerization, we explored the utility of neat conditions with excess amounts of nucleophile (20 equiv). As shown in entries 5 and 6, the neat reactions of (*αR*)-**1a** with the nucleophiles in the presence of AgOTf are completed faster than the solution reaction shown in entries 2 and 3, respectively. The reactions under neat conditions afforded (*αR*)-**4** and (*αR*)-**5** with substantially better drs of 99:1 and 98:2, respectively. However, the reaction of the least reactive toluene produced (*αR*)-**6** with a slightly improved dr of 77:23 under neat conditions (entry 7). Lowering the reaction temperature to 0°C produced (*αR*)-**6** with 86:14 dr, while the reaction was very slow (entry 8).

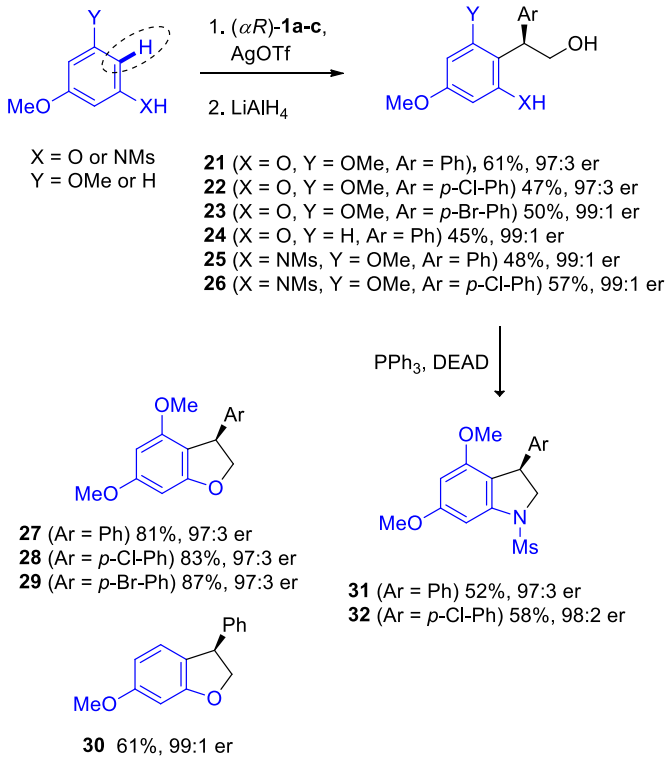
Chiral 2,2-diarylethanols are important intermediates in the organic syntheses of many biologically active compounds.[2] Highly enantioenriched 2,2-diarylethanols can be obtained using the Friedel-Crafts alkylation method developed in Tables 1 and 2 along with the following reduction to remove the chiral auxiliary. In order to evaluate the scope of the reactions leading to highly enantioenriched diarylethanols, we examined the Friedel-Crafts reactions of **1a-c** with five selected heteroarenes and five selected anisole derivatives and the results are summarized in Scheme 1. The Friedel-Crafts reactions proceeded efficiently in the presence of AgOTf under neat conditions using 10 equiv of (hetero)arene and the subsequent reduction with $LiAlH_4$ afforded 2,2-diarylethanols **7**-**20** with high enantioselectivities up to an enantiomeric ratio (er) of 99:1. We investigated the feasibility of a procedure that avoids the purification of the acetate product and uses the crude material in the subsequent reduction step. After the extractive workup of the reaction mixture of Friedel-Crafts reaction, subjecting the



Scheme 1. Highly enantioenriched 2,2-diarylethanols

crude reaction mixture to the reduction condition afforded 2,2-diarylethanols in comparable overall yields ranging from 43% to 90%. The highly regioselective substitutions of (*αR*)-**1a** at the 3-position of 1,2,5-trimethylpyrrole, 3-position of 1-methylindole, 3-position of 1,5-dimethylfuran, 2-position of 1-methylpyrrole and 3-position of indole and following reduction produced 2,2-diarylethanols **7**, **8**, **9**, **10** and **11**, respectively with 99:1 er. In addition, the highly regioselective Friedel-Crafts reactions of (*αR*)-**1a** with 1,3,5-trimethoxybenzene, 1,3-dimethoxybenzene, 1,2-dimethoxybenzene, and 2-methylanisole under neat conditions using 10 equiv of (hetero)arene and the subsequent reduction produced 2,2-diarylethanols **12**, **13**, **14** and **15**, respectively with >98:2 er. In the substitution with the most

weakly nucleophilic anisole, the competitive epimerization gave a slight reduction of enantioselectivity to afford **16** with 96:4 er. The same two-step reactions of *p*-bromophenylacetate **1b** and *p*-chloro phenylacetate **1c** with 1-methylindole and 1,2,5-trimethylpyrrole afforded 2,2-diarylethanols **17-20** with 99:1 er in overall yields of 88–53%.



Scheme 2. Preparation of highly enantioenriched 3-aryl substituted 2,3-dihydrobenzofuran and indoline derivatives.

