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Efficient kinetic resolution in the asymmetric transfer hydrogenation of 3-aryl-indanones: applications to a short synthesis of (+)-indatraline and a formal synthesis of (*R*)-tolterodine†

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Efficient kinetic resolution (KR) occurs in asymmetric transfer hydrogenation (ATH) reactions of racemic 3-aryl-1-indanones using commercial (*R*,*R*)- or (*S*,*S*)-Ts-DENEB as a catalyst, a 1 : 5 mixture of HCO_2H and Et_3N as a hydrogen source and MeOH as solvent. This process at room temperature produces near equal yields of *cis*-3-arylindanols with high dr and ee, and unreacted 3-arylindanones with excellent ee. Stereoselective transformations of 3-arylindanols and 3-arylindanones, generated by using the ATH-KR protocol, were carried out to form (+)-indatraline and synthetically valuable (*R*)-6-methyl-4-phenylcoumarine, which is a key intermediate in the preparation of (*R*)-tolterodine, (*S*)-4-aryl-3,4-dihydroquinoline-2(1*H*)-one and (*S*)-4-aryl-3,4-dihydroisoquinoline-1(2*H*)-one.

Introduction

Indane frameworks are found in natural products that possess diverse biological activities and that serve as drug candidates.[1–3] Among members of this family, 3-arylindanols and 3-arylindanones are privileged structural components of many pharmaceutical agents and key intermediates in the synthesis of a variety of bioactive compounds (Fig. 1).[4–7] Typical examples of this type are (+)-indatraline used for the treatment of depression and cocaine addiction,[8–10] the antihypertensive agent (+) irindalone,[11] the neuroprotective agent (+)-quadrangularin A,[12] (+)-isopaucifloral F used for the treatment of osteoporosis[12] and α-diisoeugenol that has cytotoxic and antioxidant activities.[13] An example of a bioactive indane bearing a 3-alkenyl group is (+)-multisianthol, which has antitumor activity.[14,15] In addition, 3-arylindanoles and 3-arylindanones are valuable intermediates in routes for the synthesis medicinal agents.

Consequently, the development of methods for convenient and stereoselective syntheses of 3-arylindanol and 3-arylindanone is an important goal in organic synthesis. Typically, enantioenriched 3-aryl-1-indanols are prepared by reduction[7] ($NaBH_4$ or K-selectride for 1,3-*syn* indanols) of enantioenriched 3-aryl-1-indanones. Also, Corey's oxazaborolidine-catalyzed reduction of racemic 3-aryl-1-indanones is known to produce mixtures containing almost equal amount of *cis*- and *trans*-3-aryl-1-indanols.[16,17] Furthermore, resolution of racemic 3-aryl-1-indanol has been accomplished using a commercially available lipase (Novozyme 435®).[18] Previous efforts have shown that enantioenriched 3-aryl-1-indanones can be prepared by intramolecular Friedel–Crafts acylation of enantioenriched 3,3-diaryl propanoic acids under strongly acidic conditions,[19–22] or by Ir-catalysed asymmetric hydrogenation of 3-arylinden-1-ones (58–90% ee).[23] Bakers' yeast-promoted conjugate reduction of 3-arylinden-1-ones to form enantioenriched 3-aryl-1-indanones has also been described.[24,25] Recent approaches devised to generate enantioenriched 3-aryl-1-indanones rely on metal (Pd or Ni)-catalyzed asymmetric intramolecular reductive Heck reaction of 2′-halochalcones,[7,26–28] and Rh-catalyzed asymmetric intramolecular 1,4-addition of aryl boronates to enones.[29]

Asymmetric transfer hydrogenation (ATH) reactions, using hydrogen sources other than molecular hydrogen, have proven to be among the most powerful processes for asymmetric reduction of ketones to produce enantioenriched alcohols. These processes have advantages associated with operational simplicity, ready availability of various hydrogen sources, and use of readily accessible and less sensitive catalysts.[30–35] Indeed, stereoselective ATH of 1-indanones or 2-substituted-1-indanones to produce corresponding 1-indanols or 2-substituted-1-indanols, which utilize chiral transition metal (Ru, Rh) catalysts and a HCO_2H/Et_3N mixture as a hydrogen source, have already been described.[36–38] However, no examples have been reported thus far of ATH promoted transformations of 3-aryl-1-indanones to 3-aryl-indanols having stereogenic

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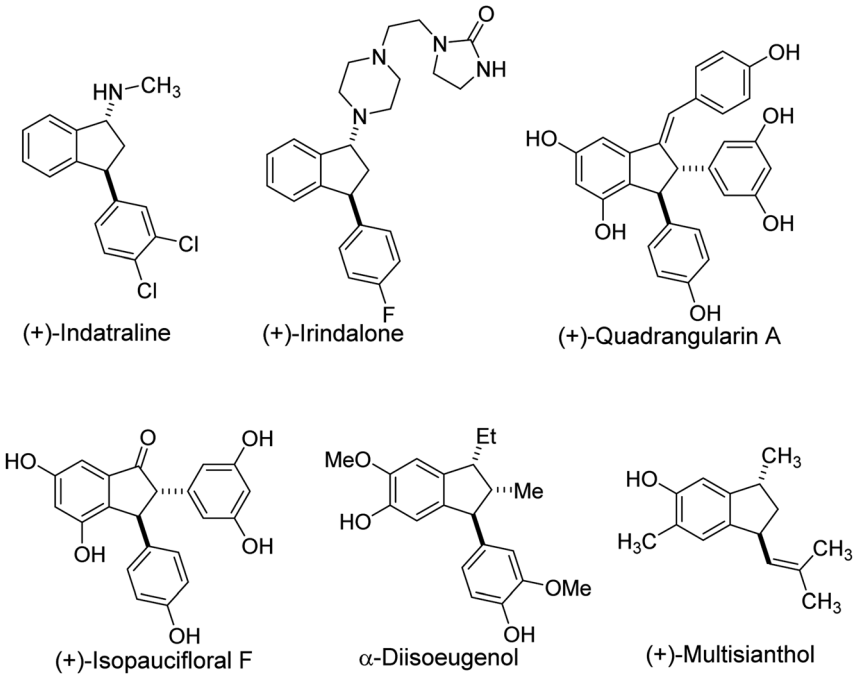

Fig. 1 Examples of biologically active 3-(aryl)-substituted indanes.

centers at C-3. This deficiency encouraged us to explore the stereochemical outcome of ATH reactions of 3-aryl-indanones using enantioenriched chiral transition metal catalysts and a HCO_2H/Et_3N mixture as the hydrogen source.

Results and discussion

Previously, it was reported that ATH reaction of 3-methoxycarbonyl-1-indanone (**3**) with Mohar's Ru-catalyst (**C4**, Scheme 1d), containing benzosultam (*syn*-ULTAM) ligand and HCO_2H/Et_3N (5 : 2) as hydrogen source (40 °C, 6 h), produces *cis*-(1*R*,3*S*)-3-methoxycarbonyl-1-indanol with high levels of diastereoselectivity and enantioselectivity, owing to dynamic kinetic resolution (DKR) resulting from rapid racemization of the dually activated C-3 hydrogen (Scheme 1a).[39,40] Because Mohar's catalyst **C4** is not commercially available, we assessed whether the ATH reaction of 3-methoxycarbonyl-1-indanone (**3**) would take place efficiently employing commercial (*R*,*R*)-Ts-DENEB (**C3**) instead of **C4** as catalyst under the same reaction conditions. The oxo-tethered Ru-catalysts (*R*,*R*)- and (*S*,*S*)-Ts-DENEB (**C3**) which were developed by T. Touge and T. Ikariya *et al.* generally showed, among the Noyori-type chiral Ru-catalysts, enhanced catalytic performance with excellent levels of stereoselectivity in the asymmetric transfer hydrogenation reactions of ketonic substrates.[36,41]

The results show that **C3** also promotes ATH reaction of **3** that forms the *cis*-(1*R*,3*S*)-indanol **4** with excellent levels of stereoselectivity (95%, 99% ee) accompanying DKR (Scheme 1b). This finding led us to speculate that ATH reaction of the 3-arylindanone **1s** using **C3** as catalyst under similar reaction conditions would also produce the corresponding 3-arylindanol stereoselectively, hopefully accompanying DKR.

Contrary to expectation, subjection of 3-(3,4-dichlorophenyl)-1-indanone (**1s**) to the same conditions used for reduction of 3-methoxycarbonyl-1-indanone (**3**) (**C3** as catalyst, FA/TEA = 5 : 2, 40 °C) leads to incomplete reaction (72%) and formation of a 76 : 24 mixture of *cis* (99% ee) and *trans* indanol **2s**, and 28% of enantioenriched indanone **1s** (99% ee) (Scheme 1c). In an attempt to find ATH reaction conditions which induce DKR, we employed stronger base of DBU ($pK_a = 24.3$)[42] instead of Et_3N ($pK_a = 18.8$) in the ATH reaction of **1s**. However, ATH of **1s** with FA/DBU (5 : 2) for 24 h, otherwise under the same reaction conditions, is still incomplete (60% conversion) affording 87 : 13 mixture of *cis* (87% ee) and *trans* indanol **2s**, and 40% of unreacted indanone **1s** (99% ee) (Scheme 1d). When the reaction temperature of ATH reaction of **1s** with FA/DBU (5 : 2) was increased to 60 °C for 24 h, the conversion of the ATH reaction was increased to 81% but, dr (*cis*-**2s**: *trans* **2s** = 73 : 27) and ee of *cis*-**2s** (67% ee) was rapidly decrease. Therefore, since ATH reaction of **1s** in the presence of (*R*,*R*)-Ts-DENEB (**C3**) and FA/Et_3N (5 : 2) as hydrogen source provided *cis*-indanol **2s** (99% ee) and of enantioenriched indanone **1s** (99% ee) in a single step we changed our attention to ATH accompanying kinetic resolution using FA/Et_3N rather than attempted ATH-DKR employing FA/DBU (Scheme 1c).

To uncover conditions that would make this process more selective, ATH reaction of **1s** was conducted under the same reaction conditions but at 23 °C rather than 40 °C for 24 h. Interestingly, the process was found to generate a 92 : 8 mixture of *cis* (99% ee) and *trans* indanol **2s** in 56% yield along with 44% of enantioenriched 3-arylindanone **1s** (99% ee). These results show that ATH reaction of **1s** is not accompanied by DKR and that it proceeds with kinetic resolution (KR) to generate near equal amounts of enantioenriched 3-arylindanol **2s** and 3-arylindanone **1s** with excellent stereoselectivities for both of the *cis*-3-arylindanol **2s** (99% ee) and recovered 3-arylindanone **1s** (99% ee). Thus, the nature of 3-substituent governed lability of the

