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Two aspects of the desymmetrization of selected prochiral aromatic or vinylic dihalides: enantioselective halogen–lithium exchange and prochiral recognition in chiral liquid crystals

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Dedicated to Professor Miguel Yus

ABSTRACT

Several classes of prochiral dihalides have been identified as potential candidates for asymmetric halogen–lithium exchange. Bis-aryl compounds **1** and **2**, 2,3-dibromonorbornadiene **3,** and 1,2-diiodoferrocene **4** were prepared and used as substrates in the asymmetric halogen–lithium exchange reaction. The enantioselective mono-lithiation was achieved in good yields by various combinations of *n*-BuLi and chiral ligands. Enantioselectivities in the range of 20–35% ee have been detected for this new type of asymmetric synthesis. The prochiral compounds **3** and **4** were also dissolved in a chiral liquid crystal based on organic solutions of poly-γ-benzyl-L-glutamate and analyzed using natural abundance deuterium 2D NMR spectroscopy. The spectroscopic discrimination of enantiotopic sites in these solutes has been observed and discussed from the point of view of orientational order.

1. Introduction

The halogen–lithium exchange reaction was independently developed by Wittig and Gilman in 1938,[1,2] and has become one of the most fundamental synthetic methods for preparing various organolithium compounds,[3a–g] which have been extensively used in both organic and inorganic chemistry.[4] Over the past six decades, most of research efforts were substantially focused on various original synthetic applications[3,4] as well as some mechanistic insights.[3a,3d,5] To the best of our knowledge, however, there is no report on the asymmetric version of the above process.[6] Recently, we have explored the possibility of an enantioselective mono-halogen–lithium exchange on some achiral dibromo-aromatic compounds. Dibromides **1** and *meso*-**2** with an average C_s symmetry were devised as models as shown in Figure 1.

In the prochiral diaryl derivative **1,** the stereoselective replacement of one of two enantiotopic bromines should allow us to generate various chiral atropoisomeric structures. A similar principle was pioneered by Hayashi et al., wherein diaryl *ortho*,*ortho*′-bis-triflates were described for an enantioselective mono cross-coupling in the presence of a chiral Pd catalyst leading to an atropoisomer with up to 93% ee.[7] The enantioselective monolithiation of *meso*-dibromide **2** could provide another approach where the molecular mirror symmetry breaking creates a chiral structure with two differentiated stereocenters.[8] Dibromide **3** can also be considered as a *meso* compound, the monolithiation should give access to a product with two asymmetric centers. Similarly, the ferrocene diiodide **4** is a potential substrate for the enantioselective monosubstitution with planar chirality. Concomitantly with the desymmetrization approach proposed here, we will examine the possibility of discriminating between the enantiotopic directions of prochiral dihalides, **3** and **4,** interacting with a polypeptide chiral liquid crystal. The enantiotopic discriminations will be revealed by natural abundance deuterium NMR spectroscopy.

2. Results

2.1. Synthesis of the prochiral dihalides

One of the most straightforward potential routes for the synthesis of the dibromide **1** is the Suzuki–Miyaura cross-coupling reaction between an aryl halide and an organoboronic reagent.[9] However, an aryl–aryl coupling between *ortho*-dibromoaromatic iodide and pyrene pinacol boronic ester has been unsuccessful due to steric hindrance.[10] Several tunable influencing factors (e.g., catalyst, ligand, base, and solvent) in the Suzuki–Miyaura cross-coupling reaction prompted us to search for an appropriate

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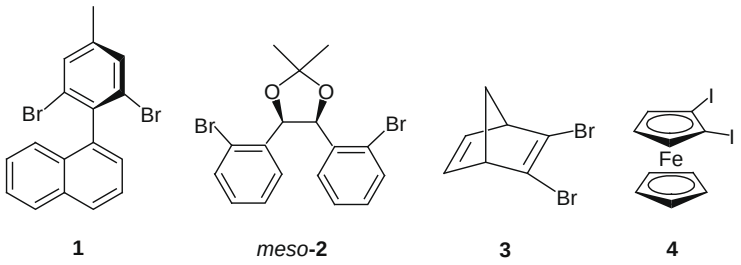


Figure 1. Four different types of prochiral dihalides.

reaction conditions for access to the dibromide **1** on the basis of this concise coupling strategy. After optimization of experimental conditions, the expected prochiral compound **1** could be smoothly obtained via a chemoselective cross-coupling of sterically hindered 1,3-dibromo-2-iodo-5-methylbenzene **5** and 1-naphthylboronic acid **6** with 82% yield on the gram scale (Scheme 1 and Table 1).

The *meso*-dibromide **2** was synthesized in three steps from 2-bromobenzaldehyde **7** (Scheme 2). The cyanide-catalyzed benzoin condensation of **7** under classical conditions[11] gave about 30% yield of **8**. Among the reducing agents examined in the diastereoselective reduction of benzoin **8**,[12] commercially available L-Selectride provided the best results, while *meso*-diol **9** was obtained in 78% yield with >95% de after careful purification by column chromatography. The desired *meso*-dibromoketal **2** could be finally obtained in 95% yield by standard ketalization.[13]

2,3-Dibromonorbornadiene **3** has been prepared according to the literature by deprotonation of norbornadiene by a Schlosser base (*t*-BuOK/*n*-BuLi) and treatment with 1,2-dibromoethane.[14a] The 1,2-diiodoferrocene **4** was synthesized in good yields from *p*-tolylsulfoxide **10** by the reactions depicted in Scheme 3. The preparation from **11**[14b] of 1,2-bis-Sn(*n*-Bu)$_3$-ferrocene (precursor of **4**) is described in Section 5. This new synthesis of **4** avoids the use of mercury salts as previously reported.[14c]

Table 1
Optimization for the synthesis of prochiral dibromide **1**

Entry	Pd(PPh$_3$)$_4$ (equiv)	Base	Solvent	*T* (°C)	*t* (h)	Yield[a] (%)
1	0.5	CsF	[b]	110	27	43
2	0.5	CsF	[b]	90	48	37
3	0.5	NaOH	[b]	85	18	45
4	0.5	Cs_2CO_3	[b]	85	95	25
5	0.5	Cs_2CO_3	[c]	70	12	70
6	0.1	LiOH	[d]	70	12	82

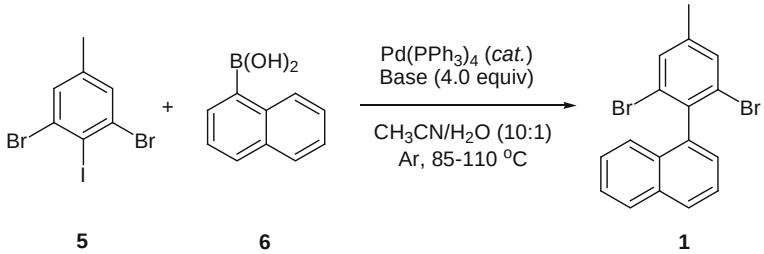
[a] Isolated yields.
[b] CH_3CN/H_2O (10:1) as solvent was used without degassing. During this coupling, the aryl iodide **5** could not be completely consumed, and the desired product was always contaminated by some uncharacterized by-products.
[c] The solvent CH_3CN/H_2O (10:1) was strictly degassed.
[d] The solvent CH_3CN/H_2O (10:1) was strictly degassed three times according to the standard cooling-vacuum process under argon.

2.2. Analysis of prochiral compounds 3 and 4 using NAD NMR in chiral oriented solvents

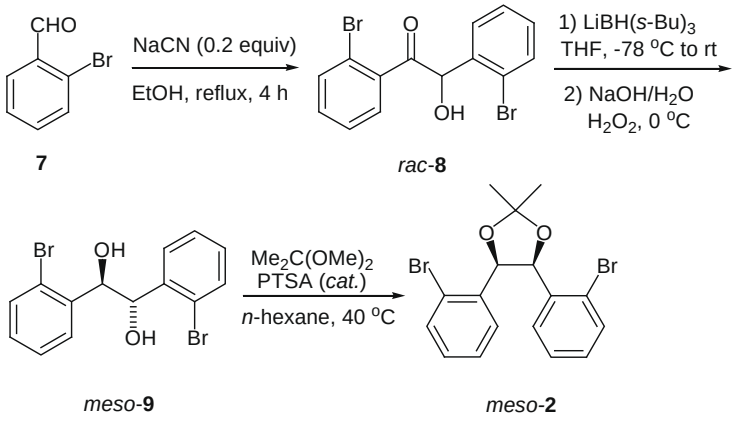
Concurrent to the synthetic developments, we have studied the orientational behavior of compounds **3** and **4** (precursors of **23** and **25**) interacting with chiral oriented media by using natural abundance deuterium (NAD) NMR spectroscopy in a polypeptide liquid crystal.[15,16] From a stereochemical point of view, molecule **3** is a rigid prochiral molecule of C_s symmetry, and thus possesses both enantiotopic (a,a′ and b,b′) and diastereotopic (c,d) C–H directions (see Fig. 2a). For ferrocene derivative **4**, the cyclopentadienyl ring is fast rotating (10^{12} s^{-1} at 300 K).[17] Therefore, the exchange between the protons of the cyclopentadienyl ring is fast on the NMR timescale, and these nuclei are homotopic. In the fast exchange regime, the enantiodiscriminations can be predicted from the average symmetry.[18] Compound **4** belongs to the average symmetry point group C_s, and can thus be considered as a flexible prochiral molecule. In particular, the C–H directions denoted b and b′ (see Fig. 2b) in the substituted Cp ring are enantiotopic.