Furthermore, to extend the applicability of the present methodology, we explored the asymmetric synthesis of 3-aryl substituted dihydrobenzofuran and indoline derivatives, the core structures present in a number of important pharmaceuticals and natural products.[14] Our approach to these heterocycles is based on the Friedel-Crafts alkylation at the *ortho* position of phenol or aniline derivatives with α-bromo arylacetates **1a-c**, followed by reduction and cyclodehydration as shown in Scheme 2. With the 3,5-dimethoxyphenol nucleophile, the *C*-alkylation at the *ortho* position to the hydroxy group was maximized, and the following reduction provided *ortho*-substituted phenol **21** with 97:3 er in 61% overall yield without any isomers derived from *O*-alkylation and *para*-*C*-alkylation. When the cyclodehydration of **21** proceeded by means of an intramolecular Mitsunobu protocol (DEAD, PPh_3), 3-phenyl substituted dihydrobenzofuran **27** was produced in 81% yield without racemization. The three-step synthetic method was readily extended to *p*-bromo and *p*-chloro substituted arylacetates **1b** and **1c** to give dihydrobenzofurans **28** and **29**, respectively with 97:3 er in excellent yields. In addition, we observed that the substitution of **1a** with *meta*-methoxyphenol and following reduction produced *ortho*-substituted phenol **24** in 45% yield with 99:1 er and a regioisomeric *para*-substituted phenol as a minor product in a ratio of 2:1. When major product **24** was treated with DEAD and PPh_3, 6-methoxy-3-phenyl-dihydrobenzofuran **30** was produced in 61% yield with 99:1 er.

We also attempted to synthesize 3-aryl substituted indolines from *N*-protected aniline derivatives using similar protocols. In the Friedel-Crafts reaction of *N*-acyl protected 3,5-dimethoxyaniline with (α*R*)-**1a**, we observed that only *ortho*-*C*-alkylation product was afforded successfully with 99:1 dr and that no other regioisomer was detected. However, the reduction of the substitution product initially proved to be problematic. Using $LiAlH_4$ in THF at room temperature provided 2,2-diarylethanol in low yields of 5-10%. The other procedures including the use of DIBAL or $LiBH_4$ did not proceed properly. We found that the use of $NaBH_4$ in methanol cleanly provided 2,2-diarylethanol in high yield, but with a somewhat reduced er of 90:10 after the reduction. In order to circumvent the low yield and low er of the 2,2-diarylethanol, we examined *N*-mesyl-protected 3,5-dimethoxyaniline as a nucleophile under the same conditions. Pleasingly, the substitution reactions of **1a** and **1c** with *N*-mesyl-3,5-dimethoxyaniline and the subsequent reduction by $LiAlH_4$ produced *ortho*-substituted anilines **25** and **26**, respectively with a high er of 99:1. When they were treated with DEAD and PPh_3, 3-aryl substituted indolines **31** and **32** were successfully produced in yields of 52 and 58% with 97:3 er and 98:2 er, respectively.

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. ^1H and ^{13}C NMR spectra were acquired on Bruker (400 MHz ^1H, 100.6 MHz ^{13}C) or Jeol (500 MHz ^1H, 125 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 ^1H, 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. HRMS spectra were measured on a JEOL JMS-700 by using FAB method.

General Procedure for the asymmetric preparation of 2,2-diarylacetates 2-6 (conditions B): To a solution of *L*-threonine-derived α-bromo ester **1a** (1.0 equiv, >99:1 dr) at room temperature were added a nucleophile (20 equiv) and AgOTf (1.0 equiv). After the mixture was stirred at rt for the specified time (Table 2), the resulting mixture was washed with saturated $NaHCO_3$ solution, dried with anhydrous $MgSO_4$, filtered, concentrated and purified by column chromatography to afford a diarylacetate (**2**-**6**). The dr of **2-6** was determined by the ^1H NMR integration of the hydrogens of the two diastereomers.

***N*-Benzoyl-*O*-[α-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)phenylacetyl]-L-threonine Isopropyl Ester (2)** A yellow oil was obtained in 90% yield with 99:1 dr from **1a**. ^1H NMR ($CDCl_3$, 400 MHz) 7.66-7.20 (m, 10H), 6.55 (d, *J* = 9.2 Hz, 1H), 5.83 (s, 1H), 5.56-5.50 (m, 1H),

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4.96-4.87 (m, 2H), 4.85 (s, 1H), 3.29 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1, 169.2, 167.4, 139.8, 133.8, 131.8, 128.6, 128.4, 128.3, 127.2, 127.1, 126.8, 124.9, 114.6, 105.3, 71.1, 69.9, 56.2, 49.6, 30.2, 21.8, 21.5, 17.5, 12.5, 10.2; HRMS: calcd. for $C_{29}H_{35}N_2O_5$ [M^++1] 491.2546; found 491.2548.

***N*-Benzoyl-*O*-[α-(1-methyl-1*H*-indol-3-yl)phenylacetyl]-L-threonine Isopropyl Ester (3)** A yellow oil was obtained in 92% yield with 98:2 dr from **1a**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.47-6.98 (m, 15H), 6.54 (d, *J* = 9.2 Hz, 1H), 5.62-5.56 (m, 1H), 5.56 (s, 1H), 4.98-4.91 (m, 2H), 3.67 (s, 3H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.7, 169.3, 167.5, 138.4, 137.1, 133.6, 131.9, 128.6, 128.4, 128.0, 127.3, 127.2, 127.0, 122.0, 119.3, 111.7, 109.4, 71.7, 70.0, 56.1, 49.2, 32.8, 21.8, 21.6, 17.3; HRMS: calcd. for $C_{31}H_{33}N_2O_5$ [M^++1] 513.2389; found 513.2389.