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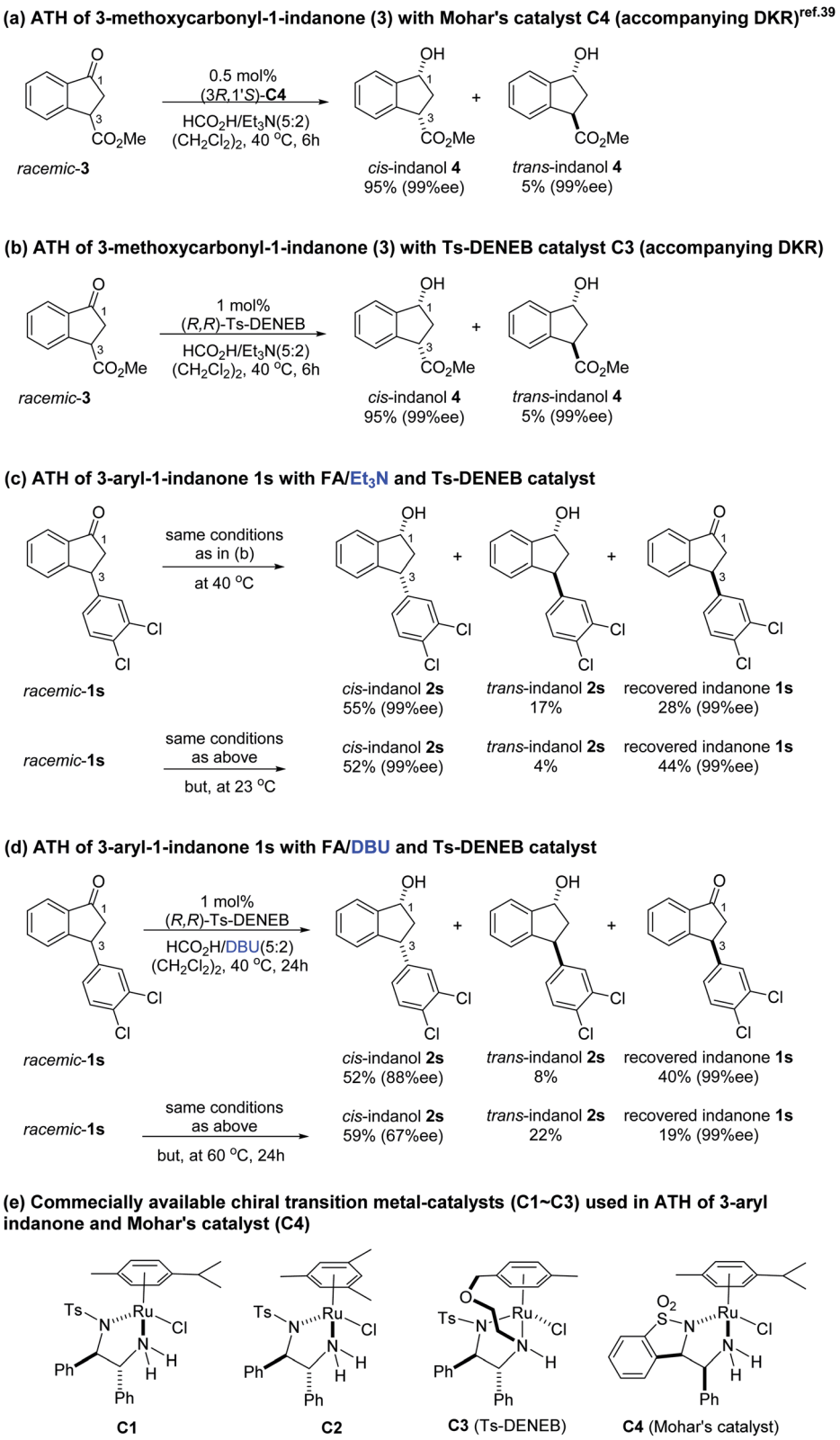

Scheme 1 ATH reactions of 3-methoxycarbonyl-1-indanone (**3**) and 3-aryl-1-indanone **1s**.

proton at C-3 center controls whether or not the ATH process is attended by DKR. This is further demonstrated by the observation that treatment of enantioenriched (*S*)-3-methoxycarbonyl-1-indanone ((*S*)-**3**, 99% ee) with a 5 : 2 FA/TEA mixture in the absence of **C3**, as expected, does not promote formation of the reduction product **4** but instead leads to quantitative recovery of almost completely racemized indanone **3** (1.3% ee) (Scheme 2a). In contrast, reaction of

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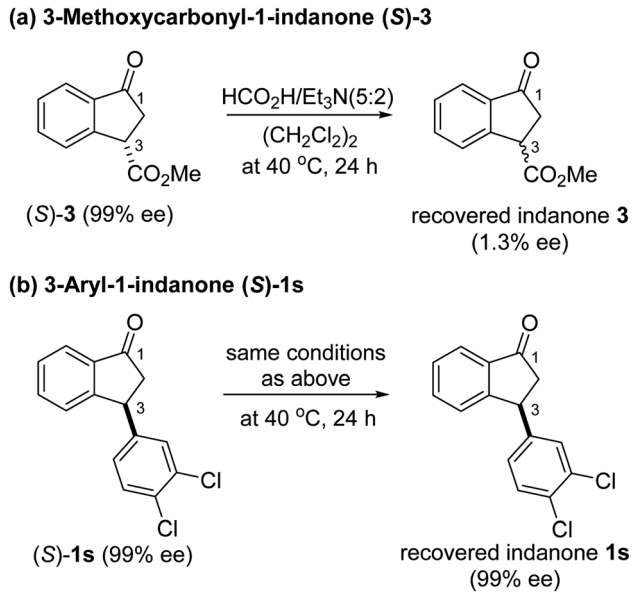
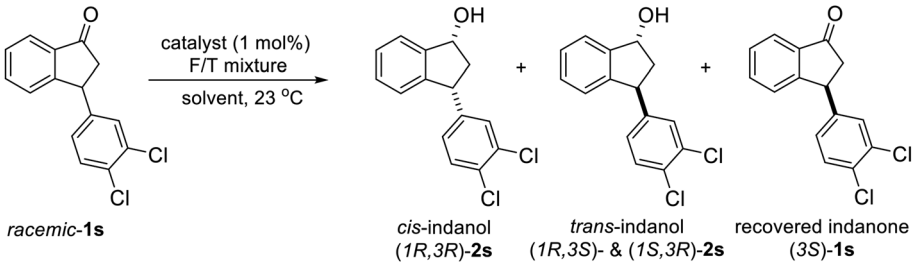


Scheme 2 Racemization experiments of optically active 3-substituted-1-indanones.

enantioenriched (*S*)-3-arylindanone ((*S*)-**1s**) (99% ee) under the same conditions generates (*S*)-**1s** quantitatively without a noticeable decrease in enantiomeric purity (99% ee) (Scheme 2b).

Because enantioenriched forms of variously substituted 3-arylindanols **2** and 3-arylindanones **1** are core motifs in many bioactive natural product and important intermediates in stereoselective syntheses of pharmaceuticals and biologically active compounds, we extended our study to uncover optimal conditions for ATH reactions of racemic 3-arylindanones **1** to produce 3-arylindanols and 3-arylindanones with high levels of stereoselectivity. In the first phase of this investigation, we explored the use of different commercially available chiral Ru-catalysts to promote ATH reaction of racemic 3-arylindanone **1s**. ATH reaction of **1s** (FA : TEA = 5 : 2) using Noyori catalyst (*R*,*R*)-RuCl[TsDPEN](cymene) (**C1**) or (*R*,*R*)-RuCl[TsDPEN](mesitylene) (**C2**) was found to occur for 6 h to form 3-arylindanol **2s** with 53–56% conversions (entries 1 and 2, Table 1), and slightly higher conversions take place when the reaction time is extended to 24 h (65–77% conversion, entries 4 and 5). These processes produce slightly lower *cis*/*trans* ratios of **2s** compared with those catalyzed by (*R*,*R*)-Ts-DENEB (**C3**) but the conversions of **1s** to **2s** in ATH reactions using **C3** are nearly time independent (6 h,

Table 1 Optimization of conditions for ATH-KR reactions of 3-arylindanone **1s**[a]



						Indanol (**2s**)			Indanone (**1s**)
Entry	Cat.	F/T ratio	Solvent	Rxn time (h)	Conv.[b] (%)	*cis* : *trans*[b]	ee (%) of *cis*-**2s**[c]	ee (%) of *trans*-**2s**[c]	ee (%) of recovered **1s**[c]
1	**C1**	5 : 2	DCE	6	53	93 : 7	99	47	97
2	**C2**	5 : 2	DCE	6	56	92 : 8	99	15	99
3	**C3**	5 : 2	DCE	6	56	92 : 8	>99	40	>99
4	**C1**	5 : 2	DCE	24	65	80 : 20	>99	58	96
5	**C2**	5 : 2	DCE	24	77	76 : 24	98	29	91
6	**C3**	5 : 2	DCE	24	57	88 : 12	>99	42	>99
7	**C3**	1 : 1	DCE	6	53	83 : 17	>99	51	57
8	**C3**	1 : 1	DCE	24	58	87 : 13	>99	50	93
9	**C3**	1 : 5	DCE	6	53	89 : 11	>99	53	83
10	**C3**	1 : 5	DCE	24	55	91 : 9	>99	58	95
11	**C3**	1 : 5	CH_3CN	6	32	100 : 0	99	—	48
12	**C3**	1 : 5	CH_2Cl_2	6	28	99 : 1	>99	—	36
13	**C3**	1 : 5	THF	6	31	100 : 0	99	—	46
14	**C3**	1 : 5	EtOAc	6	44	99 : 1	>99	—	80
15	**C3**	1 : 5	DMF	6	46	100 : 0	99	—	83
16	**C3**	1 : 5	Neat	6	50	95 : 5	99	—	96
17	**C3**	**1 : 5**	**MeOH**	**6**	**50**	**100 : 0**	**99**	**—**	**99**
18	**C3**	1 : 5	MeOH	20	50	100 : 0	99	—	99

[a] Reaction conditions: substrate (1 eq., 0.25 mmol), Cat. (1 mol%); FA : TEA = 10 eq. : 4 eq. (5 : 2), 4 eq. : 4 eq. (1 : 1), or 3 eq. : 15 eq. (1 : 5); solvent (0.2 M); rt, under N_2 atmosphere. [b] Determined by using ^{1}H-NMR. [c] Determined by using chiral HPLC.

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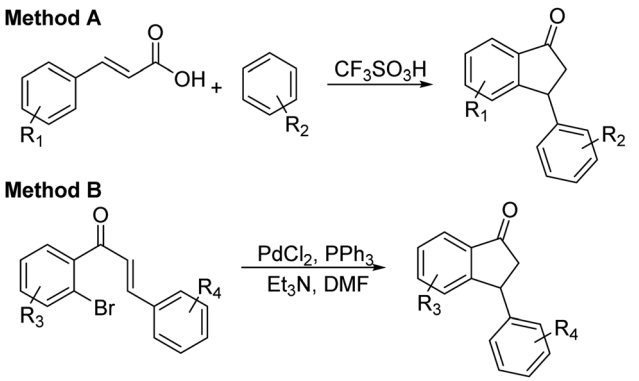
56% and 24 h, 57%) (entries 3 and 6). Because longer time (>24 h) ATH reactions of **1s** under acidic conditions provided by 5 : 2 FA : TEA are accompanied by formation of small quantities of undesired side-products (*e.g.*, indenes resulting from dehydration of indanol **2s**), the process was carried out under non-acidic conditions using 1 : 1 or 1 : 5 FA : TEA mixtures and **C3** as catalyst. ATH reaction using 1 : 5 FA : TEA occurs in a **1s** to **2s** conversion of 53% after 6 h, which remains almost the same after 24 h (55%, entries 9 and 10). Moreover, no indene side-products are detected in the crude product mixture using ^{1}H-NMR analysis. An investigation of the influence of solvents on the ATH reaction of **1s** (entries 11–17) shows that reactions in the CH_3CN, CH_2Cl_2, THF and EtOAc produce *cis*-indanol **2s** in high ee (99% ee), but that the conversion of **1s** to **2s** is less than 50% after 6 h and the % ee of the recovered indanone **1s** is not high (36–83% ee). However, reaction in MeOH for 6 h using 1 : 5 FA/TEA and **C3** as the catalyst (entry 17) leads to reduction of only (3*R*)-**1s** to form (1*R*,3*R*)-**2s** (50%, 99% ee) and recovery of unreacted (3*S*)-**1s** (50%, 99% ee). In addition, when the time for reaction in MeOH is extended to 20 h, the yields and % ee's of (1*R*,3*R*)-**2s** (50%, 99% ee) and (3*S*)-**1s** (50%, 99% ee) remain the same (entry 18).

Having identified optimal conditions (**C3** catalyst, 1 : 5 mixture of FA/TEA, in MeOH at rt for 6 h), the scope and limitations of the ATH-KR reaction were explored using variously substituted 3-aryl-indanones. The requisite racemic 3-aryl-indanones used for this purpose were prepared by triflic acid-catalyzed condensation reactions between the requisite of cinnamic acids and arenes (Scheme 3, Method A),[43–45] or Pd-catalyzed intramolecular reductive Heck cyclization of the corresponding 2′-bromochalcones (Method B).[46,47]

The results show that 3-arylindanones **1**, containing an assortment of electron-donating and -withdrawing substituents, undergo ATH-KR reactions under the optimized conditions within 10 h to generate in most cases the corresponding *cis*-3-aryl-1-indanols (*R*,*R*)-**2** and unreacted 3-aryl-1-indanones (*S*)-**1** with excellent stereoselectivities (Table 2).

Most reactions reach to 50% conversion within 10 h at room temperature and produce almost equal amounts of the corresponding indanols and indanones. Moreover, extending the reaction times to more than 10 h does not affect the conversion ratios and stereoselectivities (Table 1, entries 17 and 18).