Whatever the flexibility of the prochiral molecule is, the enantiotopic C–H directions should be oriented differently (and so spectrally discriminated) using chiral oriented systems made of poly-γ-benzyl-L-glutamate dissolved in the usual organic solvents (e.g., $CHCl_3$, DMF or THF).[16,19] In ^{2}H–{^{1}H} NMR, this enantiodiscrimination is revealed when two ^{2}H quadrupolar doublets (generally) centered on the same ^{2}H chemical shift are observed on the spectra. The origin of this inequivalence lies with the symmetry breaking of the molecular orientational distribution function when prochiral solute interacts with a D_∞ symmetry environment (chiral medium).[20]

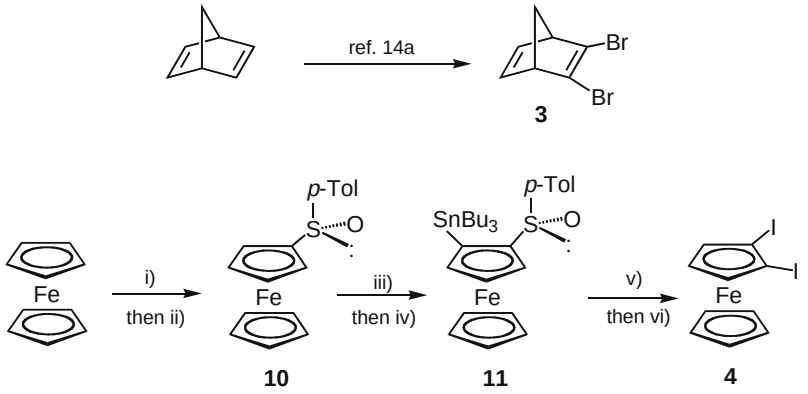
To reveal this phenomenon, we recorded the NAD NMR spectrum of **3** and **4** in a PBLG/$CHCl_3$ mesophase using 14.1 T spectrometer (600 MHz) equipped with selective 5-mm ^{2}H cryoprobe. This technological combination allows us to either record NAD spectra in a very short time or analyze small amounts of solute with large molecular weights.[21] Figures 2a and b show the NAD 1D spectrum of **3** recorded in 1 h (100 mg of solute/Mw = 254 g mol^{-1}) and the tilted NAD *Q*-COSY Fz 2D spectrum[22] of **4** recorded in 5 h (40 mg of solute/Mw = 439 g mol^{-1}), respectively. Proton decoupling is applied all along the 1D and 2D NMR experiments. Details on the oriented sample preparation and the NMR method can be found in Refs. 16 and 19. It should be noted that in NAD NMR in a chiral ori-



Scheme 1. Synthesis of prochiral dibromide **1**.



Scheme 2. Preparation of *meso*-dibromide **2**.



Scheme 3. Synthesis of prochiral dibromide **3** and diiodide **4**. Reagents: (i) *t*-BuLi/*t*-BuOK; (ii) (*S*)-(−)-menthyl *p*-tolylsulfinate; (iii) LDA; (iv) $ClSn(n\text{-}Bu)_3$; (v) 2 equiv *t*-BuLi then 2 equiv $ClSn(n\text{-}Bu)_3$; (vi) 2 equiv I_2.

ented medium, the discrimination between enantiotopic C–D directions in prochiral molecules is not possible because the probability to observe dideuterated isotopomers is too low (2.42×10^{-6} %). Actually in NAD NMR, only monodeuterated isotopomers are detected and can be enantiodiscriminated if they are chiral by virtue of the isotopic substitution.[23] In both cases, the molecular recognition mechanisms are the same, and so with the exception of the signal intensity, the NAD spectrum of an isotopically unmodified compound is identical to the ^2H spectrum of the related uniformly deuterated molecule.[24] Hence, in the following, NAD results are discussed indifferently in terms of stereo-isotopomers or stereochemical topicity.

The 1D spectrum of **3** shows six distinct quadrupolar doublets (see Fig. 2a, bottom) centered on four distinct chemical shifts: (i) two pairs of doublets (located around 7 and 3.8 ppm, respectively) corresponding to the ethylenic and bridgehead deuterium sites (denoted a and b); (ii) two doublets associated with the diastereotopic sites of the bridge (denoted c and d). The assignment of doublets has been made using 2D *Q*-COSY Fz experiment (not shown). The presence of two doublets for sites a/a′ and b/b′ demonstrates that the enantiotopic directions (that can be also seen as enantiomeric isotopomers) are spectrally discriminated since they are characterized by distinct local order parameters, $S_{CD}^{pro\text{-}R} \neq S_{CD}^{pro\text{-}S}$. This result reveals the existence of solute-polypeptide enantioselective interactions that are able to discriminate between the two faces of molecular symmetry plane of compound **3**.

The analysis of NAD tilted *Q*-COSY Fz map of **4** shows four quadrupolar doublets centered on three distinct chemical shifts. The most intense doublet is assigned to the five equivalent deuterons of the unsubstituted pentadienyl ring, thus showing the homotopocity of these sites as expected due to the fast rotation of cyclopentadienyl ring. The most deshielded doublet pair corresponds to the enantiotopic directions (denoted b and b′) of the disubstituted cyclopentadienyl ring. The presence of the two iodide atoms from each side of the symmetry plane plays the same role as the bromide atoms in **3**. Finally, the doublet located intermediately (denoted a) was assigned to the single deuteron contained in the symmetry plan. Here again, we show that **4** interacts selectively with the polypeptide fibers, thus producing a discrimination of enantiotopic directions in this particular prochiral metallic complex.

2.3. Enantioselective halogen–lithium exchange reaction

n-BuLi, *s*-BuLi, and *t*-BuLi are well-known for their ability to give the halogen–lithium exchange reactions with aryl halides in an appropriate reaction medium.[3a] In the model system shown in Scheme 4, the lithiated intermediate **12**, which should result from the asymmetric bromide–lithium exchange reaction of the prochiral dibromide **1** in the presence of a series of chiral ligands (Fig. 3), was quenched by electrophilic di-*tert*-butyl azodicarboxylate (BocN=NBoc)[25,26] to generate the dissymmetric molecule **13a**.

The halogen–lithium mono-exchange was first investigated with a combination of *n*-BuLi/(−)-sparteine **14**[27] prepared in situ from premixing *n*-BuLi and **14** in toluene at −78 °C for 30 min. An enantiomeric excess of 24% was measured by HPLC analysis of **13a** (Table 2, entry 1). However, the isolated yield was only 36% yield in this case. Sometimes, this halogen–lithium exchange process only proceeded *partially* at −78 °C, presumably because

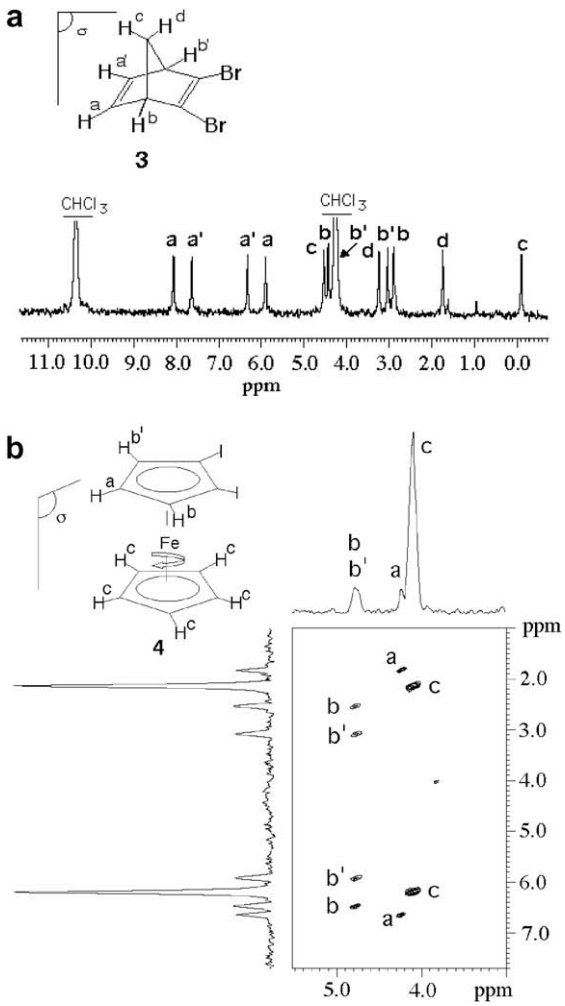


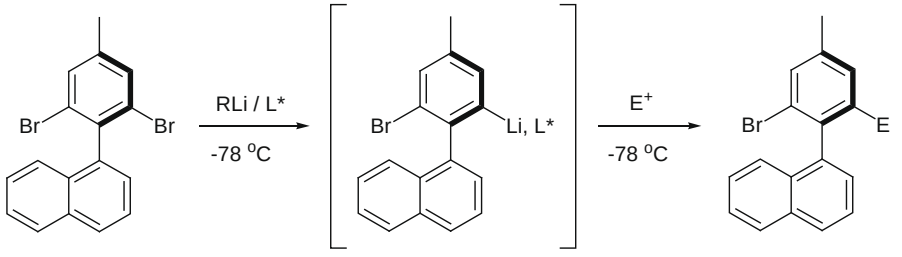
Figure 2. (a) 92.1 MHz NAD 1D spectrum of **3** recorded at 300 K and obtained by adding 2500 scans. (b) NAD Tilted *Q*-COSY Fz 2D map of **4** after a double FT. The 2D spectrum was recorded at 305 K using 96 scans *per* t_1 increment and a 2D matrix of $2500(t_2) \times 256(t_1)$ data points. The assignment x/x′ reported on the spectra is arbitrary relative to the enantiotopic direction labeling shown in the corresponding structures.

of moisture. We found that the addition of calcium hydride powder[28] to the current reaction system could realize the complete consumption of starting material with a satisfying reproducibility of results on our experiment scale (4.0×10^{-2} mmol). Following this modified experimental condition, a yield of over 71% and an ee value of 26% were readily afforded (Table 2, entry 2), in which the absolute configuration of **13a** is yet to be established.

To investigate the influence of reaction medium on the enantioselectivity, diethyl ether as a coordinative polar solvent (Table 2, entry 3) and hexane as a non-chelating apolar medium (Table 2, entry 4) were used. However, lower ee values of around 15% were obtained in comparison with that in toluene. Based on the above screening, *Procedure A* in the Experimental was developed for the halogen–lithium exchange on dibromide **1** with *n*-BuLi as the standard lithiating reagent in combination with the use of toluene as a solvent in the presence of CaH_2.