***N*-Benzoyl-*O*-[α-(2,5-dimethylfuran-3-yl)phenylacetyl]-L-threonine Isopropyl Ester (4)** A yellow oil was obtained in 89% yield with 99:1 dr from **1a**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.69-7.24 (m, 15H), 6.58 (d, *J* = 9.2 Hz, 1H), 6.01 (s, 1H), 5.57-5.51 (m, 1H), 4.99-4.92 (m, 2H), 4.75 (s, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 1.33 (d, *J* = 6.4 Hz, 3H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.2, 169.2, 167.5, 149.8, 146.8, 138.4, 133.7, 131.9, 128.7, 128.0, 127.2, 127.1, 116.7, 106.9, 71.7, 70.0, 56.0, 48.2, 21.8, 21.4, 17.3, 13.5, 11.6; HRMS: calcd. for $C_{28}H_{32}NO_6$ [M^++1] 478.2230; found 478.2231.

***N*-Benzoyl-*O*-[α-(2,4-dimethoxylphenyl)phenylacetyl]-L-threonine Isopropyl Ester (5)** A yellow oil was obtained in 96% yield with 98:2 dr from **1a**. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.59-7.25 (m, 10H), 6.91 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 9.2 Hz, 1H), 6.45-6.39 (m, 2H), 5.59-5.45 (m, 1H), 5.24 (s, 1H), 5.05-4.89 (m, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 1.30 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.19 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 171.7, 169.3, 167.5, 160.3, 157.9, 137.9, 131.9, 129.8, 129.1, 128.7, 128.6, 127.3, 127.2, 120.1, 104.1, 98.6, 71.4, 69.9, 56.2, 55.5, 55.4, 50.9, 21.8, 21.7, 17.3; HRMS: calcd. for $C_{30}H_{34}NO_7$ [M^++1] 520.2335; found 520.2336.

***N*-Benzoyl-*O*-[α-(4-methylphenyl)phenylacetyl]-L-threonine Isopropyl Ester (6)** A mixture of inseparable two regioisomers (90:10) was obtained in 85% yield from **1a**. ^{1}H NMR ($CDCl_3$, 500 MHz, major regioisomer) 7.68-7.11 (m, 14H), 6.55 (d, *J* = 9.2 Hz, 1H), 5.61-5.59 (m, 1H), 4.98-4.89 (m, 3H), 2.31 (s, 3H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.13 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 171.4, 169.3, 167.6, 138.6, 137.1, 135.5, 133.7, 131.9, 129.0, 129.4, 128.7, 128.6, 128.5, 128.0, 127.4, 127.3, 71.7, 70.1, 57.0, 56.1, 21.8, 21.6, 21.2, 17.3; HRMS: calcd. for $C_{29}H_{32}NO_5$ [M^++1] 474.2280; found 474.2281.

General Procedure for the asymmetric preparation of 2,2-diarylethanols 7-26: To a solution of *L*-threonine-derived α-bromo ester **1a-c** (1.0 equiv, >99:1 dr) at room temperature were added a nucleophile (10 equiv) and AgOTf (1.0 equiv). (if needed for solubility reason, we used least possible amount of solvent, $CHCl_3$.) After the mixture was stirred at rt for 0.5 h, the resulting mixture was washed with saturated $NaHCO_3$ solution, dried with anhydrous $MgSO_4$, filtered, and concentrated. To a solution of 2,2-diarylacetate (crude material after work-up) in THF (0.5 M) was added the solution of $LiAlH_4$ (1.0 M in THF, 3 equiv) at 0˚C, and 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 a highly enantioenriched a 2,2-diarylethanol (**7**-**26**). The ers of **7**-**26** were determined by CSP-HPLC.

(*R*)-2-Phenyl-2-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)ethanol (7) A yellow oil was obtained in 54% overall yield from **1a**. The spectral data of **7** were identical to those of the authentic material reported previously.[4n] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.27-7.09 (m, 5H), 5.81 (s, 1H), 4.06-4.03 (m, 1H), 3.97-3.92 (m, 2H), 3.33 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H), 1.72 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 143.1, 128.5, 128.0, 127.5, 126.3, 125.2, 117.0, 66.9, 45.9, 30.3, 12.6, 10.2; Chiral HPLC: >99:1 er, t_R (*R*)-major enantiomer, 29.9 min; t_R (*S*)-minor enantiomer, 33.7 min; (Chiralcel OD column; 3% 2-propanol in hexane; 0.5 mL/min).