Scheme 3 Synthesis of substituted 3-aryl-indanones **1**.

However, in contrast to that of the unsubstituted analog, reactions of 3-arylindanones, containing electron-donating substituents such as Me or OMe on the indanone aromatic ring (Table 2, entries 2–5 and 7), require slightly longer reaction times to attain 50% conversions but the stereoselectivities for both 3-aryl-1-indanol and unreacted 3-aryl-1-indanone formation are excellent. Moreover, ATH-KR reactions of 4-Me-3-phenylindanone (**1b**, Table 2, entry 2) and 7-Me-3-phenylindanone (**1e**, Table 2, entry 5) which have Me substituents near to carbonyl moiety or 3-phenyl substituent are not complete (<50% conversion) even after 20 h. However, by carrying out these reactions using 2 mol% of **C3** as catalyst, 50% conversions are attained after 6 h for **1b** and **1e** (entries 2 and 5). These observations suggest that not only electronic nature but also steric factor of substituents on the indanone ring have an influence on the ATH-KR process, perhaps by affecting formation of the catalyst–substrate complex.

Unlike substituents on the indanone ring, the electronic nature and position of substituents on the 3-aryl ring do not noticeably affect the times required to reach 50% conversion, and stereoselectivities of the 3-arylindanols **2** and recovered 3-arylindanones **1** products remain high. For example, ATH-KR reactions of 3-(2-Cl-phenyl), 3-(3-Cl-phenyl)-, or 3-(4-Cl-phenyl)-1-indanones (**1h–1j**) and 3-(2-Me-phenyl), 3-(3-Me-phenyl)-, or 3-(4-Me-phenyl)-1-indanones (**1k–1m**) reach 50% conversion after 7–8 h and produce the corresponding 3-arylindanols and 3-arylindanones with excellent stereoselectivities (entries 8–13). ATH-KR reactions of 3-arylindanones containing diverse electron-rich or electron-deficient 3-aryl groups (**1n–1q**) proceed in a similar manner to form the corresponding 3-aryl-indanols and unreacted 3-aryl-indanones after 6–8 h with good stereoselectivities (entries 14–17). 3-Arylindanones possessing various substituents on both the indanone and 3-phenyl rings also are suitable substrates for the ATH-KR reaction (entries 20–24). The results show that ATH-KR reactions of 3-arylindanones containing 3-furan (**1y**) and 3-thiophene (**1z**) substituents also produce the corresponding 3-arylindanols and unreacted 3-arylindanones with similar efficiencies and stereoselectivities (entries 25 and 26). In addition, ATH-KR reaction of **1c** under the same conditions, except employing (*S*,*S*)-Ts-DENEB instead of (*R*,*R*)-Ts-DENEB as catalyst, yields the antipodal (*S*,*S*)-3-arylindanol **2c** (45%, 98% ee) and unreacted (*R*)-3-arylindanone **1c** (47%, 99% ee) with excellent levels of stereoselectivity (entry 3). Similarly, ATH-KR reaction of **1s** under the same conditions using (*S*,*S*)-Ts-DENEB as catalyst forms (*S*,*S*)-3-arylindanol **2s** (47%, >99% ee) and unreacted (*R*)-3-arylindanone **1s** (47%, 98% ee) (entries 19 and 27).

The absolute configurations of resulting **2a** as (1*R*,3*R*) and recovered **1a** as (*S*) were determined by comparison of optical rotations and NMR data with those of the known compounds.[7,23,27] The stereochemical outcomes of the ATH reaction can be rationalized by the well-known attractive C–H/π interaction[48,49] in the transition state between η^6 of (*R*,*R*)-Ts-DENEB catalyst (**C3**) and the aromatic ring moiety of indanone **1a** as shown in Fig. 2. The *cis* product of **2a** might be favored as a consequence of 3-phenyl substituent of **1a** keeping away from the reaction site in the transition state.[41]

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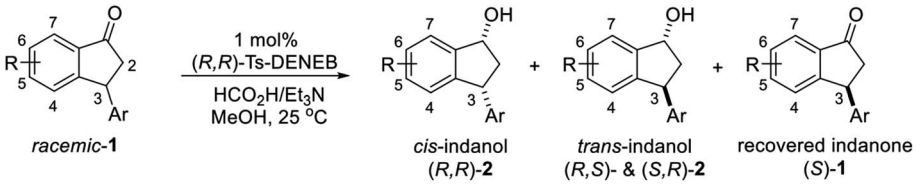
Table 2 ATH-KR reactions of 3-arylindanones[a]



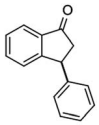
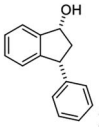
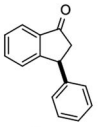
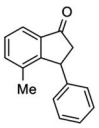
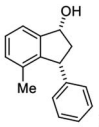
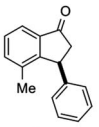
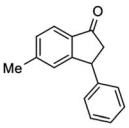
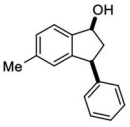
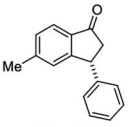
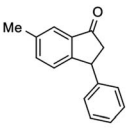
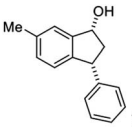
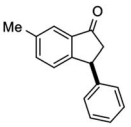
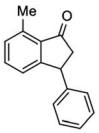
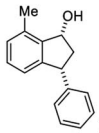
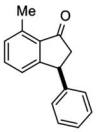
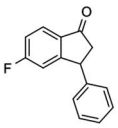
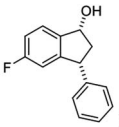
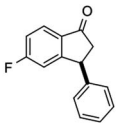
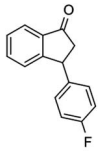
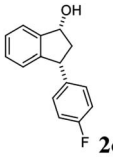
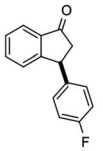
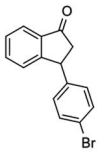
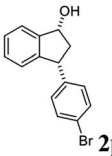
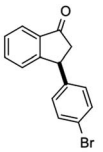
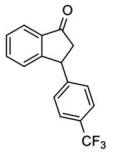
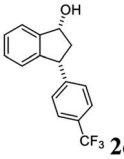
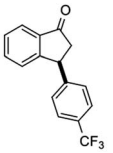
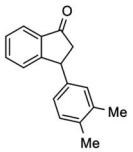
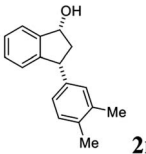
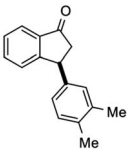
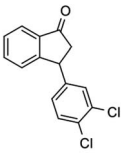
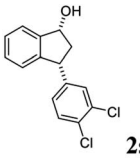
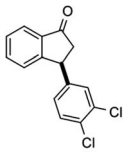
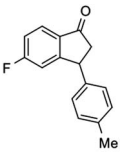
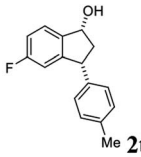
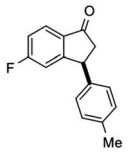
Entry	Substrate (1)	Time (h)	Conv[b] (%)	Indanol (2)[c]	Recovered indanone[c]
1	 **1a**	9	50	 **2a** 45% (97% ee) *cis:trans*=99:1	 (*S*)-**1a** 35% (96% ee)
2	 **1b**	6[d]	50	 **2b** 43% (95% ee) *cis:trans*=99:1	 (*S*)-**1b** 47% (94% ee)
3[e]	 **1c**	10	50	 **2c** 45% (97% ee) *cis:trans*=99:1	 (*R*)-**1c** 47% (>99% ee)
4	 **1d**	10	50	 **2d** 45% (98% ee) *cis:trans*=99:1	 (*S*)-**1d** 39% (96% ee)
5	 **1e**	6[d]	50	 **2e** 42% (>99% ee) *cis:trans*=>99:1	 (*S*)-**1e** 47% (94% ee)
6	 **1f**	10	50	 **2f** 41% (94% ee) *cis:trans*=>99:1	 (*S*)-**1f** 45% (>99% ee)
15	 **1o**	6	50	 **2o** 45% (98% ee) *cis:trans*=>99:1	 (*S*)-**1o** 46% (94% ee)
16	 **1p**	8	51	 **2p** 41% (99% ee) *cis:trans*=>99:1	 (*S*)-**1p** 42% (94% ee)
17	 **1q**	8	52	 **2q** 49% (97% ee) *cis:trans*=99:1	 (*S*)-**1q** 46% (94% ee)
18	 **1r**	9	50	 **2r** 45% (99% ee) *cis:trans*=>99:1	 (*S*)-**1r** 50% (>99% ee)
19	 **1s**	6	50	 **2s** 47% (99% ee) *cis:trans*=99:1	 (*S*)-**1s** 47% (99% ee)
20	 **1t**	11	50	 **2t** 42% (99% ee) *cis:trans*=99:1	 (*S*)-**1t** 43% (99% ee)

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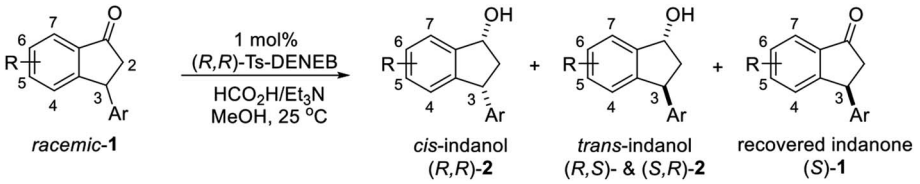
Table 2 (*Contd.*)



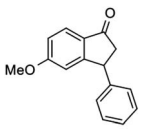
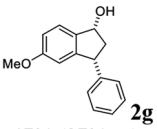
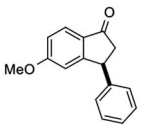
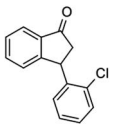
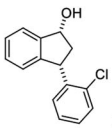
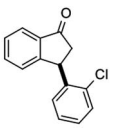
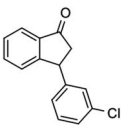
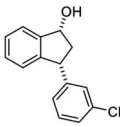
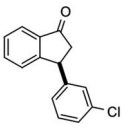
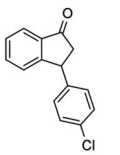
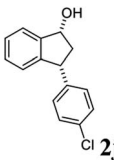
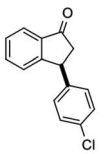
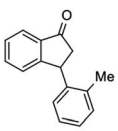
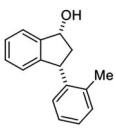
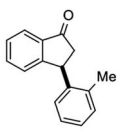
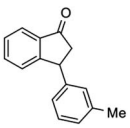
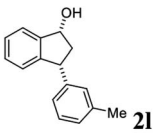
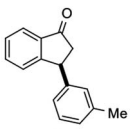
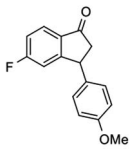
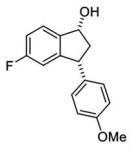
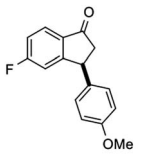
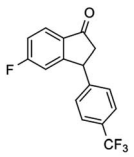
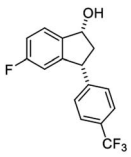
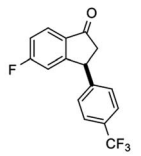
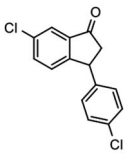
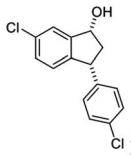
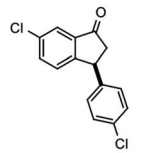
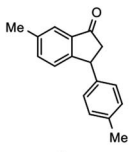
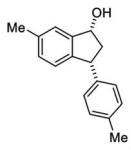
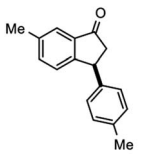
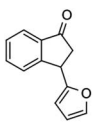
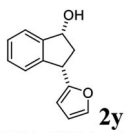
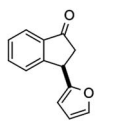
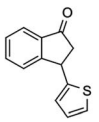
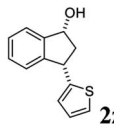
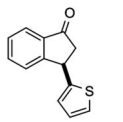
Entry	Substrate (1)	Time (h)	Conv[b] (%)	Indanol (2)[c]	Recovered indanone[c]
7	 **1g**	17[d]	50	 **2g** 47% (97% ee) *cis:trans*=>99:1	 (*S*)-**1g** 48% (98% ee)
8	 **1h**	7	50	 **2h** 42% (92% ee) *cis:trans*=99:1	 (*R*)-**1h** 43% (97% ee)
9	 **1i**	7	50	 **2i** 38% (99% ee) *cis:trans*=98:2	 (*S*)-**1i** 41% (92% ee)
10	 **1j**	7	50	 **2j** 44% (98% ee) *cis:trans*=99:1	 (*S*)-**1j** 45% (90% ee)
11	 **1k**	8	50	 **2k** 43% (98% ee) *cis:trans*=>99:1	 (*S*)-**1k** 43% (97% ee)
12	 **1l**	7	50	 **2l** 43% (94% ee) *cis:trans*=99:1	 (*S*)-**1l** 41% (96% ee)
21	 **1u**	11	52	 **2u** 42% (95% ee) *cis:trans*=98:2	 (*S*)-**1u** 45% (98% ee)
22	 **1v**	10	52	 **2v** 43% (92% ee) *cis:trans*=99:1	 (*S*)-**1v** 43% (99% ee)
23	 **1w**	5	51	 **2w** 50% (98% ee) *cis:trans*=>99:1	 (*S*)-**1w** 45% (99% ee)
24	 **1x**	10	51	 **2x** 42% (98% ee) *cis:trans*=>99:1	 (*S*)-**1x** 46% (99% ee)
25	 **1y**	7	51	 **2y** 40% (98% ee) *cis:trans*=99:1	 (*R*)-**1y** 41% (95% ee)
26	 **1z**	8	50	 **2z** 43% (98% ee) *cis:trans*=99:1	 (*R*)-**1z** 50% (94% ee)