According to the above optimization, a number of chiral ligands with different structural frameworks (**15**–**19** in Fig. 3) were screened in the lithiation process, and some results are shown in entries 7–12 of Table 2. We can see that the enantioselectivity and isolated yields vary with ligand structure. For example, the bisoxazoline **15** (Table 2, entry 7) led to a reversal of enantioselectivity with 30% ee as evidenced by the specific rotation and chiral HPLC analysis. It should be noted that this halogen–lithium exchange in the presence of **15** proceeded readily as seen by thin layer chromatography (TLC). However, the desired quenching product **13a** was obtained in only 19% yield, while the predominant isolated product was monobromide **13b** (Scheme 4). Two explanations can be tentatively proposed: (i) an intrasystem protonation of the lithiated intermediate **12** in the presence of the oxazoline-type ligand **15** occurred before quenching with BocN=NBoc; (ii) the generation of hetero-aggregates incorporating the organolithium **12**[29] and preventing the quenching by BocN=NBoc. Analogously, only 20% yield of **13a** was obtained with 8% ee when another bisoxazoline **16** was subjected to this protocol in diethyl ether (Table 2, entry 9), but no quenching product **13a** could be isolated if carried out in toluene (Table 2, entry 8). The aminoether ligand **18** (Table 2, entry 11),[30] which was derived from the commercially available (−)-*N*-methylephedrine, furnished a 15% ee with an opposite enantioselectivity in comparison with that of (−)-sparteine **14**.

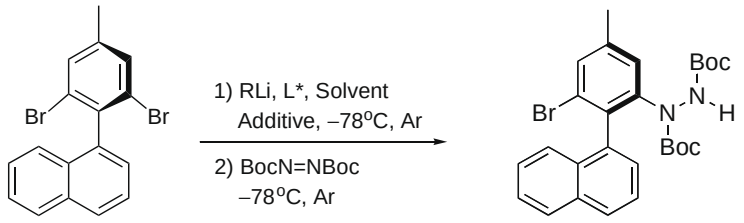
We have established that the expected halogen–lithium exchange of **1** with *n*-BuLi essentially did not proceed in toluene at −78 °C in the absence of a ligand (Table 2, entry 13). This observation indicates that the formation of a ligand-solvated organolithium crucially activates the halogen–lithium exchange process in toluene at low temperature. Consequently, the *Procedure B* described in the Experimental Section was then developed, in which the chiral ligand and the starting material were premixed in a suspension of toluene and CaH_2 at −78 °C followed by the addition of *n*-BuLi. Under stoichiometric conditions, product **13a** was obtained in 63% yield with 25% ee (Table 2, entry 5). Remarkably, further investigation revealed that substoichiometric amounts of (−)-sparteine **14** also could promote this lithiation process in 66% yield with 26% ee (Table 2, entry 6), displaying a potential in the development of *catalytic* asymmetric fashion on the halogen–lithium exchange protocol.



13a E = N(Boc)NHBoc
13b E = H
13c E = D

Scheme 4. Asymmetric halogen–lithium exchange protocol of **1**.

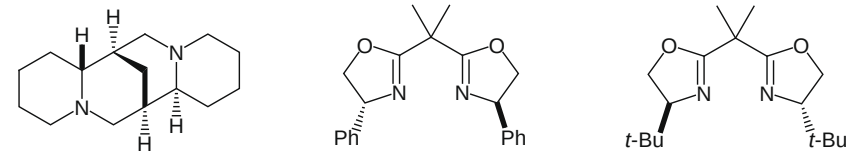
Table 2
One-pot enantioselective monolithiation/amination sequence of **1**



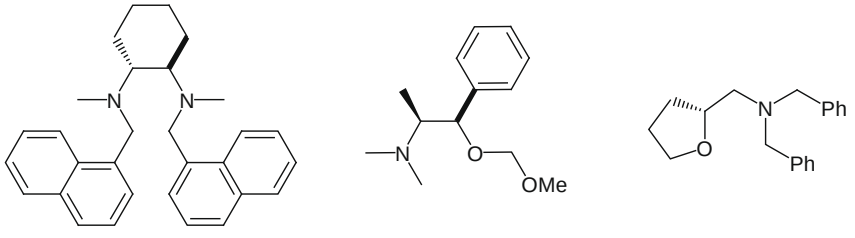
1 **13a**

Entry	Procedure[a]	L*	*n*-BuLi/L* (equiv)	Solvent	Additive	Product[b]	Yield[c] (%)	ee[d] (%)
1	*A*	**14**	1.3:1.3	Toluene	None	(−)-**13a**	36[e]	24
2	*A*	**14**	1.3:1.3	Toluene	CaH_2	(−)-**13a**	71	26
3	*A*	**14**	1.3:1.3	OEt_2	CaH_2	(−)-**13a**	60	16
4	*A*	**14**	1.3:1.3	*n*-Hexane	CaH_2	(−)-**13a**	53	15
5	*B*	**14**	1.3:1.3	Toluene	CaH_2	(−)-**13a**	63	25
6	*B*	**14**	1.3:0.3	Toluene	CaH_2	(−)-**13a**	66	26
7	*A*	**15**	1.3:1.3	Toluene	CaH_2	(+)-**13a**	19	30
8	*A*	**16**	1.3:1.3	Toluene	CaH_2	—	[f]	—
9	*A*	**16**	1.3:1.3	OEt_2	CaH_2	(−)-**13a**	20	8
10	*A*	**17**	1.3:1.3	Toluene	CaH_2	(+)-**13a**	76	4
11	*A*	**18**	1.3:3.0	Toluene	CaH_2	(+)-**13a**	62	15
12	*A*	**19**	1.3:1.3	Toluene	CaH_2	(+)-**13a**	69	4
13	*A*	None	1.3:0.0	Toluene	CaH_2	—	[g]	—

[a] *Procedure A*: L*, Additive and solvent were added into a Schlenk flask. The mixture was cooled to −78 °C, and *n*-BuLi was then introduced. Sequentially, the dibromide **1** in toluene was added. After 15 min, the reaction mixture was quenched with BocN=NBoc at −78 °C; *Procedure B*: L*, dibromide **1**, additive (CaH_2) and solvent were added into a Schlenk flask. The mixture was cooled to −78 °C, and *n*-BuLi was then introduced. After 15 min, the reaction mixture was quenched with BocN=NBoc at −78 °C.
[b] The specific rotation was measured in $CHCl_3$.
[c] Isolated yields.
[d] Undetermined absolute configuration.
[e] About 60% reaction conversion.
[f] No expected quenching product **13a** could be isolated although the halogen–lithium exchange process proceeded readily.
[g] No halogen-lithium reaction could be observed.



14 **15** **16**

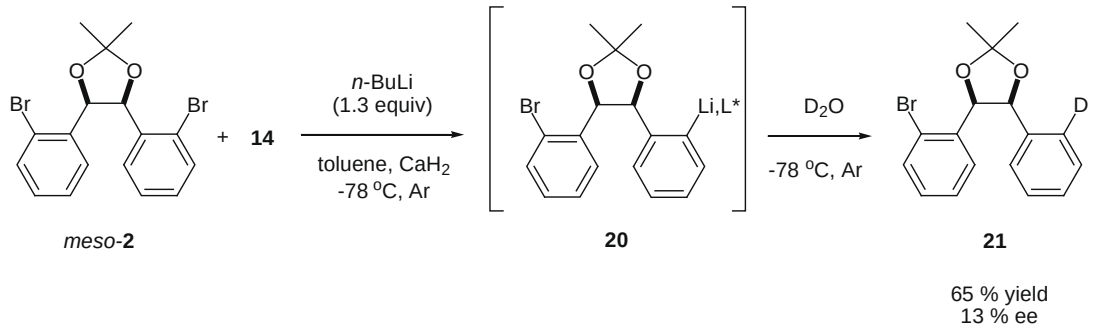


17 **18** **19**

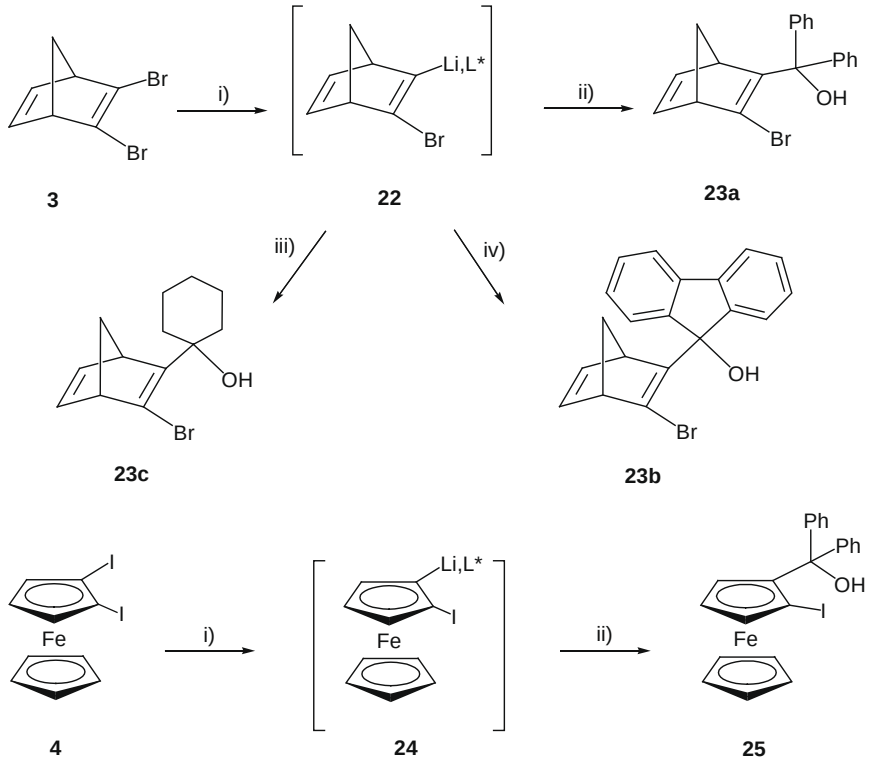
Figure 3. Several kinds of chiral ligands.