(*R*)-2-(1-Methyl-1*H*-indol-3-yl)-2-phenylethanol (8) A yellow oil was obtained in 88% overall yield from **1a**. The spectral data of **8** were identical to those of the authentic material reported previously.[15a,4n,4k] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.46-7.18 (m, 8H), 7.05-7.02 (m, 1H), 6.94 (s, 1H), 4.48-4.45 (m, 1H), 4.23-4.11 (m, 2H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 141.8, 137.2, 128.7, 128.3, 127.5, 126.7, 121.9, 119.5, 119.1, 114.4, 109.3, 66.5, 45.6, 32.8; $[\alpha]_D^{20}$ = +1.2° (c = 0.021, $CHCl_3$); Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 36.4 min; t_R (*S*)-minor enantiomer, 19.6 min; (Chiralcel OD column; 20% 2-propanol in hexane; 0.5 mL/min).

(*R*)-2-(2,5-Dimethylfuran-3-yl)-2-phenylethanol (9) A yellow oil was obtained in 64% overall yield from **1a**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.33-7.20 (m, 5H), 5.92 (s, 1H), 4.00-3.90 (m, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 1.56 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 150.0, 147.0, 141.4, 128.7, 127.9, 126.7, 118.9, 105.5, 66.3, 44.6, 13.6, 11.7; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 29.4 min; t_R (*S*)-minor enantiomer, 39.8 min; (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{14}H_{17}O_2$ [M^+ + 1] 217.1229; found 217.1228.

(*R*)-2-Phenyl-2-(1-methyl-1*H*-pyrrol-2-yl)ethanol (10) A colorless oil was obtained in 87% overall yield from **1a**. The spectral data of **10** were identical to those of the authentic material reported previously.[15b,4n] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.31-7.14 (m, 5H), 6.59-6.58 (m, 1H), 6.17-6.14 (m, 2H), 4.19-4.15 (m, 1H), 4.11-4.06 (m, 1H), 3.97-3.91 (m, 1H), 3.32 (s, 3H), 1.85 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.2, 131.6, 128.8, 128.3, 127.0, 122.5, 106.8, 105.5, 66.4, 46.5, 33.8; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 26.3 min; t_R (*S*)-minor enantiomer, 19.2 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min).

(*R*)-2-(1*H*-indol-3-yl)-2-phenylethanol (11) A colorless oil was obtained in 43% overall yield from **1a**. The spectral data of **11** were identical to those of the authentic material reported previously.[15a,4n,4k] ^{1}H NMR ($CDCl_3$, 500 MHz) 8.09 (br, 1H), 7.46-7.03 (m, 9H), 4.49 (t, *J* = 6.9 Hz, 1H), 4.25 (dd, *J* = 6.9 and 10.9 Hz, 1H), 4.25 (dd, *J* = 7.2 and 10.9 Hz, 1H), 1.67 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 141.7, 136.6, 128.7, 128.4, 127.1, 126.9, 122.4, 122.0, 119.7, 119.5, 116.1, 111.3, 66.5, 45.7; Chiral HPLC: 99:1

er, t_R (*R*)-major enantiomer, 71.4 min; t_R (*S*)-minor enantiomer, 60.2 min; $[\alpha]_D^{20}$ = +10.3° (c = 0.010, $CHCl_3$); (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min).

(*R*)-2-(2,4,6-Trimethoxyphenyl)-2-phenylethanol (12) A colorless oil was obtained in 63% overall yield from **1a**. The spectral data of **12** were identical to those of the authentic material reported previously.[15c] ^{1}H NMR ($CDCl_3$, 500 MHz) 7.29-7.11 (m, 5H), 6.14 (s, 2H), 4.82-4.79 (m, 1H), 4.29-4.27 (m, 2H), 3.79 (s, 3H), 3.73 (s, 6H), 1.68 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.2, 159.6, 142.6, 128.1, 128.0, 125.8, 110.8, 91.5, 65.0, 55.8, 55.4, 43.4; $[\alpha]_D^{20}$ = +11.5° (c = 0.011, $CHCl_3$); Chiral HPLC: 98:2 er, t_R (*R*)-major enantiomer, 30.7 min; t_R (*S*)-minor enantiomer, 26.5 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min).

(*R*)-2-(2,4-Dimethoxyphenyl)-2-phenylethanol (13) A yellow oil was obtained in 75% overall yield from **1a**. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.30-7.17 (m, 5H), 7.08-7.06 (m, 1H), 6.47-6.45 (m, 2H), 4.59-4.56 (m, 1H), 4.15-4.08 (m, 2H), 3.75 (s, 6H), 1.66 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 159.7, 158.5, 141.8, 128.8, 128.5, 126.5, 122.3, 104.3, 99.0, 65.5, 55.6, 55.4, 46.1; Chiral HPLC: 98:2 er, t_R (*R*)-major enantiomer, 38.1 min; t_R (*S*)-minor enantiomer, 20.9 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{16}H_{19}O_3$ [M^++1] 259.1334; found 259.1333.

(*R*)-2-(3,4-Dimethoxyphenyl)-2-phenylethanol (14) A pale yellow oil was obtained in 62% overall yield from **1a**. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.31-7.22 (m, 5H), 6.83-6.76 (m, 3H), 4.17-4.09 (m, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 1.63 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 149.2, 148.0, 141.7, 134.0, 128.8, 128.3, 126.9, 120.2, 112.0, 111.4, 66.3, 56.0, 55.9, 53.3; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 57.9 min; t_R (*S*)-minor enantiomer, 42.0 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{16}H_{19}O_3$ [M^++1] 259.1334; found 259.1334.