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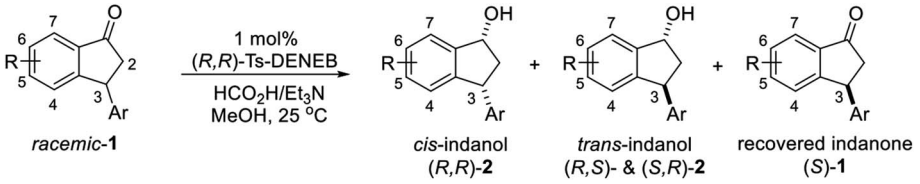
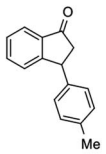
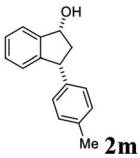
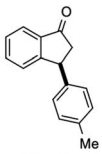
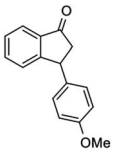
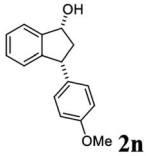
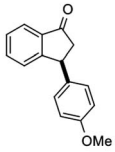
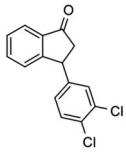
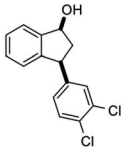
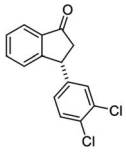
Table 2 (*Contd.*)



Entry	Substrate (1)	Time (h)	Conv[b] (%)	Indanol (2)[c]	Recovered indanone[c]
13	 **1m**	7	49	 **2m** 42% (95% ee) *cis:trans*=>99:1	 (*S*)-**1m** 41% (>99% ee)
14	 **1n**	7	51	 **2n** 45% (99% ee) *cis:trans*=>99:1	 (*S*)-**1n** 44% (>99% ee)
27[e]	 **1s**	6	50	 **2s** 47% (99% ee) *cis:trans*=99:1	 (*R*)-**1s** 47% (98% ee)

[a] Reaction conditions: substrate **1** (1 eq., 0.5 mmol), (*R*,*R*)-Ts-DENEB catalyst (1 mol%), FA : TEA (3 eq. : 15 eq.), MeOH (0.2 M, 2.5 mL), rt (23 °C) under N_2 atmosphere. [b] Determined by using ^{1}H NMR. [c] Yields correspond to isolated yields, % ee's were determined by chiral HPLC. Absolute stereochemistry was determined by comparison with optical rotation of known compounds. [d] 2 mol% of (*R*,*R*)-Ts-DENEB catalyst was used. [e] (*S*,*S*)-Ts-DENEB catalyst (1 mol%) was used.

Highly enantiomerically enriched 3-aryl-1-indanols **2** and 3-aryl-1-indanones **1** produced in the ATH-KR reactions are valuable intermediates for the synthesis of medicinally important compounds such as (+)-indatraline[8] or (*R*)-tolterodine.[50] To demonstrate this assertion, (*S*,*S*)-3-(3,4-dichlorophenyl)-1-indanol (**2s**), formed by ATH-KR reaction of **1s**, was converted to (+)-indatraline *via* mesylation and subsequent reaction of the formed mesylate with methylamine in the same flask (Scheme 4a).[7,18] In a route for the synthesis of (*R*)-tolterodine, a potent and competitive muscarinic antagonist that is currently used for the treatment of urinary urge incontinence,[50] (*R*)-5-methyl-3-phenyl-1-indanone (**1c**) obtained from ATH-KR reaction of **1c** was transformed to (*R*)-6-methyl-4-phenylcoumarine (**5**) *via* Baeyer–Villiger oxidation without deterioration of optical purity (Scheme 4b). Because the conversion of (*R*)-**5** to (*R*)-tolterodine *via* DIBAL-H reduction to a lactol and subsequent reductive amination with diisopropylamine has been reported,[7,51–53] this route constitutes a formal synthesis of (*R*)-tolterodine (Scheme 4b). Finally, to demonstrate applications to the synthesis of quinoline derivatives, treatment of (*S*)-3-(3,4-dichlorophenyl)-1-indanone oxime *O*-tosylate (**6**), obtained from (*S*)-**1s**, using 1.5 equiv. of $AlCl_3$ at room temperature,[54] produces the readily separable mixture of (*S*)-4-aryl-3,4-dihydroquinoline-2(1*H*)-one ((*S*)-**7**) and (*S*)-4-aryl-3,4-dihydroisoquinoline-1(2*H*)-one ((*S*)-**8**).

Conclusions

In summary, this effort demonstrates that efficient kinetic resolution (KR) attends asymmetric transfer hydrogenation

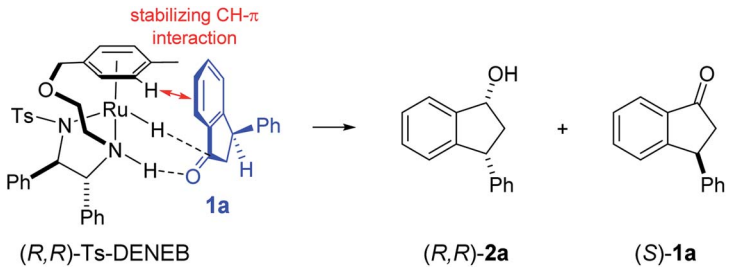


Fig. 2 Proposed asymmetric induction model[41] in the ATH-KR of racemic-**1a** to (*R*,*R*)-**2a** and (*S*)-**1a**.

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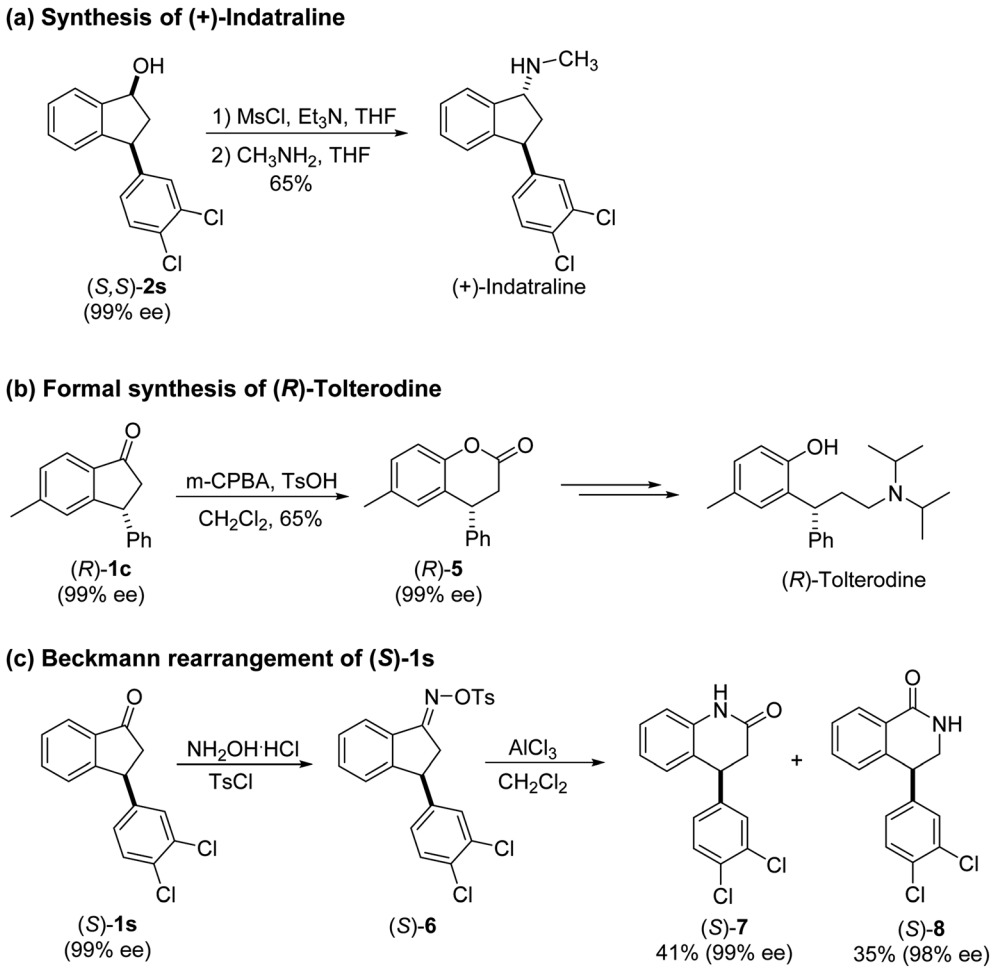

Scheme 4 Synthetic applications.

(ATH) reactions of diverse racemic 3-aryl-1-indanones when commercial (*R*,*R*)- or (*S*,*S*)-Ts-DENEB is employed as catalyst, a 1 : 5 mixture of HCO_2H and Et_3N is used as a hydrogen source and MeOH is utilized as solvent. These processes, carried out at room temperature, produce near equal amounts of the corresponding *cis*-3-arylindanols and unreacted 3-arylindanones with excellent levels of diastereo- and enantio-selectivity. The key merit of the process is that it forms both highly enantiomerically enriched *cis*-3-arylindanols and 3-arylindanones in a single step. In addition, selected stereoselective transformations of 3-arylindanol and 3-arylindanones generated by the ATH-KR process, demonstrate the usefulness of this method in producing key intermediates for the preparation of (+)-indatraline, (*R*)-tolterodine, (*S*)-4-aryl-3,4-dihydroquinoline-2(1*H*)-one and (*S*)-4-aryl-3,4-dihydroisoquinoline-1(2*H*)-one.

Experimental section

General

Synthetic procedure and characterization data of starting 3-aryl-1-indanones **1a–1z** are included in the ESI.† All reactions were conducted under an inert atmosphere of nitrogen using anhydrous solvents. Mixtures of HCO_2H/Et_3N (5 : 2 and 1 : 1) are commercially available and 1 : 5 mixture of HCO_2H/Et_3N was prepared by adding 1 equiv. of Et_3N to 5 equiv. of HCO_2H at 0 °C under a nitrogen atmosphere and used as such. Chiral transition metal catalysts **C1–C3** were purchased from commercial vendors. The progress of reactions was monitored using thin layer chromatography (TLC) and visualized using UV light and by staining with ethanolic phosphomolybdic acid (PMA) solution or ninhydrin solution followed by heating. Flash column chromatography was carried out on silica gel (38–75 μm). Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates. Preparative thin layer chromatography (PLC) was performed on Merck silica gel 60 F_{254} 2 mm plates. Syntheses under microwave system were conducted by using CEM Discover SP. Nuclear magnetic resonance (NMR) spectra were recorded using Bruker 500 MHz NMR instrument (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) or Bruker 400 MHz NMR instrument (^{1}H NMR at 400 MHz and ^{13}C NMR at 101 MHz). ^{1}H NMR data are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constants (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). High performance liquid chromatography (HPLC) was carried out on a Young Lin HPLC system (7725i Injector,

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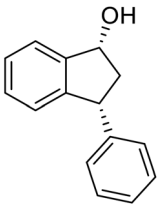
SDV 30 Plus Solvent Degassor & Valve Module (Helium Sparging), SP930D Solvent Delivery Pump, UV 730D Absorbance Detector) equipped with a Chiralpak IA, IB, IC, ID or Chiralpak AD-H, Chiralcel OD-H column. Specific rotations were measured on a Rudolph Autopol IV (Automatic polarimeter). High-resolution mass spectra and elemental analysis were obtained from the Korea Research Institute of Chemical Technology. HR-MS were measured with electron impact (EI) *via* double focusing mass analyzer (magnetic and electric fields) or electrospray ionization (ESI) *via* time of flight (TOF) analyzer.