The behavior of *meso*-dibromide **2** was subsequently explored in the presence of (−)-sparteine **14** following *Procedure B* (Scheme 5). The quenching of lithiated intermediate **20** with D_2O gave the desired monobromide product **21**, its absolute configuration unknown. The enantiomeric excess of 13% was rather modest, but the level of deuterium incorporation was excellent.

The monolithiation of dibromonorbornadiene **3** (Scheme 6) into **22** was realized by 1 equiv of the combination *n*-BuLi/sparteine at −78 °C. The quenching by benzophenone gave the tertiary alcohol **23a** in 82% yield. The enantiomeric excess was measured by HPLC and found to be 20%. When the monolithonorbornadiene was left at −120 °C for 1 h before the addition of benzophenone, the product **23a** was obtained in 30% yield and 35% ee. We are currently trying to determine the absolute configuration of this compound. The monolithiation of 1,2-diiodoferrocene **4** treated under the standard conditions followed by an electrophilic quenching of **24** by benzophenone gave compound **25** in 86% yield with 27% ee (Scheme 6). The exchange reaction at −78 °C and then at room temperature (all others conditions unchanged) followed by quenching at −78 °C gave **25** in 86% yield with 34% ee.



Scheme 5. Enantioselective halogen–lithium exchange of *meso*-**2**.



Scheme 6. Enantioselective halogen–lithium exchange on **3** and **4**. Reagents: (i) *n*-BuLi/sparteine; (ii) benzophenone; (iii) cyclohexanone; (iv) fluorenone.

3. Discussion

3.1. Aryl dibromide 1

The aforementioned experimental results show that some chiral recognition may occur between the chiral alkyllithium generated in situ and the aryl dibromide **1**, wherein the formation of the aryllithium intermediate **12** was confirmed by the isolation of **13b** and **13c** after its protonolysis and deuterolysis, respectively (Scheme 4).[31,32] Aryllithium **12** should be enantiomerically stable at −78 °C. Indeed, the quenching with BocN=NBoc led to the stable enantioenriched atropoisomeric **13a,** where the ee value was measured by chiral HPLC. The possibility of thermodynamic control by racemization of **12** (see Scheme 4) via the rotation around the aryl-aryl bond at −78 °C followed by an equilibration between the diastereomeric pairs of *rac*-**12** and the chiral ligand (L*) was ruled out in the following way. (−)-Sparteine **14** as a ligand was added to the solution of *dl*-**12** firstly prepared from **1** and *n*-BuLi in diethyl ether at −78 °C followed by subsequent stirring at the same temperature. In contrast to entry 3 in Table 2, the product **13a** was obtained only in a racemic form. This is a good support for the kinetic enantioselective discrimination occurring at the halogen–lithium exchange step, thus eliminating a dynamic thermodynamic resolution process.[27d]

3.2. 1,2-Dibromonorbornadiene 3

The quenching of **22** (Scheme 6) with ketones less reactive than benzophenone suggests that the selectivity is dependent on the nature of the electrophile. For example, cyclohexanone and fluorenone gave the expected alcohol in excellent yield (87% and 85%, respectively), but the enantioselectivity is decreased (8% ee with cyclohexanone and 2% ee with fluorenone). Thus, in the norbornadiene series a dynamic racemization may be present during the quenching, resulting in decreased ee of **23**. Despite our various trials with different concentrations and ligands, no significant improvement was observed. The absolute configuration of products **23** has not been established.

3.3. 1,2-Diiodoferrocene 4

The absolute configuration of the products generated by the enantioselective lithiation with sparteine was established in the following way. The quenching of lithiated ferrocene **24** with DMF gave (S_p)-2-iodoferrocenecarboxaldehyde **26**, a known compound,[14b] in 20% ee (Scheme 7). To confirm this result, alcohol **25** was synthesized starting from sulfoxide (S_S)-**10** (Scheme 8). It was deprotonated by LDA, and the lithiated derivative was quenched with benzophenone. Two equivalents of *t*-BuLi were added to deprotonate the alcohol and to remove the sulfinyl group, a subsequent addition of 1,2-diiodoethane led to the expected product (S_p)-**25** (Scheme 8).

The stereochemical course of the formation of 1,2-disubstituted ferrocenes from (S_S)-**10** (similar to those depicted in Scheme 8) has been firmly established.[33,34] We have thus clearly proved that the *pro-R* iodide in **4** had been exchanged preferentially when (−)-sparteine is the chiral auxiliary (Scheme 7).[35] It is interesting to notice that the use of two or more equivalent of *n*-BuLi does not yield to the double iodide–lithium exchange reaction in ferrocene and norbornadiene series. Only the mono-exchanged compounds were obtained. This result originates from the unfavorable charge repulsion of vicinal dianionic species.

3.4. Possible correlation between anisotropic NMR and chemical desymmetrization

From a comparison of the results obtained in chemistry and in NMR in chiral mesophases arises an intriguing conceptual question. Is it possible to draw a parallel between the magnitude of spectroscopic enantiodiscriminations occurring in a series of analoguous prochiral compounds interacting with PBLG systems and the efficiency of desymmetrization of those same molecules when using a chiral reagent? Here, the role of the chiral auxiliary and the polypeptide is rather similar with regards to the site recognition phenomenon. In this context, it could be useful to find empirical correlations or rules between both phenomena (ee vs magnitude of spectral enantiotiopic discriminations) in order to predict, from NMR measurements, the ee that could be obtained by desymmetrizing a given prochiral substrate, or vice versa. Such challenging investigations are currently underway.

4. Conclusion

We have, for the first time, shown an enantioselective halogen–lithium mono-exchange reaction of some prochiral and *meso* aromatic or vinylic dihalides. This exploratory study paves the way to the design and use of structurally diverse achiral substrates in asymmetric halogen–metal exchange reaction. Presently, (−)-sparteine is the best ligand for the protocol of enantioselective halogen–lithium exchange. The preliminary screening of various chiral ligands showed some positive results giving hope of the discovery of more effective ligands, even efficient in a catalytic amount. A systematic screening of chiral ligands and prochiral substrates is now being actively pursued. From the NMR results obtained in chiral oriented solvents arise pertinent and exciting questions on a possible correlation between the magnitude of spectral enantiotopic discriminations in prochiral compounds dissolved in those media and the ee measured after the chemical desymmetrization of the molecule.

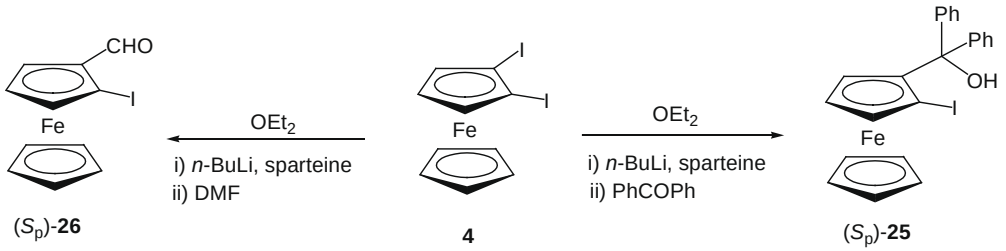
5. Experimental

5.1. General

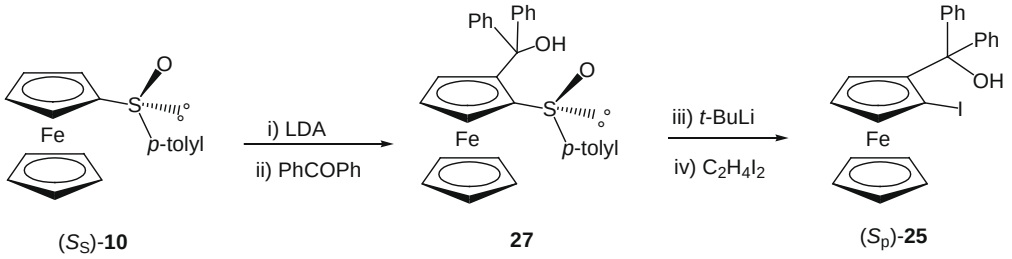
All reactions involving air-sensitive compounds were carried out under an argon atmosphere in an oven or flame-dried Schlenk flasks, which were cooled by the vacuum-argon cycle. The solvents used were purified by distillation over the drying agents (indicated in brackets), and were transferred under argon: hexane (CaH_2), OEt_2 (Na), THF (Na), CH_2Cl_2 (CaH_2), and toluene (CaH_2). *n*-BuLi (1.6 M and 2.5 M in hexanes), *t*-BuLi (1.5 M in pentane), and CaH_2 (93%, 0–2 mm) were purchased from Acros Organics and used as received. Other commercially available compounds were also used as received (unless otherwise noted). (*R*)-Tetrahydrofuran-2-carboxylic acid (Acros) is 99% purity and 98% ee. All reactions were monitored by thin-layer chromatography (TLC) on Merck Silica Gel 60 F_{254} plates using UV light as a visualizing agent, and a 5% solution of phosphomolybdic acid in EtOH and heat as developing agents. Merck silica gel (230–400 mesh) was used for the flash column chromatography. Preparative thin-layer chromatography (PLTC) separations were carried out on self-made 0.3 mm Merck Silica Gel 60 F_{254} plates. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution (unless otherwise noted) on an AC–200 Bruker spectrometer (ν_{1_H} = 200 MHz and (ν_{13_C} = 50 MHz). Chemical shifts (δ) are denoted in ppm and calibrated by using residual undeuterated solvent as an internal reference. Coupling constants are reported in Hertz. The GC–MS and MS data were obtained with EI (70 eV) or ESI technique, and the relative intensity (%) is given in brackets. High-resolution mass spectral analysis (HRMS) data were measured on a MS Finnigan-MAT-95-S by means of EI or ESI technique. Optical rotations were measured using a 1 mL cell with a 1 dm path length on Perkin Elmer 341 polarimeter, and concentrations (*c*) were reported in g/100 mL. Analytical HPLC was recorded on a HPLC machine equipped with a Spectra Series P100 pump and a Spectra Series UV100 detector. The chiral stationary phases were either Daicel Chiralcel OD-H, (*S,S*)-Whelk 01, Chiralpak AD or (*S,S*)-ULMO.