(*R*)-2-(4-Methoxy-3-methylphenyl)-2-phenylethanol (15) A yellow oil was obtained in 50% overall yield from **1a**. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.33-7.21 (m, 5H), 7.11-7.03 (m, 2H), 6.82-6.79 (m, 1H), 4.18-4.09 (m, 3H), 3.80 (s, 3H), 2.22 (s, 3H), 1.65 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.1, 142.0, 133.1, 130.8, 128.8, 128.3, 126.8, 126.6, 126.5, 110.2, 66.4, 55.4, 53.0, 16.5; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 104.2 min; t_R (*S*)-minor enantiomer, 88.2 min; (Chiralcel OJ-H column; 5% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{16}H_{19}O_2$ [M^++1] 243.1385; found 243.1383.

(*R*)-2-(4-Methoxyphenyl)-2-phenylethanol (16) A colorless oil was obtained in 90% overall yield from **1a**. The spectral data of **16** were identical to those of the authentic material reported previously.[15c] ^{1}H NMR ($CDCl_3$, 500 MHz) 7.32-7.17 (m, 7H), 6.86 (d, *J* = 6.8 Hz, 2H), 4.16-4.12 (m, 3H), 3.78 (s, 3H), 1.51 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.5, 141.8, 133.5, 129.4, 128.8, 128.6, 128.5, 128.3, 126.8, 114.2, 66.3, 55.4, 52.9; Chiral HPLC: 96:4 er, t_R (*R*)-major enantiomer, 86.5 min; t_R (*S*)-minor enantiomer, 83.2 min; (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min).

(*R*)-2-(4-Bromophenyl)-2-(1-methyl-1*H*-indol-3-yl)ethanol (17) A colorless oil was obtained in 88% overall yield from **1b**. The spectral data of **17** were identical to those of the authentic material reported previously.[15a] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.42-7.02 (m, 8H), 6.93 (s, 1H), 4.43-4.40 (m, 1H), 4.19-4.11 (m, 2H), 3.76 (s, 3H), 1.61 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 141.0, 137.3, 131.7, 130.1, 127.2, 126.8, 122.0, 120.5, 119.3, 119.2, 113.9, 109.4, 66.2, 45.0, 32.8; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 33.2 min; t_R (*S*)-minor enantiomer, 20.3 min; (Chiralcel OD column; 20% 2-propanol in hexane; 0.5 mL/min).

(*R*)-2-(4-Bromophenyl)-2-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)ethanol (18) A yellow oil was obtained in 53% overall yield from **1b**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.39 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 5.77 (s, 1H), 4.03-3.91 (m, 3H), 3.35 (s, 3H), 2.19 (s, 3H), 2.09 (s, 3H), 1.62 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 142.2, 131.5, 129.8, 127.7, 125.3, 120.0, 103.4, 66.6, 45.3, 30.2, 12.5, 10.2; Chiral HPLC: >99:1 er, t_R (*R*)-major enantiomer, 36.1 min; t_R (*S*)-minor enantiomer, 43.0 min; (Chiralcel OD column; 3% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{15}H_{19}BrNO$ [M^++1] 308.0650; found 308.0653.

(*R*)-2-(4-Chlorophenyl)-2-(1-methyl-1*H*-indol-3-yl)ethanol (19) A colorless oil was obtained in 87% overall yield from **1c**. The spectral data of **19** were identical to those of the authentic material reported previously.[15d] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40-7.01 (m, 8H), 6.92 (s, 1H), 4.43-4.39 (m, 1H), 4.17-4.08 (m, 2H), 3.74 (s, 3H), 1.70 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 140.5, 137.3, 132.4, 129.7, 128.7, 127.3, 126.7, 122.0, 119.4, 119.2, 114.0, 109.4, 66.2, 45.0, 32.8; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 61.9 min; t_R (*S*)-minor enantiomer, 37.8 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min).

(*R*)-2-(4-Chlorophenyl)-2-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)ethanol (20) A pale yellow oil was obtained in 68% overall yield from **1c**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.24-7.19 (m, 4H), 5.77 (s, 1H), 4.04-3.90 (m, 3H), 3.34 (s, 3H), 2.18 (s, 3H), 2.08 (s, 3H), 1.71 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 141.7, 131.9, 129.4, 128.6, 127.7, 125.3, 116.5, 103.4, 66.7, 45.2, 30.2, 12.5, 10.2; Chiral HPLC: >99:1 er, t_R (*R*)-major enantiomer, 33.6 min; t_R (*S*)-minor enantiomer, 36.2 min; (Chiralcel OD column; 3% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{15}H_{19}ClNO$ [M^++1] 264.1155; found 264.1155.