Representative procedure for the ATH of 3-phenyl-1-indanone (1a) accompanying kinetic resolution

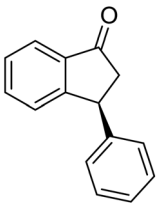
To a solution of 3-phenyl-1-indanone (**1a**, 104 mg, 0.5 mmol) and triethylamine (1.06 mL, 7.5 mmol) dissolved in methanol (1.5 mL) was added formic acid (63.4 μL, 1.5 mmol) followed by (*R*,*R*)-Ts-DENEB catalyst (3.2 mg, 0.005 mmol dissolved in 1.0 mL of methanol). The reaction mixture was stirred at 25 °C under of N_2 atmosphere. After the reaction time specified in the Table 2 (6–14 h), the reaction mixture was diluted with chloroform (30 mL) and washed with water and brine (20 mL) successively. The organic layer was dried with $MgSO_4$, filtered and concentrated by rotary evaporation. The resulting mixture of 3-phenyl-1-indanol (**2a**) and unreacted remaining **1a** were easily separated by flash column chromatography (ethyl acetate : *n*-hexane 1 : 7). dr and ee's of the resulting indanol **2a** and unreacted remaining indanone **1a** were determined by chiral HPLC. (Racemic *cis*- and *trans*-3-phenyl-1 indanols (**2a**) were obtained by $NaBH_4$ reduction of **1a** in MeOH.) Absolute configurations were determined by comparison of optical rotations and NMR data with those of the known compounds.

(1*R*,3*R*)-3-Phenyl-2,3-dihydro-1*H*-inden-1-ol (2a)



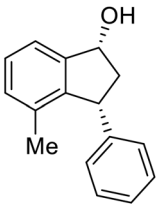
Yield 45% (46.7 mg as white solid); mp 95.2–95.9 °C; 97% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 23.2 min, t_R(minor) = +16.9 min); $[\alpha]_D^{24}$ = −15.6 (*c* 1.13, CH_2Cl_2). Literature values: $[\alpha]_D^{23}$ = −11 (*c* 1, $CHCl_3$ for 95% ee).[27] $[\alpha]_D^{23}$ = +16.1 (*c* 0.1, CH_2Cl_2 for 86% ee)[23] for (1*S*,3*S*)-**2a**; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48 (d, 1H, *J* = 7.5 Hz), 7.36–7.27 (m, 3H), 7.27–7.18 (m, 4H), 6.95 (d, 1H, *J* = 7.5 Hz), 5.34–5.23 (m, 1H), 4.19 (t, 1H, *J* = 8.4 Hz), 3.03 (dt, 1H, *J* = 12.9, 7.2 Hz), 2.07–1.90 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 145.6, 145.2, 144.2, 128.6, 128.4, 128.3, 127.2, 126.6, 125.1, 123.7, 75.1, 48.3, 47.2; HRMS (EI, double focusing) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{14}O$ 210.1045; found 210.1054.

(*S*)-3-Phenyl-2,3-dihydro-1*H*-inden-1-one, (*S*)-1a



Yield 35% (36.4 mg as white solid); 98% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 15.0 min, t_R(minor) = 16.2 min); $[\alpha]_D^{20}$ = +72.8 (*c* 1.5, CH_2Cl_2). Literature values: $[\alpha]_D^{25}$ = +64.9 (*c* 0.4, CH_2Cl_2 for 86% ee).[23] $[\alpha]_D^{23}$ = −49 (*c* 1.0, $CHCl_3$) for 91% ee of (*R*)-**1a**;[7] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (d, 1H, *J* = 7.7 Hz), 7.57 (t, 1H, *J* = 7.4 Hz), 7.42 (t, 1H, *J* = 7.4 Hz), 7.32 (t, 2H, *J* = 7.4 Hz), 7.29–7.24 (m, 2H), 7.2–7.09 (m, 2H), 4.58 (dd, 1H, *J* = 8.1, 3.9 Hz), 3.24 (dd, 1H, *J* = 19.2, 8.1 Hz), 2.70 (dd, 1H, *J* = 19.2, 3.9 Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$,101 MHz) δ 206.0, 158.0, 143.7, 136.7, 135.1, 128.9, 127.9, 127.6, 127.0, 126.9, 123.4, 46.8, 44.5; HRMS (EI, double focusing) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{12}O$ 208.0888; found 208.0883.

(1*R*,3*R*)-4-Methyl-3-phenyl-2,3-dihydro-1*H*-inden-1-ol (2b)



Yield 43% (48.2 mg as white solid); mp 122.6–123.3 °C; 95% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 16.6 min, t_R(minor) = 25.4 min); $[\alpha]_D^{29}$ = −5.6 (*c* 2.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 (d, 1H, *J* = 7.5 Hz), 7.30–7.23 (m, 3H), 7.18 (t, 1H, *J* = 7.3 Hz), 7.13 (d, 2H, *J* = 7.1 Hz), 7.09 (d, 1H, *J* = 7.3 Hz), 5.21 (s, 1H), 4.29 (dd, 1H, *J* = 8.6, 5.3 Hz), 3.00 (dt, 1H, *J* = 13.8, 8.6, 7.3 Hz), 1.97 (dt, 1H, *J* = 13.8, 4.8 Hz), 1.89 (s, 3H), 1.81 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 145.8, 145.4, 143.4, 135.5, 130.4, 128.6, 127.9, 127.8, 126.2, 121.9, 75.6, 48.4, 46.3, 19.1; HRMS (EI, double focusing) *m*/*z*: $[M]^+$ calcd for $C_{16}H_{16}O$ 224.1201; found 224.1191.

(*S*)-4-Methyl-3-phenyl-2,3-dihydro-1*H*-inden-1-one, (*S*)-1b

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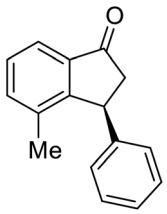
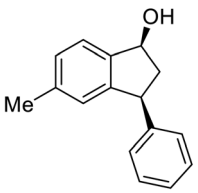


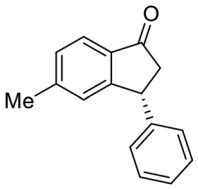
Yield 47% (52.1 mg as white solid); 94% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 14.6 min, t_R(minor) = 16.1 min); $[\alpha]_D^{29}$ = +36.3 (*c* 2.77, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (d, 1H, J = 6.6 Hz), 7.41–7.34 (m, 2H), 7.29–7.25 (m, 2H), 7.21 (t, 1H, J = 7.3 Hz), 7.02 (d, 2H, J = 7.1 Hz), 4.58 (dd, 1H, J = 8.3, 2.6 Hz), 3.24 (dd, 1H, J = 19.2, 8.3 Hz), 2.60 (dd, 1H, J = 19.2, 2.6 Hz), 2.02 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 206.6, 155.6, 143.7, 137.2, 136.8, 136.4, 128.9, 128.4, 127.4, 126.7, 121.0, 47.6, 43.9, 18.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{14}O$ 222.1045; found 222.1037.

(1*S*,3*S*)-5-Methyl-3-phenyl-2,3-dihydro-1*H*-inden-1-ol (2c)



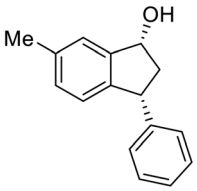
Yield 44% (49 mg as white solid); mp 118.3–118.7 °C; 97% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 16.6 min, t_R(minor) = 23.9 min); $[\alpha]_D^{25}$ = +7.3 (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38–7.30 (m, 3H), 7.28–7.21 (m, 3H), 7.11 (d, 1H, J = 7.7 Hz), 6.75 (s, 1H), 5.28–5.22 (m, 1H), 4.15 (t, 1H, J = 8.3 Hz), 3.01 (dt, 1H, J = 12.9, 7.3 Hz), 2.28 (s, 3H), 1.99–1.90 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.9, 144.4, 142.4, 138.3, 128.6, 128.3, 128.1, 126.5, 125.6, 123.5, 74.9, 48.3, 47.2, 21.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{16}O$ 224.1201; found 224.1207.

(*R*)-5-Methyl-3-phenyl-2,3-dihydro-1*H*-inden-1-one, (*R*)-1c



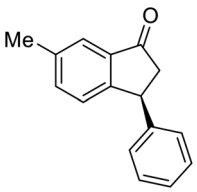
Yield 47% (52.2 mg as white solid); >99% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 16.0 min, t_R(minor) = 15.1 min); $[\alpha]_D^{21}$ = −29.4 (*c* 1.7, CH_2Cl_2). Literature values for (*S*)-**1c**: $[\alpha]_D^{23}$ = +28.9° (*c* 1.0, $CHCl_3$ for 97% ee).[7] $[\alpha]_D^{25}$ = +20.3 (*c* 0.1, CH_2Cl_2 for 86% ee);[23] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, 1H, J = 7.9 Hz), 7.34–7.28 (m, 2H), 7.28–7.24 (m, 1H), 7.22 (d, 1H, J = 7.9 Hz), 7.12 (d, 2H, J = 7.1 Hz), 7.05 (s, 1H), 4.51 (dd, 1H, J = 8.0, 3.8 Hz), 3.21 (dd, 1H, J = 19.1, 8.0 Hz), 2.67 (dd, 1H, J = 19.1, 3.8 Hz), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 205.6, 158.5, 146.4, 143.9, 134.5, 129.2, 128.9, 127.7, 127.1, 126.9, 123.2, 47.0, 44.3, 22.1; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{14}O$ 222.1045; found 222.1038.

(1*R*,3*R*)-6-Methyl-3-phenyl-2,3-dihydro-1*H*-inden-1-ol (2d)



Yield 45% (49.9 mg as white solid); mp 130.1–130.7 °C; 98% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 24.5 min, t_R(minor) = 16.3 min); $[\alpha]_D^{25}$ = −32.7 (*c* 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35–7.27 (m, 3H), 7.27–7.20 (m, 3H), 7.05 (d, 1H, J = 7.7 Hz), 6.84 (d, 1H, J = 7.7 Hz), 5.29–5.21 (m, 1H), 4.15 (t, 1H, J = 8.3 Hz), 3.01 (dt, 1H, J = 12.9, 7.2 Hz), 2.38 (s, 3H), 2.01–1.89 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.4, 144.5, 142.7, 137.0, 129.3, 128.6, 128.2, 126.5, 124.8, 124.2, 75.1, 48.0, 47.4, 21.3; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{16}O$ 224.1201; found 224.1192.

(*S*)-6-Methyl-3-phenyl-2,3-dihydro-1*H*-inden-1-one, (*S*)-1d



Yield 39.4% (43.7 mg, white solid); mp 92.8–92.9 °C; 96% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 14.4 min, t_R(minor) = 15.4 min); $[\alpha]_D^{23}$ = +60.1 (*c* 1.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61 (s, 1H), 7.39 (d, 1H, J = 7.8 Hz), 7.30 (t, 2H, J = 7.4 Hz), 7.24 (t, 1H, J = 7.4 Hz), 7.16 (d, 1H, J = 7.8 Hz), 7.11 (d, 2H, J = 7.1 Hz), 4.53 (dd, 1H, J = 7.9, 3.7 Hz), 3.22 (dd, 1H, J = 19.2, 8.0 Hz), 2.68 (dd, 1H, J = 19.2, 3.8 Hz), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 206.1, 155.4, 143.9, 137.9, 137.0, 136.4, 128.9, 127.6, 126.9, 126.5, 123.3, 47.2, 44.1, 21.1; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{14}O$ 222.1045; found 222.1038.