5.2. Preparation of 1,3-dibromo-5-methyl-2-(1′-naphthyl)benzene 1

To a Schlenk flask cooled by the vacuum-argon cycle were separately added 1,3-dibromo-2-iodo-5-methylbenzene **5** (600.0 mg, 1.6 mmol), 1-naphthaleneboronic acid **6** (274.5 mg, 1.6 mmol), LiOH (153.6 mg, 6.4 mmol), and $Pd(PPh_3)_4$ (184.4 mg, 1.6×10^{-1} mmol).



Scheme 7. Synthesis of (S_p)-**25** and (S_p)-**26** from **4**.



Scheme 8. Synthesis of (S_p)-**25** from (S_S)-**10** via **27**.

This Schlenk flask was kept in vacuo and then backfilled with argon 3 times. A freshly prepared solution of CH_3CN/H_2O (10:1, 200 mL) was strictly degassed 3 times following the standard freezing-vacuum/warming-vacuum process under argon to give the oxygen-free solution of CH_3CN/H_2O (10:1, 120 mL). This solution was transferred into the above Schlenk flask through a double-tipped needle under argon. The mixture was stirred and heated at about 70 °C under argon, in which the yellowish reaction solution faded slowly and a white suspension was generated gradually. After 12 h, the heating was stopped, and the distilled *n*-pentane (300 mL) was added to the above reaction mixture which was cooled to rt. *n*-Pentane phase was separated, and the aqueous CH_3CN layer was extracted with *n*-pentane (5 × 300 mL), and the combined *n*-pentane phases were dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel eluting with distilled *n*-pentane to afford aryl dibromide **1** (492.0 mg, 1.3 mmol, 82%). ^{1}H NMR: δ = 7.99–7.95 (m, 2H), 7.64–7.34 (m, 7H), 2.44 (s, 3H); ^{13}C NMR: δ = 140.7, 138.8, 138.4, 133.5, 132.4 (2 × CH), 131.1, 128.5, 128.4, 127.2, 126.4, 126.0, 125.3, 125.0 (2 × C), 124.9, 20.5; GC–MS (70 eV): *m/z* (%): 378 (7.9) $[M(^{81}Br_2)]^+$, 376 (15.2) $[M(^{81}Br,^{79}Br)]^+$, 374 (7.5) $[M(^{79}Br_2)]^+$, 217 (16.8) $[M-2Br+H]^+$, 216 (100) $[M-2Br]^+$, 215 (64.6) $[M-2Br-H]^+$, 213 (18.6), 189 (8.4), 108 (29.0), 94 (31.3); HRMS (EI): *m/z* calcd for $C_{17}H_{12}{}^{79}Br_2$: 373.9300; found: 373.9330 $[M]^+$.

5.3. Preparation of *meso*-2,2-dimethyl-4,5-bis(2′-bromophenyl)-1,3-dioxolane 2

Meso-**9** (227.0 mg, 6.1×10^{-1} mmol), 1,2-dimethoxypropane (2.0 mL, 16.2 mmol), and *p*-toluene-sulfonic acid (8.0 mg, 4.6×10^{-2} mmol) were stirred in anhydrous hexane (10 mL) under argon. After stirring for 30 min at 50 °C, the reaction mixture was kept at 40 °C for 6 h. A saturated aqueous solution of $NaHCO_3$ was added and stirring continued for 30 min. The mixture was extracted with OEt_2 (3 × 150 mL), and the extract dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with *n*-pentane/ethyl acetate 100/0→100/1, to give *meso*-**2** (238.8 mg, 5.8×10^{-1} mmol, 95%). ^{1}H NMR: δ = 7.31 (dd, *J* = 1.2, 7.8 Hz, 2 × 1H; 3-ArH), 7.29 (dd, *J* = 1.7, 7.8 Hz, 2 × 1H; 6-ArH), 7.08 (td, *J* = 1.2, 7.8 Hz, 2 × 1H; 5-ArH), 6.95 (td, *J* = 1.7, 7.8 Hz, 2 × 1H; 4-ArH), 6.02 (s, 2 × 1H), 1.84 (s, 3H), 1.66 (s, 3H); ^{13}C NMR: δ = 136.4 (2 × C), 132.1 (2 × CH), 129.8 (2 × CH), 128.9 (2 × CH), 126.4 (2 × CH), 123.5 (2 × C), 108.7, 79.4 (2 × CH), 26.7, 24.4; GC–MS (70 eV): *m/z* (%): 414 (0.1) $[M(^{81}Br_2)]^+$, 412 (0.2) $[M(^{81}Br,^{79}Br)]^+$, 410 (0.1) $[M(^{79}Br_2)]^+$, 399 (0.2) $[M(^{81}Br_2)-CH_3]^+$, 397 (0.4) $[M(^{81}Br,^{79}Br)-CH_3]^+$, 395 (0.2) $[M(^{79}Br_2)-CH_3]^+$, 228 (79.0) $[M(^{81}Br,Br)-BrC_6H_4CHO]^+$, 226 (84.3) $[M(^{79}Br,Br)-BrC_6H_4CHO]^+$, 171 (29.8), 169 (32.4), 165 (30.8), 147 (100), 129 (33.0), 90 (10.6), 89 (86.7), 77 (14.3), 63 (9.8), 43 (26.6); HRMS (EI): *m/z* calcd for $C_{16}H_{13}O_2{}^{79}Br_2$: 394.9277; found: 394.9262 $[M-CH_3]^+$.

5.4. Preparation of 2,3-dibromonorbornadiene 3

This compound was prepared according to the literature procedure.[14a]

5.5. Preparation of 1,2-diiodoferrocene 4

(*S*)-Ferrocenylsulfoxide (S_S)-**10** was prepared according to the literature.[14b] It was treated by LDA and then by $ClSnBu_3$ giving sulfoxide (S_S,R_p)-**11** in 87% isolated yield, in agreement with Ref. 14a. The preparation of 1,2-bis(tri-*n*-butyltin)ferrocene from **11** has been achieved as follows. Under argon, **11** (2.9 g, 4.7 mmol) was dissolved in Et_2O (30 mL). At −78 °C, *t*-BuLi (3.77 mL, 5.65 mmol) was added dropwise to the mixture, and the stirring was maintained for 30 min. Then *tri*-*n*-butyltin chloride (1.66 mL, 6.11 mmol) was added dropwise. The mixture was stirred for a further 30 min at this low temperature and then 2 h at rt. The mixture was quenched by adding water (20 mL) and diluted with Et_2O (30 mL). The organic layer was washed twice with water, dried over Na_2SO_4, filtered, and the solvent was then removed under reduced pressure. By-products were evaporated by heating the crude oil at 60 °C under vacuum. Most of *t*-Bu *p*-Tol sulfoxide was removed by crystallization with pentane in the freezer (−30 °C). The bis(*tri*-*n*-butyltin)ferrocene isolated was not analyzed but used as such to undergo the iodide–tin exchange reaction. The transformation of the bis–tin compound into **4** was carried out by the addition of 2 equiv of I_2 in CH_2Cl_2 (stirring overnight at rt). Isolated yield: 83% (from **11**), as a red oily solid. ^{1}H NMR: δ = 4.51 (d, 2H, *J* = 2.5 Hz, H *ortho*), 4.24 (t, 1H, *J* = 2.5 Hz, H *meta*), 4.18 (s, 5H, Cp); ^{13}C NMR: δ = 74.5 (2 × CH), 74.1 (5 × CH), 70.5, 51.9 (2 × C); Anal. Calcd for $C_{10}H_8FeI_2$: C, 27.43; H, 1.84. Found: C, 27.63; H, 1.89. Spectroscopic data in agreement with the literature.[14b]

5.6. Preparation of 1,3-dibromo-2-iodo-5-methylbenzene 5

4-Methyl-2,6-dibromoaniline (10.0 g, 38.0 mmol) was dissolved in concentrated AcOH (200 mL) and added to concentrated H_2SO_4 (40 mL) at 0 °C. This solution was added slowly at 0 °C to a mixture of $NaNO_2$ (6.9 g, 100.0 mmol), concentrated H_2SO_4 (50 mL), and concentrated AcOH (100 mL) under argon for 1 h at 0 °C, and the reaction temperature was maintained in the range −5 °C to +5 °C. After stirring for 1 h at 0 °C, the mixture was warmed to rt. The resulting mixture was added to a freshly prepared solution of KI (34.7 g, 209.0 mmol), I_2 (48.0 g, 189.0 mmol), urea (4.6 g, 76.0 mmol), H_2O (400 mL), and $CHCl_3$ (100 mL). The above solution was strongly stirred at rt overnight, and then Na_2SO_3 (46.0 g, 365.0 mmol) was added. The aqueous layer was separated and extracted with $CHCl_3$ (2 × 300 mL). The combined organic phases were washed with a saturated aqueous solution of Na_2CO_3 (300 mL), and then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography on silica gel eluting with *n*-pentane to yield dibromo iodide **5** (12.2 g, 32.4 mmol, 86%). ^{1}H

NMR (200 MHz): δ = 7.38 (s, 2H), 2.25 (s, 3H); ^{13}C NMR: δ = 141.0, 131.9 (2 × CH), 130.7 (2 × C), 104.8, 20.4; GC–MS (70 eV): *m/z* (%): 378 (51.8) [M(^{81}Br$_2$)]$^+$, 376 (100) [M(^{81}Br,^{79}Br)]$^+$, 374 (62.4) [M(^{79}Br$_2$)]$^+$, 297 (27.5) [M(^{81}Br,Br)−Br]$^+$, 295 (24.9) [M(^{79}Br,Br)−Br]$^+$, 251 (4.0) [M(^{81}Br$_2$)−I]$^+$, 249 (8.6) [M(^{81}Br,^{79}Br)−I]$^+$, 247 (4.2) [M(^{79}Br$_2$)−I]$^+$, 170 (40.7) [M(^{81}Br,Br)−Br−I], 168 (36.4) [M(^{79}Br,Br)−Br−I], 127 (8.4) [I]$^+$, 90 (10.0), 89 (93.5) [M−2Br−I]$^+$, 86 (21.5), 63 (31.0), 44 (24.6).