(*R*)-2-(2-Hydroxy-4,6-dimethoxyphenyl)-2-phenylethanol (21) A yellow oil was obtained in 61% overall yield from **1a**. The spectral data of **21** were identical to those of the authentic material reported previously.[15e] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.23-7.11 (m, 5H), 6.09 (d, *J* = 2.4 Hz, 1H), 6.04 (d, *J* = 2.4 Hz, 1H), 4.80 (dd, *J* = 2.8 and 4.8 Hz, 1H), 4.33 (dd, *J* = 5.2 and 11.2 Hz, 1H), 4.05 (dd, *J* = 2.8 and 10.8 Hz, 1H), 3.69 (s, 3H), 3.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 160.1, 159.1, 157.0, 140.8, 128.5, 128.1, 126.3, 109.2, 95.0, 91.4, 65.7, 55.9, 55.3, 41.7; Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 38.1 min; t_R (*S*)-minor enantiomer, 32.6 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min).

(*R*)-2-(4-Chlorophenyl)-2-(2-hydroxy-4,6-dimethoxyphenyl)ethanol (22) A brownish yellow oil was obtained in 47% overall yield from **1b**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.23-7.17 (m, 4H), 6.10 (d, *J* = 2.4 Hz, 1H), 6.06 (d, *J* = 2.4 Hz, 1H), 4.80 (dd, *J* = 3.2 and 4.4 Hz, 1H), 4.38 (dd, *J* = 4.8 and 10.8 Hz, 1H), 4.10 (dd, *J* = 3.2 and 11.2 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz)160.2, 158.9, 156.9, 139.2, 132.0, 129.4, 128.5, 108.7, 95.0, 91.3, 65.6, 55.8, 55.3, 41.0; Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 32.0 min; t_R (*S*)-minor

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enantiomer, 29.3 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{16}H_{18}ClO_4$ [M⁺+1] 309.0894; found 309.0893.

(*R*)-2-(4-Bromophenyl)-2-(2-hydroxy-4,6-dimethoxyphenyl)ethanol (23) A brownish yellow oil was obtained in 50% overall yield from **1c**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.40 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.14 (m, 2H), 4.82 (br, 1H), 4.38 (dd, *J* = 5.2 and 10.8 Hz, 1H), 4.14 (dd, *J* = 2.8 and 10.4 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 160.1, 159.2, 156.6, 140.4, 131.3, 130.0, 120.0, 109.0, 95.1, 91.5, 65.2, 55.9, 55.3, 41.4; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 36.6 min; t_R (*S*)-minor enantiomer, 33.6 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{16}H_{18}BrO_4$ [M⁺+1] 353.0388; found 353.0390.

(*R*)-2-(2-Hydroxy-4-methoxyphenyl)-2-phenylethanol (24) A colorless oil was obtained in 45% overall yield from **1a**. The spectral data of **24** were identical to those of the authentic material reported previously.[15e] ^{1}H NMR ($CDCl_3$, 500 MHz) 7.72 (br, 1H), 7.39-7.18 (m, 3H), 6.95-6.83 (m, 1H), 6.47-6.38 (s, 2H), 4.41-4.33 (m, 1H), 4.22-4.11 (m, 2H), 3.71 (s, 3H), 2.87 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 159.7, 155.7, 140.7, 130.5, 128.8, 128.4, 126.9, 120.9, 106.3, 102.9, 66.6, 55.4, 47.9; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 37.6 min; t_R (*S*)-minor enantiomer, 35.7 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{15}H_{17}O_3$ [M⁺+1] 245.1178; found 245.1178.

(*R*)-2-(4-Hydroxy-2-methoxyphenyl)-2-phenylethanol (24-minor) A colorless oil was obtained in 23% overall yield from **1a**. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.31-7.18 (m, 5H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 6.35 (dd, *J* = 2.3 and 8.0 Hz, 1H), 4.69 (br, 1H), 4.38 (t, *J* = 7.5 Hz, 1H), 4.10 (m, 2H), 3.76 (s, 3H), 1.54 (br, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 158.6, 155.5, 141.7, 129.0, 128.6, 128.5, 126.5, 122.2, 107.0, 99.3, 65.5, 55.6, 46.0; HRMS: calcd. for $C_{15}H_{17}O_3$ [M⁺+1] 245.1178; found 245.1179.

(*R*)-2-(2-Mesylamino-4,6-dimethoxyphenyl)-2-phenylethanol (25) A yellow oil was obtained in 48% overall yield from **1a**. ^{1}H NMR ($CDCl_3$, 500 MHz) 8.82 (br, 1H), 7.34-7.15 (m, 5H), 6.87 (s, 1H), 6.34 (s, 1H), 4.95-4.93 (m, 1H), 4.57-4.54 (m, 1H), 4.13-4.09 (m, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 2.92 (br, 1H), 2.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.1, 159.0, 142.4, 138.2, 128.7, 128.0, 126.3, 115.4, 98.4, 95.6, 64.8, 56.1, 55.5, 40.4, 38.4; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 28.2 min; t_R (*S*)-minor enantiomer, 39.3 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{17}H_{22}NO_5S$ [M⁺+1] 352.1219; found 352.1218.

(*R*)-2-(4-Chlorophenyl)-2-(2-mesylamino-4,6-dimethoxyphenyl)ethanol (26) A yellow oil was obtained in 57% overall yield from **1c**. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.25-7.22 (m, 4H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.33 (d, *J* = 2.9 Hz, 1H), 4.87 (br, 1H), 4.49-4.47 (m, 1H), 4.11-4.07 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.23 (br, 1H), 2.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) 160.2, 159.0, 140.6, 138.0, 132.0, 129.4, 128.6, 115.1, 98.6, 95.7, 64.7, 56.0, 55.5, 40.1, 38.8; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 82.1 min; t_R (*S*)-minor enantiomer, 89.3 min; (Chiralcel OD column; 5% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{17}H_{21}ClNO_5S$ [M⁺+1] 386.0829; found 386.0826.