(1*R*,3*R*)-7-Methyl-3-phenyl-2,3-dihydro-1*H*-inden-1-ol (2e)

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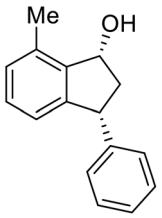
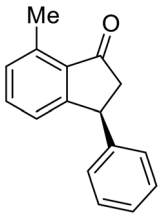


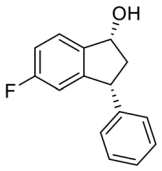
Yield 42% (46 mg as white solid); mp 87.5–88.9 °C; >99% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 21.3 min, t_R(minor) = 15.9 min); $[\alpha]_D^{26}$ = −88.7 (*c* 0.73, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34–7.26 (m, 2H), 7.24–7.19 (m, 3H), 7.16 (t, 1H, *J* = 7.5 Hz), 7.07 (d, 1H, *J* = 7.4 Hz), 6.85 (d, 1H, *J* = 7.5 Hz), 5.37 (s, 1H), 4.26–4.17 (m, 1H), 3.01 (dt, 1H, *J* = 13.7, 8.6, 7.2 Hz), 2.49 (s, 3H), 2.02 (ddd, 1H, *J* = 13.7, 6.4, 4.8 Hz), 1.78 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.0, 145.5, 142.7, 135.4, 128.9, 128.8, 128.6, 128.0, 126.4, 122.9, 75.1, 48.7, 45.7, 18.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{16}O$ 224.1201; found 224.1209.

(*S*)-7-Methyl-3-phenyl-2,3-dihydro-1*H*-inden-1-one, (*S*)-1e



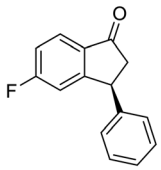
Yield: 47% (52.6 mg, white solid); mp 90.0–90.2 °C; 94% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 13.7 min, t_R(minor) = 14.1 min); $[\alpha]_D^{24}$ = +127.4 (*c* 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (t, 1H, *J* = 7.5 Hz), 7.30 (t, 2H, *J* = 7.4 Hz), 7.24 (d, 1H, *J* = 7.4 Hz), 7.13 (t, 3H, *J* = 7.7 Hz), 7.06 (d, 1H, *J* = 7.7 Hz), 4.50 (dd, 1H, *J* = 8.2, 4.0 Hz), 3.19 (dd, 1H, *J* = 19.0, 8.2 Hz), 2.74–2.63 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 206.9, 158.8, 144.1, 138.5, 134.3, 134.1, 129.6, 128.8, 127.7, 126.8, 124.2, 47.3, 43.9, 18.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{14}O$ 222.1045; found 222.1038.

(1*R*,3*R*)-5-Fluoro-3-phenyl-2,3-dihydro-1*H*-inden-1-ol (2f)



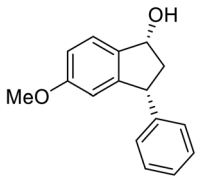
Yield 41% (47 mg as white solid); mp 88.5–89.0 °C; 94% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 24.9 min, t_R(minor) = 17.3 min); $[\alpha]_D^{27}$ = −27.4 (*c* 1.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (dd, 1H, *J* = 8.3, 5.2 Hz), 7.38–7.30 (m, 2H), 7.30–7.19 (m, 3H), 7.08–6.93 (m, 1H), 6.62 (d, 1H, *J* = 8.9 Hz), 5.26 (t, 1H, *J* = 7.1 Hz), 4.16 (t, 1H, *J* = 8.4 Hz), 3.04 (dt, 1H, *J* = 13.0, 7.3 Hz), 2.08–1.82 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.4 (d, J_{C-F} = 245.5 Hz), 148.0 (d, J_{C-F} = 8.0 Hz), 143.5, 140.8 (d, J_{C-F} = 2.4 Hz), 128.7, 128.2, 126.9, 125.1 (d, J_{C-F} = 9.0 Hz), 114.5 (d, J_{C-F} = 23.0 Hz), 111.9 (d, J_{C-F} = 22.4 Hz), 74.4, 48.2, 47.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{13}FO$ 228.0950; found 228.0948.

(*S*)-5-Fluoro-3-phenyl-2,3-dihydro-1*H*-inden-1-one, (*S*)-1f



Yield 45% (50.8 mg, yellow solid); mp 107.5–108.3 °C; >99% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 15.3 min, t_R(minor) = 17.2 min); $[\alpha]_D^{24}$ = +54.9 (*c* 2.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (dd, 1H, *J* = 8.5, 5.3 Hz), 7.37–7.30 (m, 2H), 7.30–7.26 (m, 1H), 7.16–7.07 (m, 3H), 6.92 (d, 1H, *J* = 8.5 Hz), 4.54 (dd, 1H, *J* = 8.1, 3.9 Hz), 3.25 (dd, 1H, *J* = 19.2, 8.1 Hz), 2.73 (dd, 1H, *J* = 19.2, 3.9 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.0, 168.7–166.1 (d, J_{C-F} = 256.5 Hz), 160.9–160.8 (d, J_{C-F} = 9.5 Hz), 142.9, 133.2 (d, J_{C-F} = 1.6 Hz), 129.1, 127.6, 127.3, 125.8–125.7 (d, J_{C-F} = 10.3 Hz), 116.5–116.2 (d, J_{C-F} = 23.9 Hz), 113.6–113.3(d, J_{C-F} = 22.7 Hz), 46.9, 44.3; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{11}FO$ 226.0794; found 226.0796.

(1*R*,3*R*)-5-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-ol (2g)



Yield 48% (57 mg as white solid); mp 127.9–128.3 °C; 97% ee (Chiralpak IB, 0 to 6% IPA for 9 min in *n*-hexane, 0.9 mL min^{-1}, 270 nm, t_R(major) = 25.9 min, t_R(minor) = 22.4 min); $[\alpha]_D^{27}$ = +17.4 (*c* 2.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 (d, 1H, *J* = 8.3 Hz), 7.35–7.29 (m, 2H), 7.28–7.20 (m, 3H), 6.85 (dd, 1H, *J* = 8.3, 2.3 Hz), 6.47 (s, 1H), 5.24 (s, 1H), 4.16 (t, 1H, *J* = 8.2 Hz), 3.71 (s, 3H), 3.02 (dt, 1H, *J* = 13.0, 7.3 Hz), 2.00–1.83 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.3, 147.4, 144.2, 137.6, 128.6, 128.2, 126.6, 124.6, 113.8, 109.9, 74.7, 55.4, 48.5, 47.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{16}O_2$ 240.1150; found 240.1155.

(*S*)-5-Methoxy-3-phenyl-2,3-dihydro-1*H*-inden-1-one, (*S*)-1g

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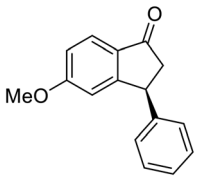
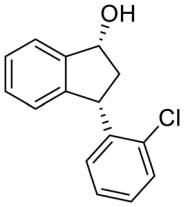


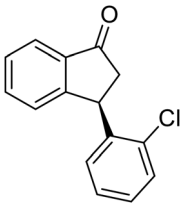
Yield 47.9% (54.1 mg, white solid); mp 129.8–130.0 °C; 98% ee; (Chiralpak IB, 0 to 6% IPA for 9 min in *n*-hexane, 0.9 mL min^{-1}, 270 nm, t_R(major) = 20.8 min, t_R(minor) = 20.3 min); $[\alpha]_D^{25}$ = −11.8 (*c* 3.1, CH_2Cl_2). Literature values: $[\alpha]_D^{25}$ = −10.0 (*c* 0.2, CH_2Cl_2 for 84% ee).[23] $[\alpha]_D^{23}$ = +17 (*c* 1.0, $CHCl_3$ for 96% ee) for (*R*)-**1g**;[27] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, 1H, *J* = 8.5 Hz), 7.31 (t, 2H, *J* = 7.3 Hz), 7.29–7.21 (m, 1H), 7.13 (d, 2H, *J* = 7.0 Hz), 6.94 (dd, 1H, *J* = 8.5, 2.2 Hz), 6.65 (s, 1H), 4.50 (dd, 1H, *J* = 8.0, 3.8 Hz), 3.78 (s, 3H), 3.20 (dd, 1H, *J* = 19.0, 8.1 Hz), 2.66 (dd, 1H, *J* = 19.0, 3.8 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.1, 165.6, 160.9, 143.7, 130.2, 128.9, 127.6, 127.0, 125.1, 116.0, 109.8, 55.7, 47.1, 44.5; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{14}O_2$ 238.0994; found 238.1006.

(1*R*,3*S*)-3-(2-Chlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (2h)



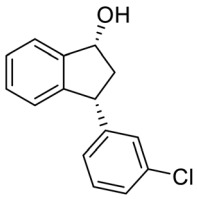
Yield 42% (51 mg as white solid); mp 103.2–104.3 °C; 92% ee (Chiralpak IB, 0 to 3% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 27.5 min, t_R(minor) = 19.8 min); $[\alpha]_D^{27}$ = +42.8 (*c* 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, 1H, *J* = 7.4 Hz), 7.44–7.38 (m, 1H), 7.35–7.25 (m, 2H), 7.21–7.14 (m, 2H), 7.14–7.07 (m, 1H), 7.02 (d, 1H, *J* = 7.5 Hz), 5.31 (s, 1H), 4.77 (t, 1H, *J* = 8.1 Hz), 3.09 (dt, 1H, *J* = 13.1, 7.4 Hz), 2.01–1.79 (m, 2H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 145.4, 144.4, 142.1, 134.1, 129.4, 129.1, 128.5, 127.7, 127.4, 127.2, 125.2, 124.1, 75.1, 45.3, 44.5; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{13}ClO$ 244.0655; found 244.0654.

(*R*)-3-(2-Chlorophenyl)-2,3-dihydro-1*H*-inden-1-one, (*R*)-1h



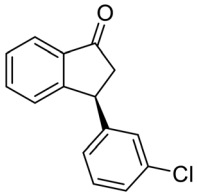
Yield 42.6% (51.7 mg, pale yellow solid); mp 56.5–57.7 °C; 97% ee (Chiralpak IB, 0 to 3% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 16.5 min, t_R(minor) = 16.9 min); $[\alpha]_D^{26}$ = −56.6 (*c* 1.7, CH_2Cl_2). Literature value $[\alpha]_D^{25}$ = −36.0 (*c* = 0.4, CH_2Cl_2 for 70% ee);[23] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, 1H, *J* = 7.7 Hz), 7.61 (t, 1H, *J* = 7.5 Hz), 7.49–7.40 (m, 2H), 7.34 (d, 1H, *J* = 7.7 Hz), 7.24–7.10 (m, 2H), 6.88 (s, 1H), 5.12 (s, 1H), 3.30 (dd, 1H, *J* = 19.2, 8.2 Hz), 2.61 (d, 1H, *J* = 18.7 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 205.5, 156.6, 141.2, 137.3, 135.1, 134.0, 129.8, 128.4, 128.2, 128.1, 127.4, 126.9, 123.7, 45.4, 41.0; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{11}ClO$ 242.0498; found 242.0499.

(1*R*,3*R*)-3-(3-Chlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (2i)



Yield 38% (46 mg as white solid); mp 104.2–104.6 °C; 99% ee (Chiralpak IB, 0 to 3% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 24.3 min, t_R(minor) = 20.3 min); $[\alpha]_D^{28}$ = −15.1 (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, 1H, *J* = 7.5 Hz), 7.31 (t, 1H, *J* = 7.4 Hz), 7.27 (s, 1H), 7.24–7.19 (m, 3H), 7.14–7.08 (m, 1H), 6.95 (d, 1H, *J* = 7.5 Hz), 5.34–5.24 (m, 1H), 4.17 (t, 1H, *J* = 8.4 Hz), 3.02 (dt, 1H, *J* = 13.0, 7.1 Hz), 2.06–1.86 (m, 2H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 146.4, 145.2, 144.8, 134.4, 129.9, 128.6, 128.4, 127.5, 126.8, 126.5, 125.0, 123.8, 75.0, 48.0, 46.9; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{13}ClO$ 244.0655; found 244.0659.