5.7. Preparation of 1,2-bis(2′-bromophenyl)-2-hydroxyethanone 8

To a 100 mL flask fitted with a reflux condenser were added 2-bromobenzaldehyde **7** (12.6 g, 68.1 mmol) and EtOH (99%, 15 mL). A solution of NaCN (667.0 mg, 13.6 mmol) in 95% EtOH (15 mL) was added. It was stirred and refluxed for 4 h under argon, and then cooled to rt. The reaction solvent was directly evaporated in vacuo followed by the addition of saturated brine (75 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL) (*Caution: this aqueous cyanide solution is highly toxic*), and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product, which was purified by flash column chromatography on silica gel (*n*-pentane/ethyl acetate 50/1→20/1) to give oily *rac*-benzoin **8** (3.8 g, 10.3 mmol, 30%). ^{1}H NMR: δ = 7.58–7.10 (m, 8H), 6.37 (s, 1H), 4.55 (br s, 1H; OH); ^{13}C NMR: δ = 201.4, 137.4, 136.1, 133.5, 133.1, 132.2, 130.2, 129.2, 128.8, 127.9, 126.9, 124.1, 119.6, 77.2; GC–MS (70 eV): *m/z* (%): 291 (2.1) [M(^{81}Br,Br)−Br]$^+$, 289 (2.3) [M(^{79}Br,Br)−Br]$^+$, 187 (18.7) [^{81}BrC$_6$H$_4$CH(OH)]$^+$, 185 (100) [^{81}BrC$_6$H$_4$C=O+^{79}BrC$_6$H$_4$CH(OH)]$^+$, 183 (87.5) [^{79}BrC$_6$H$_4$C=O]$^+$, 157 (17.9), 155 (13.0), 78 (12.3), 77 (39.4), 76 (11.8).

5.8. Preparation of *meso*-1,2-bis(2′-bromophenyl)ethane-1,2-diol 9

To a 100 mL Schlenk flask were added *rac*-benzoin **8** (518.0 mg, 1.4 mmol) and dry THF (15 mL) under argon. This stirred solution was cooled to −78 °C with an acetone/dry ice bath. A solution of LiBH(*s*-Bu)$_3$ (L-Selectride) (1.0 M in THF, 5.6 mL, 5.6 mmol) was added dropwise to the above reaction mixture via microsyringe, and then stirred at −78 °C for 5 h. The reaction mixture was quenched with aqueous NaOH (3 M, 8 mL) followed by a slow addition of H_2O_2 (35%, 4 mL) at 0 °C. The resulting mixture was strongly stirred for additional 2 h at rt. After the extraction of EtOAc (3 × 100 mL), the combined organic phases were washed with saturated brine, dried over $MgSO_4$, and concentrated under reduced pressure on a rotatory evaporator. The crude product was carefully purified by flash column chromatography on silica gel (*n*-pentane/ethyl acetate 15/1→10/1) to furnish *meso*-**9** (393.0 mg, 1.1 mmol, 78% yield, >95% de). ^{1}H NMR ($CDCl_3$): δ = 7.43–7.38 (m, 2 × 1H), 7.29–7.06 (m, 2 × 3H), 5.56 (s, 2 × 1H), 3.12 (br s, 2H; 2 × OH); ^{13}C NMR: δ = 137.8 (2 × C), 132.0 (2 × CH), 129.2 (2 × CH), 129.1 (2 × CH), 127.0 (2 × CH), 123.9 (2 × C), 74.2 (2 × CH).

5.9. Procedure A for the synthesis of *N*,*N*-bis(*tert*-butoxycarbonyl)-3-bromo-5-methyl-2-(1′-naphthyl)-phenylhydrazine (13a, entry 2 of Table 2)

To a 25 mL Schlenk flask cooled by the vacuum-argon cycle were added (−)-sparteine (12.2 mg, 12.0 μL, 5.2 × 10^{-2} mmol), CaH_2 (10.0 mg, 2.4 × 10^{-1} mmol), and dry toluene (3 mL) under argon at rt. This solution was efficiently stirred for 30 min, and then was cooled to −78 °C with an acetone/dry ice bath. A solution of *n*-BuLi (2.5 M in hexane, 21.0 μL, 5.2 × 10^{-2} mmol) was added via microsyringe, and the resulting mixture was stirred for 30 min at −78 °C. Dibromide **1** (15.0 mg, 4.0 × 10^{-2} mmol) in anhydrous toluene (2 mL) was then slowly added dropwise. After 15 min, the substrate was completely consumed as monitored by TLC, and then a powder of freshly recrystallized di-*tert*-butyl azodicarboxylate, BocN=NBoc (18.4 mg, 8.0 × 10^{-2} mmol), was directly added at −78 °C. This reaction medium was vigorously stirred for 2 h at −78 °C, and quenched by saturated brine (10 mL) at the same temperature. The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organic phases dried over $MgSO_4$. Evaporation of the solvent followed by purification by flash column chromatography on silica gel, eluting with *n*-pentane/ethyl acetate 10:1, gave the product **13a** (15.0 mg, 2.85 × 10^{-2} mmol, 71%; $[\alpha]_D^{20} = -2.8$ (*c* 1.4, $CHCl_3$)). An enantiomeric excess of 26% was determined by HPLC using Chiralpak AD column (hexane/*i*-PrOH 95:5; flow rate 0.5 mL/min; τ_{major} = 11.5 - min, τ_{minor} = 14.8 min). The enantiomer with the shorter retention time is levorotatory in $CHCl_3$. ^{1}H NMR: δ = 7.91 (m, 1H), 7.87 (m, 1H), 7.56–7.35 (m, 7H), 6.33–5.26 (m, 1H), 2.44 (s, 3H, Me), 1.47–1.22 (m, 18H, *t*-Bu). The complexity of the spectra is coming from rotamers introduced by the N(Boc)–NHBoc system; MS (ESI): *m/z* (%): 552 (29.4) [M(^{81}Br)+H+Na]$^+$, 551 (100) [M(^{81}Br)+Na]$^+$, 550 (30.8) [M(^{79}Br)+H+Na]$^+$, 549 (96.3) [M(^{79}Br)+Na]$^+$, 451 (46.3) [M(^{81}Br)−CO$_2$−H$_2$C=C(CH$_3$)$_2$+Na]$^+$, 449 (45.7) [M(^{79}Br)–CO$_2$–H$_2$C=C(CH$_3$)$_2$+Na]$^+$, 395 (29.5) [*m/z* 451–H$_2$C=C(CH$_3$)$_2$]$^+$, 393 (29.8) [*m/z* 449–H$_2$C=C(CH$_3$)$_2$]$^+$, 351 (9.6) [*m/z* 395–CO$_2$]$^+$, 349 (9.6) [*m/z* 393–CO$_2$]$^+$, 311 (8.1), 275 (12.6), 231 (37.7); HRMS (EI): *m/z* calcd for $C_{27}H_{31}O_4N_2{}^{79}Br$: 526.1462; found: 526.1446 [M]$^+$.

5.10. Procedure B for the synthesis of *N*,*N*′-bis(*tert*-butoxycarbonyl)-3-bromo-5-methyl-2-(1-naphthyl)-phenylhydrazine (13a, entry 5 of Table 2)

To a 25 mL Schlenk flask were added (−)-sparteine (12.2 mg, 12.0 μL, 5.2 × 10^{-2} mmol), dibromide **1** (15.0 mg, 4.0 × 10^{-2} mmol), CaH_2 (10.0 mg, 2.4 × 10^{-1} mmol), and dry toluene (3 mL) under argon at rt. This solution was efficiently stirred for 30 min, and then cooled to −78 °C with an acetone/dry ice bath. A solution of *n*-BuLi (1.6 M in hexane, 32.0 μL, 5.2 × 10^{-2} mmol) was added via microsyringe to the above cold solution, and the resulting mixture was stirred vigorously at −78 °C. After 15 min, the substrate disappeared completely as seen by TLC. A powder of freshly recrystallized BocN=NBoc (18.4 mg, 8.0 × 10^{-2} mmol) was added directly to the above reaction mixture. It was stirred for 2 h at −78 °C, and then quenched by saturated brine (10 mL) at the same temperature. The aqueous phase was extracted with EtOAc (3 × 100 mL), and the combined extracts dried over $MgSO_4$. Evaporation of the solvent followed by purification by flash column chromatography on silica gel, eluting with *n*-pentane/ethyl acetate 10:1, gave the product **13a** (13.0 mg, 2.5 × 10^{-2} mmol, 62%; $[\alpha]_D^{20} = -5.3$ (*c* 0.3, $CHCl_3$)). An enantiomeric excess of 25% was determined by HPLC as above. All other analytical data are the same to those in the *General Procedure A* mentioned above.

5.11. Preparation of 2-bromo-4-methyl-1-(1′-naphthyl)benzene 13b

To a 25 mL Schlenk flask were added (−)-sparteine **14** (40.5 mg, 40.0 μL, 17.3 × 10^{-2} mmol), CaH_2 (20.0 mg, 4.8 × 10^{-1} mmol), and dry toluene (3 mL) under argon at rt. This solution was vigorously stirred for 30 min, and then cooled to −78 °C with an acetone/dry ice bath. A solution of *n*-BuLi (2.5 M in hexane, 69.0 μL, 17.3 × 10^{-2} mmol) was added via microsyringe to the above cold solution, and the resulting mixture was stirred for 30 min at −78 °C. Dibromide **1** (50.0 mg, 13.3 × 10^{-2} mmol) in anhydrous toluene (2 mL) was slowly added dropwise to the above cold

solution of the *n*-BuLi/**14** complex. After 15 min, the substrate was completely consumed as monitored by TLC, after which H_2O (2.0 mL) was directly added at −78 °C. The mixture was separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent at rt followed by purification by preparative TLC with *n*-pentane as eluent gave monobromide **13b** (31.5 mg, 10.6×10^{-2} mmol, 80%). The enantiomeric excess of **13b** could not be measured by chiral HPLC at rt. ^{1}H NMR: δ = 7.93–7.88 (m, 2H), 7.58–7.34 (m, 6H), 7.25–7.24 (m, 2H), 2.44 (s, 3H); ^{13}C NMR: δ = 139.2, 139.1, 138.3, 133.4, 133.1, 131.7, 131.6, 128.2, 128.0, 127.9, 127.1, 126.0 (2 × CH), 125.8, 125.1, 124.0, 20.8; GC–MS (70 eV): *m/z* (%): 298 (33.0) [M(^{81}Br)]$^+$, 296 (35.0) [M(^{79}Br)]$^+$, 217 (73.1) [M−Br]$^+$, 202 (100) [M−Br−CH_3]$^+$, 108 (16.9), 107 (44.6), 94 (24.9); HRMS (EI): *m/z* calcd for $C_{17}H_{13}{}^{79}Br$: 296.0195; found: 296.0189 [M]$^+$.