General procedure for the asymmetric preparation of dihydrobenzofurans 27-30 and indolines 31-32: To a solution of 2,2-diarylethanol in CH_3CN (0.5 M) was added PPh_3 (2.5 equiv) and DEAD (2.5 equiv) and the mixture was stirred at room temperature for 2 h. After the solvent was removed in vacuo, chromatographic separation of the crude mixture on silica gel (EtOAc/hexanes solvents) afforded a cyclized protduct.

(*R*)-4,6-Dimethoxy-3-phenyl-2,3-dihydrobenzofuran (27) A colorless oil was obtained in 81% overall yield from **21**. The spectral data of **27** were identical to those of the authentic material reported previously.[4m] ^{1}H NMR ($CDCl_3$, 400 MHz) 7.24-7.11 (m, 5H), 6.12 (d, *J* = 1.6 Hz, 1H), 5.98 (d, *J* = 2.0 Hz, 1H), 4.81-4.77 (m, 1H), 4.52 (dd, *J* = 4.0 and 8.8 Hz, 1H), 4.41 (dd, *J* = 4.4 and 8.4 Hz, 1H), 3.72 (s, 3H), 3.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 162.4, 162.3, 157.3, 143.8, 128.6, 127.3, 126.6, 109.6, 91.7, 88.5, 80.5, 55.6, 55.4, 46.1; Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 14.9 min; t_R (*S*)-minor enantiomer, 11.8 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min).

(*R*)-3-(4-Chlorophenyl)-4,6-dimethoxy-2,3-dihydrobenzofuran (28) A colorless oil was obtained in 83% overall yield from **22**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.19 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.11 (d, *J* = 2.0 Hz, 1H), 5.98 (d, *J* = 2.0 Hz, 1H), 4.80-4.76 (m, 1H), 4.49 (dd, *J* = 4.4 and 9.2 Hz, 1H), 4.36 (dd, *J* = 4.4 and 8.8 Hz, 1H), 3.72 (s, 3H), 3.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 162.5, 162.3, 157.1, 142.3, 132.3, 128.6, 109.2, 91.7, 88.5, 80.2, 55.5, 55.3, 45.4; Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 14.6 min; t_R (*S*)-minor enantiomer, 11.2 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{16}H_{16}ClO_3$ [M⁺+1] 291.0788; found 291.0786.

(*R*)-3-(4-Bromophenyl)-4,6-dimethoxy-2,3-dihydrobenzofuran (29) A colorless oil was obtained in 87% overall yield from **23**. ^{1}H NMR ($CDCl_3$, 400 MHz) 7.21 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 7.6 Hz, 2H), 6.00 (s, 1H), 5.86 (s, 1H), 4.68-4.63 (m, 1H), 4.35 (dd, *J* = 4.0 and 9.2 Hz, 1H), 4.23 (dd, *J* = 4.4 and 8.8 Hz, 1H), 3.61 (s, 3H), 3.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 162.8, 162.3, 157.1, 142.8, 131.6, 129.1, 120.4, 109.8, 91.7, 88.6, 80.1, 55.6, 55.3, 45.5; Chiral HPLC: 97:3 er, t_R (*R*)-major enantiomer, 16.1 min; t_R (*S*)-minor enantiomer, 11.9 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min $C_{16}H_{16}BrO_3$ [M⁺+1] 335.0283; found 335.0285.

(*R*)-3-Phenyl-6-methoxy-2,3-dihydrobenzofuran (30) A colorless oil was obtained in 61% overall yield from **24**. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.31-7.19 (m, 5H), 6.89 (m, 1H), 6.47-6.40 (m, 2H), 4.93-4.90 (m, 1H), 4.68-4.62 (m, 1H), 4.44-4.40 (m, 1H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 161.6, 160.8, 143.3, 128.9, 127.8, 127.1, 125.4, 122.7, 106.6, 96.2, 80.2, 55.6, 48.0; Chiral HPLC: 99:1 er, t_R (*R*)-major enantiomer, 31.1 min; t_R (*S*)-minor enantiomer, 48.3 min; (Chiralcel OJ-H column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{15}H_{15}O_2$ [M⁺+1] 227.1072; found 227.1072.

(*R*)-4,6-Dimethoxy-1-methanesulfonyl-3-phenylindoline (31) A pale yellow sticky oil was obtained in 52% overall yield from **25**. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.39-7.09 (m, 5H), 6.75 (d, *J* = 1.7 Hz, 1H), 6.17 (d, *J* = 2.3 Hz, 1H), 4.52-4.49 (m, 1H), 4.29-4.25 (m, 1H), 3.98-3.94 (m, 1H), 3.83 (s, 3H), 3.64 (s, 3H), 2.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 162.4, 157.3, 144.1, 143.2, 128.7, 127.1, 126.9, 113.4, 94.7, 91.9, 60.1, 55.8, 55.5, 43.0, 34.9; Chiral HPLC: 97:3

er, t_R (*R*)-major enantiomer, 51.9 min; t_R (*S*)-minor enantiomer, 31.4 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min); HRMS: calcd. for $C_{17}H_{20}NO_4S$ [M^++1] 334.1113; found 334.1112.