(*S*)-3-(3-Chlorophenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1i



Yield 41.4% (50.2 mg, white solid); mp 108.5–109.1 °C; 92% ee (Chiralpak IB, 0 to 3% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 17.2 min, t_R(minor) = 19.1 min); $[\alpha]_D^{26}$ = +66.7 (*c* 2.33, CH_2Cl_2). Literature value: $[\alpha]_D^{25}$ = +41.4 (*c* 0.6, CH_2Cl_2 for 84% ee);[23] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, 1H, *J* = 7.7 Hz), 7.60 (t, 1H, *J* = 7.5 Hz), 7.45 (t, 1H, *J* = 7.5 Hz), 7.30–7.26 (m, 1H), 7.25–7.21 (m, 2H), 7.12 (s, 1H), 7.04–6.97 (m, 1H), 4.56 (dd, 1H, *J* = 8.1, 3.9 Hz), 3.23 (dd, 1H, *J* = 19.2, 8.1 Hz), 2.66 (dd, 1H, *J* = 19.2, 3.9 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 205.3, 157.0, 145.7, 136.8, 135.3, 134.7, 130.2, 128.2, 127.8, 127.2, 126.8, 125.8, 123.6, 46.6, 44.1; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{11}ClO$ 242.0498; found 242.0505.

(1*R*,3*R*)-3-(4-Chlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (2j)

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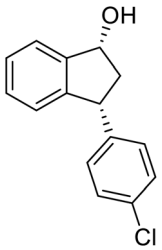
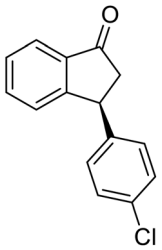


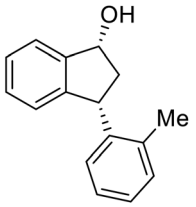
Yield 44% (56 mg as white solid); mp 111.9–120.2 °C; 98% ee (Chiralpak IB, 0 to 3% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 23.8 min, t_R(minor) = 21.6 min); $[\alpha]_D^{28}$ = −30.9 (*c* 1.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, 1H, *J* = 7.5 Hz), 7.35–7.26 (m, 3H), 7.25–7.21 (m, 1H), 7.17 (d, 2H, *J* = 8.4 Hz), 6.93 (d, 1H, *J* = 7.5 Hz), 5.35–5.23 (m, 1H), 4.17 (t, 1H, *J* = 8.3 Hz), 3.02 (dt, 1H, *J* = 12.9, 7.3 Hz), 2.01–1.82 (m, 2H); ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 145.2, 145.1, 142.8, 132.4, 129.6, 128.7, 128.5, 127.4, 125.0, 123.8, 75.0, 47.8, 47.0; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{13}ClO$ 244.0655; found 244.0651.

(*S*)-3-(4-Chlorophenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1j



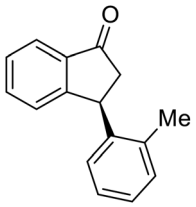
Yield 44.6% (54.1 mg, white solid); mp 75.9–76.5 °C; 90% ee (Chiralpak IB, 0 to 3% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 17.5 min, t_R(minor) = 18.4 min); $[\alpha]_D^{27}$ = +37.9 (*c* 2.6, CH_2Cl_2). Literature values: $[\alpha]_D^{27}$ = +42.9 (*c* 0.6, CHCl3 for 77% ee).[26] $[\alpha]_D^{25}$ = +48.5 (*c* 0.4, CH_2Cl_2 for 90% ee);[23] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (d, 1H, *J* = 7.7 Hz), 7.59 (t, 1H, *J* = 7.7, 1.1 Hz), 7.44 (t, 1H, *J* = 7.5 Hz), 7.31–7.22 (m, 3H), 7.06 (d, 2H, *J* = 8.3 Hz), 4.56 (dd, 1H, *J* = 8.1, 3.8 Hz), 3.23 (dd, 1H, *J* = 19.2, 8.1 Hz), 2.63 (dd, 1H, *J* = 19.2, 3.8 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 205.5, 157.3, 142.2, 136.8, 135.2, 132.8, 129.1, 129.0, 128.1, 126.8, 123.5, 46.7, 43.8; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{11}ClO$ 242.0498; found 242.0501.

(1*R*,3*R*)-3-(*o*-Tolyl)-2,3-dihydro-1*H*-inden-1-ol (2k)



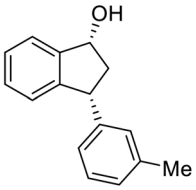
Yield 41% (45 mg as white solid); mp 122.6–123.9 °C; 98% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 26.1 min, t_R(minor) = 18.0 min); $[\alpha]_D^{28}$ = +49.3 (*c* 2.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, 1H, *J* = 7.5 Hz), 7.31 (t, 1H, *J* = 7.3 Hz), 7.25 (t, 1H, *J* = 7.0 Hz), 7.23–7.17 (m, 1H), 7.17–7.08 (m, 2H), 7.04–6.94 (m, 2H), 5.29 (s, 1H), 4.45 (t, 1H, *J* = 8.3 Hz), 3.03 (dt, 1H, *J* = 12.9, 7.3 Hz), 2.42 (s, 3H), 2.00–1.81 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.4, 145.3, 142.7, 136.1, 130.3, 128.4, 127.5, 127.1, 126.4, 126.4, 125.2, 123.9, 75.2, 45.9, 44.1, 19.8; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{16}O$ 224.1201; found 224.1203.

(*S*)-3-(*o*-Tolyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1k



Yield 43.4% (48.2 mg, yellow solid); mp 55.7–56.5 °C; 97% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 15.8 min, t_R(minor) = 16.9 min); $[\alpha]_D^{28}$ = −72.5 (*c* 2.4, CH_2Cl_2). Literature value for (*R*)-**1k**: $[\alpha]_D^{23}$ = +56 (*c* 1.0, $CHCl_3$ for 98% ee);[27] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, 1H, *J* = 7.7 Hz), 7.60 (t, 1H, *J* = 7.5 Hz), 7.44 (t, 1H, *J* = 7.5 Hz), 7.30 (d, 1H, *J* = 7.7 Hz), 7.22 (d, 1H, *J* = 7.4 Hz), 7.15 (t, 1H, *J* = 7.4 Hz), 7.08 (t, 1H, *J* = 7.4 Hz), 6.77 (d, 1H, *J* = 7.0 Hz), 4.84 (dd, 1H, *J* = 8.1, 3.9 Hz), 3.25 (dd, 1H, *J* = 19.1, 8.1 Hz), 2.57 (dd, 1H, *J* = 19.1, 3.9 Hz), 2.43 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 206.0, 157.8, 142.0, 137.3, 135.9, 135.0, 130.6, 127.8, 127.0, 126.8, 126.6, 123.5, 45.8, 29.7, 19.9; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{14}O$ 222.1045; found 222.1036.

(1*R*,3*R*)-3-(*m*-Tolyl)-2,3-dihydro-1*H*-inden-1-ol (2l)



Yield 43% (47 mg as white solid); mp 77.0–77.3 °C; 94% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 30.0 min, t_R(minor) = 19.4 min); $[\alpha]_D^{28}$ = −22.0 (*c* 0.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, 1H, *J* = 7.4 Hz), 7.29 (t, 1H, *J* = 7.4 Hz), 7.26–7.17 (m, 2H), 7.09–6.99 (m, 3H), 6.95 (d, 1H, *J* = 7.5 Hz), 5.27 (t, 1H, *J* = 7.2 Hz), 4.14 (t, 1H, *J* = 8.4 Hz), 3.01 (dt, 1H, *J* = 12.8, 7.2 Hz), 2.32 (s, 3H), 2.11–1.87 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.7, 145.2, 144.2, 138.2, 129.0, 128.5, 128.3, 127.4, 127.1, 125.3, 125.1, 123.6, 75.1, 48.2, 47.2, 21.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{16}O$ 224.1201; found 224.1200.

(*S*)-3-(*m*-Tolyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1l

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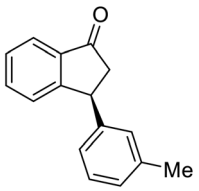
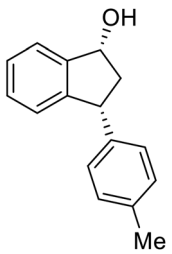


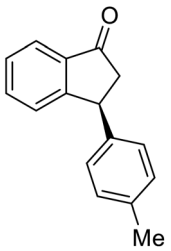
Yield 41.2% (45.8 mg, pale yellow solid); mp 62.7–63.7 °C; 96% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 15.8 min, t_R(minor) = 16.3 min); $[\alpha]_D^{28}$ = +74.2 (*c* 2.1, CH_2Cl_2). Literature value for (*R*)-**1l**: $[\alpha]_D^{23}$ = +33.2 (*c* 0.9, $CHCl_3$ for 95% ee);[7] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, 1H, *J* = 7.7 Hz), 7.57 (t, 1H, *J* = 7.5 Hz), 7.42 (t, 1H, *J* = 7.5 Hz), 7.28 (d, 1H, *J* = 7.7 Hz), 7.20 (t, 1H, *J* = 7.9 Hz), 7.06 (d, 1H, *J* = 7.5 Hz), 6.96–6.88 (m, 2H), 4.54 (dd, 1H, *J* = 8.0, 3.9 Hz), 3.22 (dd, 1H, *J* = 19.2, 8.0 Hz), 2.69 (dd, 1H, *J* = 19.2, 3.9 Hz), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 206.2, 158.1, 143.6, 138.6, 136.7, 135.1, 128.8, 128.3, 127.8, 127.7, 126.9, 124.7, 123.4, 46.8, 44.4, 21.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{14}O$ 222.1045; found 222.1032.

(1*R*,3*R*)-3-(*p*-Tolyl)-2,3-dihydro-1*H*-inden-1-ol (2m)



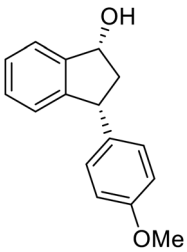
Yield 42% (47 mg as white solid); mp 97.7–98.0 °C; 95% ee (Chiralpak IB, 6% IPA in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 12.4 min, t_R(minor) = 7.1 min); $[\alpha]_D^{28}$ = −21.7 (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, 1H, *J* = 7.4 Hz), 7.29 (t, 1H, *J* = 7.4 Hz), 7.22 (t, 1H, *J* = 7.3 Hz), 7.17–7.10 (m, 4H), 6.95 (d, 1H, *J* = 7.5 Hz), 5.28 (s, 1H), 4.16 (d, 1H, *J* = 8.2 Hz), 3.01 (dt, 1H, *J* = 12.8, 7.2 Hz), 2.34 (s, 3H), 2.00–1.85 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.8, 145.2, 141.2, 136.2, 129.3, 128.3, 128.1, 127.1, 125.1, 123.6, 75.1, 47.9, 47.3, 21.0; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{16}O$ 224.1201; found 224.1190.

(*S*)-3-(*p*-Tolyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1m



Yield 41.5% (46.1 mg, yellow solid); mp 78.3–79.1 °C; >99% ee (Chiralpak IB, 6% IPA in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 6.1 min, t_R(minor) = 6.4 min); $[\alpha]_D^{28}$ = +40.8 (*c* 2.5, CH_2Cl_2). Literature values: $[\alpha]_D^{25}$ = +109.0 (*c* 0.2, CH_2Cl_2 for 84% ee).[23] $[\alpha]_D^{23}$ = −62.9 (*c* 0.7, $CHCl_3$ for 90% ee) for (*R*)-**1m**;[7] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80 (d, 1H, *J* = 7.7 Hz), 7.56 (t, 1H, *J* = 7.5 Hz), 7.41 (t, 1H, *J* = 7.4 Hz), 7.28 (d, 1H, *J* = 7.5 Hz), 7.12 (d, 2H, *J* = 7.8 Hz), 7.02 (d, 2H, *J* = 7.8 Hz), 4.54 (dd, 1H, *J* = 8.0, 3.8 Hz), 3.22 (dd, 1H, *J* = 19.2, 8.0 Hz), 2.67 (dd, 1H, *J* = 19.2, 3.8 Hz), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 206.2, 158.2, 140.7, 136.7, 136.6, 135.1, 129.6, 127.8, 127.5, 126.8, 123.4, 46.9, 44.1, 21.0; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{14}O$ 222.1045; found 222.1035.