The preparation of deuterated analog **13c** and the relative analytical data are given in Ref. 32b.

5.12. Preparation of (1*R*,2*R*)-*N*,*N*′-dimethyl-*N*,*N*′-bis((1′-naphthyl)methyl)cyclohexane-1,2-diamine 17

To a solution of (1*R*,2*R*)-*N*,*N*′-dimethylcyclohexane-1,2-diamine (0.1 g, 0.7 mmol) and AcOH (0.13 mL, 2.2 mmol) in MeOH (4 mL) was added 1-naphthaldehyde (0.3 mL, 2.2 mmol) at rt. After stirring for 0.5 h, $NaBH_3CN$ (138.0 mg, 2.2 mmol) was added. After 36 h, the solvent was removed in vacuo. Concentrated HCl was added at 0 °C until pH < 2, followed by the addition of Et_2O (10 mL). The residue was taken up in 5 mL of H_2O and extracted with three 10-mL portions of Et_2O. The aqueous solution was brought to pH > 10 with solid KOH, saturated with NaCl, and extracted with five 10-mL portions of Et_2O. The combined organic phases were dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel eluting with EtOAc to afford the oily diamine **17** (0.1 g, 2.4×10^{-1} mmol, 34%; $[\alpha]_D^{20} = +15.2$ (*c* 2.1, $CHCl_3$)). ^{1}H NMR: δ = 8.29 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.48–7.24 (m, 8H), 4.12 (ABq, *J* = 13.4 Hz, 2 × 1H), 4.06 (ABq, *J* = 13.4 Hz, 2 × 1H), 2.83–2.79 (m, 2H), 2.19 (s, 6H), 2.18–2.08 (m, 2H), 1.85–1.81 (m, 2H), 1.38–1.22 (m, 4H); ^{13}C NMR: δ = 136.0 (2 × C), 133.7 (2 × C), 132.6 (2 × C), 128.1 (2 × CH), 127.3 (2 × CH), 126.8 (2 × CH), 125.3 (2 × 2CH), 125.1 (2 × 2CH), 62.9 (2 × CH_2), 56.4 (2 × CH), 36.2 (2 × CH_3), 25.9 (2 × CH_2), 25.4 (2 × CH_2); GC–MS (70 eV): *m/z* (%): 422 (3.0) [M]$^+$, 282 (3.9), 281 (20.7) [M−$C_{10}H_7CH_2$]$^+$, 171 (12.4), 142 (14.1), 141 (100.0) [$C_{10}H_7CH_2$]$^+$, 115 (12.3), 112 (3.6), 44 (2.9); HRMS (ESI): *m/z* calcd for $C_{30}H_{35}N_2$: 423.2795; found: 423.2790 [M+H]$^+$.

5.13. Preparation of (*R*)-*N*,*N*-dibenzyl-(tetrahydrofuran-2-yl)methanamine 19

To a 100 mL Schlenk flask were added (*R*)-tetrahydrofuran-2-carboxylic acid (250.0 mg, 21.6×10^{-1} mmol) and dry CH_2Cl_2 (6 mL) under argon atmosphere. The reaction solution was cooled to about −15 °C, and treated with freshly distilled oxalyl chloride (0.28 mL, 32.6×10^{-1} mmol) followed by a few drops of DMF. The mixture was then warmed to rt, and stirred overnight. The solvent was removed from the colorless reaction solution under reduced pressure and subsequently in vacuo, and then dry CH_2Cl_2 (3 mL) was added again under argon. The resulting solution of acyl chloride was added dropwise to a solution of dibenzylamine (1.3 mL, 6.5 mmol) in dry CH_2Cl_2 (15 mL) at rt under argon. After stirring overnight, brine (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were dried over $MgSO_4$. Evaporation of the solvent followed by purification by column chromatography on silica gel (*n*-pentane/acetone 10:1) gave (*R*)-*N*,*N*-dibenzyl-tetrahydrofuran-2-carboxamide (546.8 mg, 1.8 mmol, 86%). ^{1}H NMR: δ = 7.41–7.18 (m, 10H), 4.74–4.47 (m, 5H), 4.11–4.00 (m, 1H), 3.95–3.82 (m, 1H), 2.40–2.28 (m, 1H), 2.17–1.85 (m, 3H); ^{13}C NMR: δ = 172.2, 137.0, 136.5, 128.8 (2 × CH), 128.5 (2 × CH), 128.1 (2 × CH), 127.5, 127.3, 126.7 (2 × CH), 75.8, 69.2, 49.4, 48.0, 28.9, 25.8; GC–MS (70 eV): *m/z* (%): 295 (2.1) [M]$^+$, 226 (2.4), 205 (5.5), 204 (41.2) [M−$C_6H_5CH_2$]$^+$, 106 (35.0), 91 (100) [$C_6H_5CH_2$]$^+$, 71 (53.8), 43 (11.8). With this amide intermediate in hand, the preparation of amine **19** was conducted as follows: to a 100 mL Schlenk flask were added $LiAlH_4$ (0.3 g, 7.9 mmol) and dry THF (5 mL) at −78 °C under argon atmosphere. A solution of (*R*)-*N*,*N*-dibenzyl-tetrahydrofuran-2-carboxamide (367.0 mg, 12.4×10^{-1} mmol) in dry THF (15 mL) was added to the above suspension of $LiAlH_4$ in THF. After removing the cooling bath, the reaction mixture was stirred at reflux overnight. The mixture was cooled to rt, and carefully quenched with aqueous NaOH (3M, 4 mL), followed by the addition of EtOAc (40 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined extracts were dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with *n*-pentane/EtOAc (20:1) to give the oily amine **19** (283.2 mg, 1.0 mmol, 81%; $[\alpha]_D^{20} = +30.0$ (*c* 3.0, $CHCl_3$)). ^{1}H NMR: δ = 7.46−7.23 (m, 10H), 4.18−4.05 (m, 1H), 3.89–3.69 (m, 2H), 3.80 (ABq, *J* = 13.7 Hz, 2 × 1H), 3.60 (ABq, *J* = 13.7 Hz, 2 × 1H), 2.62 (d-ABq, *J* = 5.8, 17.1 Hz, 1H), 2.58 (d-ABq, *J* = 5.9, 17.1 Hz, 1H), 2.04–1.74 (m, 3H), 1.63–1.50 (m, 1H); ^{13}C NMR: δ = 139.8 (2 × C), 128.8 (2 × 2CH), 128.1 (2 × 2CH), 126.7 (2 × CH), 77.8, 67.8, 59.0 (2 × CH_2), 57.5, 30.0, 25.3; GC–MS (70 eV): *m/z* (%): 281 (0.8) [M]$^+$, 211 (12.2) [$(C_6H_5CH_2)_2NCH_3$]$^+$, 210 (72.4) [$(C_6H_5CH_2)_2NCH_2$]$^+$, 181 (7.4), 92 (7.8) [$C_6H_5CH_3$]$^+$, 91 (100) [$C_6H_5CH_2$]$^+$, 65 (5.6); HRMS (ESI): *m/z* calcd for $C_{19}H_{24}ON$: 282.1852; found: 282.1861 [M+H]$^+$.

5.14. Preparation of 4-(2′-bromophenyl)-5-(2′-deuterophenyl)-2,2-dimethyl-1,3-dioxolane 21

To a 25 mL Schlenk flask were added (−)-sparteine **14** (11.1 mg, 11.0 μL, 4.7×10^{-2} mmol), *meso*-**2** (15.0 mg, 3.6×10^{-2} mmol), CaH_2 (10.0 mg, 2.4×10^{-1} mmol), and dry toluene (3 mL) under argon at rt. This solution was efficiently stirred for 30 min, and then cooled to −78 °C with an acetone/dry ice bath. A solution of *n*-BuLi (2.5 M in hexane, 19.0 μL, 4.7×10^{-2} mmol) was added via microsyringe, and the resulting mixture was stirred for 15 min at −78 °C. After the complete conversion as seen by TLC, it was quenched with D_2O (0.1 mL, 5.5 mmol) at −78 °C. After being stirred efficiently for 1 h at rt, it was extracted with Et_2O (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure, and purified by PTLC, elution with *n*-pentane/ethyl acetate 10:1, to give the deuterated product **21** (7.9 mg, 2.3×10^{-2} mmol, 72%). An ee of 13% was determined by HPLC using Chiralpak AD column (hexane; flow rate 0.4 mL/min; τ_{minor} = 20.6 min, τ_{major} = 24.5 min). ^{1}H NMR: δ = 7.28 (dd, *J* = 1.7 Hz, 1H), 7.23 (dd, *J* = 1.2 Hz, 1H), 7.13–6.97 (m, 5H), 6.87 (td, *J* = 1.7, 7.6 Hz, 1H), 5.84 (ABq, *J* = 7.5 Hz, 1H), 5.63 (ABq, *J* = 7.5 Hz, 1H), 1.82 (s, 3H), 1.61 (s, 3H); ^{13}C NMR: δ = 137.8, 137.1, 131.7, 128.6, 128.5, 127.3 (2 × CH), 127.2, 127.1, 126.7, 122.0, 108.7, 80.2, 80.1, 26.6, 24.3, and one carbon (C^2H) was not observed because of its weak ^{13}C NMR signal; GC–MS (70 eV): *m/z* (%): 335 (0.2) [M(^{81}Br)]$^+$, 333 (0.2) [M(^{79}Br)]$^+$, 320 (0.7) [M(^{81}Br)−CH_3]$^+$, 318 (0.7) [M(^{79}Br)−CH_3]$^+$, 278 (3.0) [M(^{81}Br)–CH_3COCH_3+H], 276 (3.1) [M(^{79}Br)–CH_3COCH_3+H], 228 (67.5) [M(^{81}Br) − $C_6H_4{}^2HCHO$]$^+$, 226 (71.7) [M(^{79}Br) − $C_6H_4{}^2HCHO$]$^+$, 171 (26.2), 169 (26.9), 149 (90.7) [M−BrC_6H_4CHO]$^+$, 148 (58.6), 147 (100), 129 (28.5), 106 (23.3), 92 (29.3), 91 (45.1), 89 (82.6), 77

(17.4), 43 (34.0); HRMS (EI): *m/z* calcd for $C_{16}H_{13}{}^{2}HO_{2}{}^{79}Br$: 318.0234; found: 318.0234 $[M-CH_3]^+$.