(*R*)-3-(4-Chlorophenyl)-4,6-dimethoxy-1-methanesulfonylindoline (32) A yellow sticky oil was obtained in 58% overall yield from **26**. ^{1}H NMR ($CDCl_3$, 500 MHz) 7.23 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.16 (d, *J* = 1.8 Hz, 1H), 4.48-4.46 (m, 1H), 4.26-4.22 (m, 1H), 3.91 (dd, *J* = 3.5 and 10.4 Hz, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 2.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 162.6, 157.2, 144.0, 141.7, 132.7, 128.8, 128.5, 113.0, 94.6, 91.9, 59.8, 55.8, 55.5, 42.5, 34.8; Chiral HPLC: 93:7 er, t_R (*R*)-major enantiomer, 48.6 min; t_R (*S*)-minor enantiomer, 28.6 min; (Chiralcel OD column; 10% 2-propanol in hexane; 0.6 mL/min); HRMS: calcd. for $C_{17}H_{19}ClNO_4S$ [M^++1] 368,0723; found 368.0722.

Conclusions

The simple procedure described in this paper provides a novel protocol for the asymmetric Friedel-Crafts alkylations of diverse biologically important (hetero)arenes such as pyrrole, indole, furan and anisole derivatives, by using α-bromo arylacetates as a new type of electrophiles. The direct C-H functionalization of the (herero)arenes with highly diastereoenriched α-bromo arylacetates is promoted in the presence of AgOTf, and subsequent reduction can afford highly enantioenriched 2,2-diarylethanols. Because highly diastereoenriched α-bromo arylacetates are readily available, our approach could serve as a new and very attractive tool in the asymmetric synthesis of various diarylmethine containing natural products. The capacity to introduce new chiral functionalities into the (hetero)arene allows for a diverse range of synthetic elaboration. An example of the synthetic utility of the methodology is demonstrated through the asymmetric synthesis of diarylmethine containing dihydrobenzofuran and indoline derivatives.

Conflicts of interest

There are no conflicts to declare.

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10 The absolute configuration of the products obtained by the reaction of (*αR*)-**1a** with pyrroles, indoles and anisole derivatives were assigned to be (*R*) by comparing the chiral HPLC analysis and/or the optical rotation of previously reported 2,2-diarylethanols **7**, **8**, **10**, **11**, and **12**.[4k,4n,15c] The complete inversion of stereochemistry indicates the occurrence of S_N2-type reaction.

11 When (*αR*)-**1a** of >99:1 dr was allowed to epimerize in the presence of AgOTf (1.0 equiv) in $CDCl_3$ (0.2M), (*αR*)-**1a** was

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recovered with 98:2 dr after 0.1 h, 91:9 dr after 0.2 h, 84:16 dr after 0.5 h, 79:21 dr after 1 h, and 71:29 dr after 5 h.

12 Mayr's nucleophilicity values (*N*)[12a] have been used as a measure for the relative reactivity of the nucleophiles; 1,2,5-trimethylpyrrole (8.69),[12b] 1-methylindole (5.75),[12c] 2-methylfuran (3.61),[12c] 1,3-dimethoxybenzene (2.48),[12d] and toluene (−4.36).[12e] Although the nucleophilicity value of 2,5-dimethylfuran is unknown, we hypothesized it would lie between 3.7 and 4.7 based on the value of 2-methylfuran. (a) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* 2003**, 36**, 66. (b) T. A. Nigst, M. Westermaier, A. R. Ofial, H. Mayr, *Eur. J. Org. Chem.*, 2008, 2369. (c) S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.*, 2006, **71**, 9088. (d) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R Loos, A. R. Ofial, G. Remennikov, H. Schimmel *J. Am. Chem. Soc.*, 2001, **123**, 9500. (e) J. Ammer, C. Nolte, H. Mayr, *J. Am. Chem. Soc.*, 2012, **134**, 13902.

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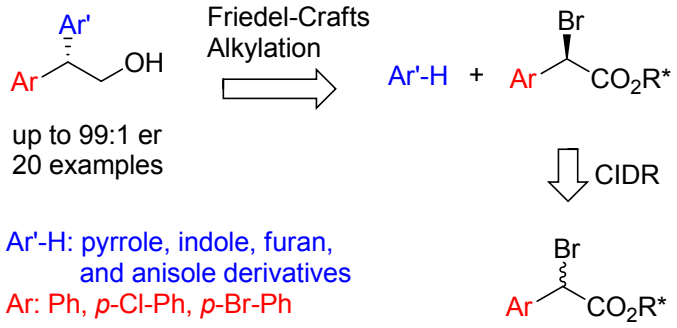
Table of Contents: Graphic



Highly enantioenriched 2,2-diarylethanols can be efficiently synthesized using AgOTf-promoted Friedel-Crafts alkylation of (hetero)arenes with configurationally labile α-bromo arylacetates.