5.15. Preparation of (3-bromobicyclo[2.2.1]hepta-2,5-dien-2-yl)-diphenyl-methanol 23a

(−)-Sparteine (101 μL, 0.56 mmol) was dissolved in Et_2O (4 mL). Under argon at −78 °C, *n*-BuLi (192 μL, 0.44 mmol) was added dropwise, and the mixture was stirred at this temperature for 30 min. 2,3-Dibromonorbornadiene (100 mg, 0.4 mmol) dissolved in Et_2O (1 mL) was added to the mixture. The mixture was stirred at −78 °C for 1.5 h, and then benzophenone (96 mg, 0.48 mmol) in diethyl ether (1 mL) was added dropwise. The temperature was maintained at this low temperature for 1 h and then the cooling bath was removed. The mixture was stirred at room temperature for another 2 h and then quenched with saturated NH_4Cl aqueous solution. The organic layer was washed twice with water, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified on TLC plate eluting with pentane/Et_2O (9/1) yielding 115 mg (85%) of an uncolored oil. ^{1}H NMR: δ = 7.35 (m, 10H), 6.83 (dd, 1H, *J* = 3.0 Hz, *J* = 4.4 Hz), 6.53 (dd, 1H, *J* = 3.0 Hz, *J* = 4.4 Hz), 3.62 (br s, 1H), 3.47 (br s, 1H), 3.05 (s, 1H), 2.41 (d, 1H, *J* = 6.0 Hz), 1.99 (d, 1H, *J* = 6.2 Hz). ^{13}C NMR: δ = 152.98, 143.79, 142.45, 140.12, 129.7, 128.04, 127.93, 127.54, 80.70, 70.26, 60.65, 54.46. HRMS (ES): *m/z* calcd for $C_{20}H_{17}BrONa$: 375.04 (100.0%), 376.04 (21.9%), 377.03 (97.3%), 378.04 (21.3%), found 375.1 (100%), 376.1 (21.5%), 377.1 (97%), 378.1 (21.7%). 25% ee (measured by HPLC on (*S*,*S*)-ULMO column with hexane/*i*-PrOH 99/1; flow rate 0.8 mL/min; τ_{minor} = 6.9 min, τ_{major} = 7.5 min).

5.16. Preparation of 9-(3-bromobicyclo[2.2.1]hepta-2,5-dien-2-yl)-9*H*-fluoren-9-ol 23b

(−)-Sparteine (101 μL, 0.56 mmol) was dissolved in Et_2O (4 mL). Under argon at −78 °C, *n*-BuLi (192 μL, 0.44 mmol) was added dropwise, and the mixture was stirred at this temperature for 30 min. 2,3-Dibromonorbornadiene (100 mg, 0.4 mmol) dissolved in diethyl ether (1 mL) was added to the mixture. The mixture was stirred at −78 °C for 1.5 h after which fluorenone (87 mg, 0.48 mmol) in Et_2O (1 mL) was added dropwise. The low temperature was maintained for 1 h and then the cooling bath was removed. The mixture was stirred at rt for another 2 h and then quenched with saturated NH_4Cl aqueous solution. The organic layer was washed twice with water, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified on TLC plate eluting with pentane/Et_2O (8/2) yielding 119 mg (85%) of a very pale yellow oil. ^{1}H NMR: δ = 7.84 (d, 2H, *J* = 6.8 Hz), 7.61 (d, 2H, *J* = 7.2 Hz, 7.53 (m, 4H, 6.82 (dd, 1H, *J* = 2.7 Hz, *J* = 4.7 Hz, 6.51 (dd, 1H, *J* = 3.0 Hz, *J* = 5.0 Hz, 3.60 (br s, 1H, 3.45 (br s, 1H), 3.05 (s, 1H), 2.39 (d, 1H, *J* = 6.2 Hz), 1.97 (d, 1H, *J* = 6.3 Hz). ^{13}C NMR: δ = 196.77, 143.88, 142.52, 140.21, 137.64, 132.44, 130.09, 129.76, 128.31, 128.12, 128.01, 127.62, 80.8, 70.35, 60.74, 54.56. HRMS (ES): *m/z* calcd for $C_{20}H_{15}BrONa$: 373.02 (99.0%), 374.02 (21.7%), 375.03 (100.0%), 376.02 (21.2%), 377.03 (2.2%), found: 373.1 (99.0%), 374.02 (21.4%), 375.1 (100.0%), 376.1 (21.2%), 377.1 (2.1%). 2% ee (measured by HPLC on (*S*,*S*)-ULMO column with hexane/*i*-PrOH 99/1; flow rate 0.8 mL/min; τ_{minor} = 8.15 min, τ_{major} = 8.53 min).

5.17. Preparation of 1-(3-bromobicyclo[2.2.1]hepta-2,5-dien-2-yl)-cyclohexanol 23c

(−)-Sparteine (101 μL, 0.56 mmol) was dissolved in Et_2O (4 mL). Under argon at −78 °C, *n*-BuLi (192 μL, 0.44 mmol) was added dropwise, and the mixture was stirred at this temperature for 30 min. 2,3-Dibromonorbornadiene (100 mg, 0.4 mmol) dissolved in Et_2O (1 mL) was added to the mixture. The mixture was stirred at −78 °C for 1 h and then cyclohexanone (50 μL, 0.48 mmol) in Et_2O (1 mL) was added dropwise. The temperature was maintained at this low temperature for 1 h and then the cooling bath was removed. The mixture was stirred at room temperature for another 2 h and then quenched with saturated NH_4Cl aqueous solution. The organic layer was washed twice with water, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified on TLC plate eluting pentane/Et_2O (8/2) yielding 93 mg (87%) of a pale yellow oil. ^{1}H NMR: δ = 6.88 (dd, 1H, *J* = 3.2 Hz, *J* = 5.0 Hz), 6.78 (dd, 1H, *J* = 3.0 Hz, *J* = 4.8 Hz), 3.71 (br s, 1H), 3.47 (br s, 1H), 2.17 (d, 1H, *J* = 6.0 Hz), 1.94 (d, 1H, *J* = 6.0 Hz), 1.67 (m, 10H), CH_2. ^{13}C NMR: δ = 154.12, 142.39, 141.79, 126.90, 72.82, 70.77, 60.55, 52.84, 35.48, 35.11, 25.45, 21.39 (2*C); HRMS (ES): *m/z* calcd for $C_{13}H_{17}BrONa$: 291.04 (100.0%), 292.04 (14.3%), 293.03 (98.4%), 294.04 (13.9%), 295.04 (1.1%), found: 291.04 (99.0%), 293.03 (100.0%). 8% ee (measured by HPLC on ODH column with hexane/*i*-PrOH 99/1; flow rate 0.8 mL/min; τ_{minor} = 8.0 min, τ_{major} = 8.38 min).

5.18. Preparation of 1-iodo, 2-diphenylmethanol-ferrocene (S_p)-25

(−)-Sparteine (60 μL, 0.25 mmol) was dissolved in Et_2O (2 mL). Under argon at −78 °C, *n*-BuLi (100 μL, 0.25 mmol) was added dropwise, and the mixture was stirred at this temperature for 30 min. 1,2-Diiodoferrocene **4** (100 mg, 0.23 mmol) dissolved in Et_2O (1 mL) was added to the mixture. The mixture was stirred at −78 °C for 1.5 h and then benzophenone (54 mg, 0.29 mmol) in Et_2O (1 mL) was added dropwise. The low temperature was maintained for 1 h and then the cooling bath was removed. The mixture was stirred at rt for another 2 h and hydrolyzed with saturated NH_4Cl aqueous solution. The organic layer was washed twice with water, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The crude product was purified on a TLC plate eluting with pentane/Et_2O (9/1) yielding 97 mg (86%) of a yellow solid. 34% ee (measured by OD-H with hexane/*i*-PrOH 99/1; flow rate 0.8 mL/min; τ_{minor} (R_p) = 7.6 min, τ_{major} (S_p) = 8.2 min). ^{1}H NMR: δ = 7.45 (m, 2H), 7.30 (m, 6H), 7.15 (m, 2H), 4.57 (br s, 1H), 4.30 (s, 5H), 4.18 (t, 1H, *J* = 2.5 Hz), 3.74 (s, 1H), 3.56 (dd, 1H, *J* = 1.5 Hz, *J* = 2.3 Hz). ^{13}C NMR: δ = 173.92, 146.46, 145.48, 127.75, 127.66, 127.26, 127.01, 126.90, 97.52, 78.20, 71.77, 71.63, 68.22, 40.85. HRMS (ES): *m/z* calcd for $C_{23}H_{19}FeIO$: 491.99 (6.4%), 493.98 (100.0%), 494.99 (25.1%), found: 491.2 (6.5%), 493.98 (100.0%), 494.99 (21.2%).

5.19. Preparation of 1-iodo, ferrocenecarboxaldehyde (S_p)-26

See Ref. 14b.

5.20. NMR in PBLG solvent

The compositions of the oriented NMR samples for compounds **3** (and **4**) are: 100 mg/(100 mg) of PBLG with DP = 782, 100 mg/(40 mg) of solute, and 450 mg/(570 mg) of dry chloroform. Further details on the method and NMR 2D experiments in PBLG can be found in Refs. 16 and 19.

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