(1*R*,3*R*)-3-(4-Methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol (2n)



Yield 45.0% (53.6 mg as white solid); mp 110.8–111.3 °C; 99% ee (Chiralpak IB, 7% IPA in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 43.4 min, t_R(minor) = 45.7 min); $[\alpha]_D^{28}$ = −20.6 (*c* 2.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.5 (d, 1H, *J* = 7.4 Hz), 7.3–7.3 (m, 1H), 7.3–7.2 (m, 1H), 7.1 (d, 2H, *J* = 8.7 Hz), 6.9 (d, 1H, *J* = 7.4 Hz), 6.9 (d, 2H, *J* = 8.7 Hz), 5.3 (q, 1H, *J* = 6.9, 5.9 Hz), 4.1 (t, 1H, *J* = 8.4 Hz), 3.8 (s, 3H), 3.0 (dt, 1H, *J* = 12.9, 7.2 Hz), 2.0–1.8 (m, 2H) ppm; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.6, 160.9, 143.7, 130.2, 128.9, 127.0, 125.1, 116.0, 109.8, 55.7, 47.1, 44.5, 29.7; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{16}O_2$ 240.1150; found 240.1161.

(*S*)-3-(4-Methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1n

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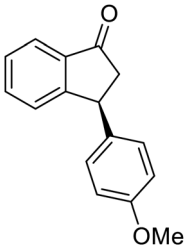
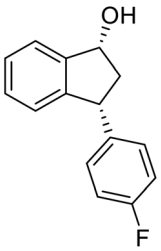


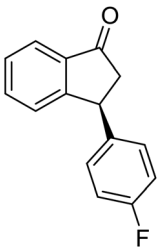
Yield 45.2% (53.8 mg, yellow solid); mp 72.7–73.1 °C; >99% (Chiralpak IB, 7% IPA in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 41.8 min, t_R(minor) = 40.9 min); $[\alpha]_D^{20}$ = +69.7 (*c* 2.1, CH_2Cl_2). Literature values: $[\alpha]_D^{25}$ = +41.1 (*c* 0.6, CHCl3 for 70% ee).[26] $[\alpha]_D^{20}$ = +59.1 (*c* 0.6, CH_2Cl_2 for 84% ee);[23] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, 1H, J = 7.7 Hz), 7.57 (t, 1H, J = 7.5 Hz), 7.41 (t, 1H, J = 7.4 Hz), 7.04 (d, 2H, J = 8.7 Hz), 6.85 (d, 2H, J = 8.7 Hz), 4.53 (d, 1H, J = 8.0 Hz), 3.79 (s, 3H), 3.21 (dd, 1H, J = 19.2, 8.0 Hz), 2.65 (dd, 1H, J = 19.2, 3.9 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 206.2, 158.6, 158.3, 136.7, 135.8, 135.1, 128.6, 127.8, 126.8, 123.3, 114.3, 55.3, 47.0, 43.7; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{14}O_2$ 238.0994; found 238.1010.

(1*R*,3*R*)-3-(4-Fluorophenyl)-2,3-dihydro-1*H*-inden-1-ol (2o)



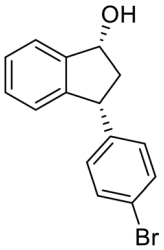
Yield 48% (54 mg as white solid); mp 111.9–112.0 °C; 98.2% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 19.0 min, t_R(minor) = 21.7 min); $[\alpha]_D^{28}$ = −14.4 (*c* 2.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, 1H, J = 7.4 Hz), 7.35–7.14 (m, 4H), 7.00 (t, 2H, J = 8.7 Hz), 6.93 (d, 1H, J = 7.4 Hz), 5.29 (t, 1H, J = 6.8 Hz), 4.17 (t, 1H, J = 8.4 Hz), 3.01 (dt, 1H, J = 13.0, 7.3 Hz), 2.02 (s, 1H), 1.90 (ddd, 1H, J = 12.9, 9.1, 7.6 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7 (d, $J_{C–F}$ = 244.6 Hz), 145.5, 145.2, 140.0 (d, $J_{C–F}$ = 3.2 Hz), 129.7 (d, $J_{C–F}$ = 8.0 Hz), 128.5, 127.3, 125.0, 123.7, 115.4 (d, $J_{C–F}$ = 21.2 Hz), 75.0, 47.6, 47.2; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{13}FO$ 228.0950; found 228.0940.

(*S*)-3-(4-Fluorophenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1o



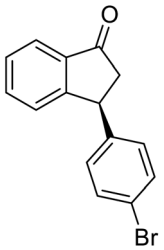
Yield 49.9% (56.4 g, white solid); mp 116.5–117.1 °C; 94.2% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 16.3 min, t_R(minor) = 17.4 min); $[\alpha]_D^{22}$ = +39.4 (*c* 2.6, CH_2Cl_2). Literature value $[\alpha]_D^{25}$ = +37.9 (*c* 0.3, CH_2Cl_2 for 90% ee);[23] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, 1H, J = 7.5 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.24 (d, 1H), 7.12–7.05 (m, 2H), 7.00 (t, 2H, J = 8.6 Hz), 4.57 (dd, 1H, J = 8.0, 3.9 Hz), 3.23 (dd, 1H, J = 19.2, 8.0 Hz), 2.64 (dd, 1H, J = 19.2, 3.9 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 205.7, 163.0–160.6 (d, $J_{C–F}$ = 245.6 Hz), 157.7, 139.5–139.4 (d, $J_{C–F}$ = 3.4 Hz), 136.7, 135.2, 129.2–129.1 (d, $J_{C–F}$ = 8.0 Hz), 128.0, 126.8, 123.5, 115.9–115.7 (d, $J_{C–F}$ = 21.5 Hz), 46.9, 43.7; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{11}FO$ 226.0794; found 226.0791.

(1*R*,3*R*)-3-(4-Bromophenyl)-2,3-dihydro-1*H*-inden-1-ol (2p)



Yield 40% (58 mg as white solid); mp 132.2–132.7 °C; 99% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 20.2 min, t_R(minor) = 21.5 min); $[\alpha]_D^{29}$ = −17.7 (*c* 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54–7.37 (m, 3H), 7.30 (t, 1H, J = 7.4 Hz), 7.27–7.20 (m, 1H), 7.10 (d, 2H, J = 8.4 Hz), 6.92 (d, 1H, J = 7.4 Hz), 5.36–5.20 (m, 1H), 4.15 (t, 1H, J = 8.3 Hz), 3.00 (dt, 1H, J = 13.0, 7.3 Hz), 2.08 (s, 1H), 1.89 (dt, 1H, J = 13.0, 8.3, 7.3 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.2, 145.0, 143.3, 131.7, 130.0, 128.5, 127.4, 125.0, 123.8, 120.4, 75.0, 47.8, 46.9; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{13}BrO$ 288.0150; found 288.0147.

(*S*)-3-(4-Bromophenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1p



Yield 42.3% (60.7 mg, pale yellow solid); mp 60.1–60.5 °C; 94% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 17.3 min, t_R(minor) = 18.2 min); $[\alpha]_D^{23}$ = +47.1 (*c* 2.9, CH_2Cl_2). Literature value: $[\alpha]_D^{25}$ = +44.0 (*c* 0.4, CH_2Cl_2 for 90% ee);[23] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, 1H, J = 7.8 Hz), 7.59 (d, 1H, J = 7.8 Hz), 7.49–7.39 (m, 3H), 7.24 (d, 1H, J = 7.8 Hz), 7.00 (d, 2H, J = 8.4 Hz), 4.55 (dd, 1H, J = 8.1, 3.8 Hz), 3.23 (dd, 1H, J = 19.2, 8.1 Hz), 2.63 (dd, 1H, J = 19.2, 3.8 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 205.4, 157.2, 142.7, 136.8, 135.2, 132.0, 129.4, 128.1, 126.8, 123.6, 120.9, 46.7, 43.9; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{11}BrO$ 285.9993; found 285.9991.

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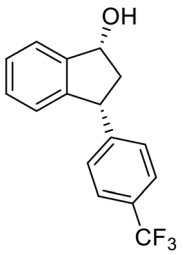
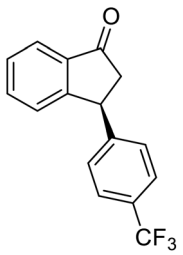
(1*R*,3*R*)-3-(4-(Trifluoromethyl)phenyl)-2,3-dihydro-1*H*-inden-1-ol (2q)



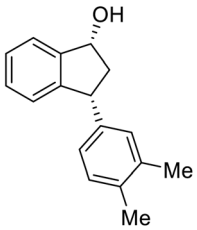
Yield 34% (47 mg as white solid); mp 98.5–99.7 °C; 97% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 20.7 min, t_R(minor) = 18.8 min) $[\alpha]_D^{29} = -8.7$ (*c* 3.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, 2H, J = 8.2 Hz), 7.49 (d, 1H, J = 7.5 Hz), 7.40–7.29 (m, 3H), 7.29–7.21 (m, 1H), 6.92 (d, 1H, J = 7.5 Hz), 5.37–5.29 (m, 1H), 4.26 (d, 1H, J = 8.9 Hz), 3.04 (dt, 1H, J = 13.0, 7.3 Hz), 2.04 (s, 1H), 1.94 (ddd, 1H, J = 13.0, 8.9, 7.3 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.5, 145.0 (d, J_{C-F} = 48.4 Hz), 128.9 (q, J_{C-F} = 32.4 Hz), 128.6, 127.6, 125.6 (t, J_{C-F} = 3.7 Hz), 125.0, 123.9, 122.9, 75.0, 48.2, 46.8; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{13}F_3O$ 278.0918; found 278.0915.

(*S*)-3-(4-(Trifluoromethyl)phenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1q



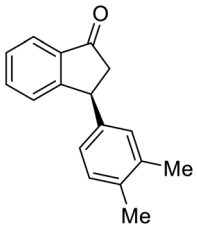
Yield 42.7% (58.9 mg, pale yellow solid); mp 84.2–84.5 °C; 94% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, 270 nm, t_R(major) = 16.9 min, t_R(minor) = 20.9 min); $[\alpha]_D^{24} = +30.7$ (*c* 3.2, CH_2Cl_2). Literature value: $[\alpha]_D^{25} = +32.0$ (*c* 0.6 CH_2Cl_2 for 88% ee);[23] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, 1H, J = 7.5 Hz), 7.64–7.52 (m, 3H), 7.46 (d, 1H, J = 7.8 Hz), 7.25 (d, 3H, J = 8.1 Hz), 4.65 (dd, 1H, J = 8.1, 3.9 Hz), 3.26 (dd, 1H, J = 19.2, 8.1 Hz), 2.67 (dd, 1H, J = 19.2, 3.9 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.9, 147.8–147.8 (m), 136.8, 135.3, 129.4 (q, J_{C-F} = 32.5 Hz), 128.3, 128.0, 126.8, 125.9 (q, J_{C-F} = 3.8 Hz), 125.4–122.7 (d, J_{C-F} = 272.0 Hz), 123.7, 46.5, 44.2; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{11}F_3O$ 276.0762; found 276.0762.

(1*R*,3*R*)-3-(3,4-Dimethylphenyl)-2,3-dihydro-1*H*-inden-1-ol (2r)



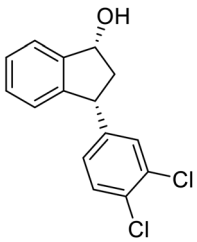
Yield 44% (52 mg as white solid); mp 89.8–90.8 °C; 99% ee (Chiralpak IB, 0 to 2% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 29.7 min, t_R(minor) = 24.3 min); $[\alpha]_D^{29} = -21.3$ (*c* 2.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, 1H, J = 7.4 Hz), 7.29 (t, 1H, J = 7.4 Hz), 7.22 (d, 1H, J = 7.2 Hz), 7.09 (d, 1H, J = 7.7 Hz), 7.00 (s, 1H), 6.96 (d, 2H, J = 7.5 Hz), 5.27 (d, 1H, J = 7.2 Hz), 4.12 (d, 1H, J = 8.3 Hz), 3.00 (dt, 1H, J = 12.8, 7.2 Hz), 2.25 (s, 3H), 2.24 (s, 3H), 2.01–1.86 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.9, 145.2, 141.7, 136.7, 134.8, 129.8, 129.5, 128.3, 127.1, 125.6, 125.1, 123.6, 75.1, 47.9, 47.3, 19.8, 19.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{17}H_{18}O$ 238.1358; found 238.1358.

(*S*)-3-(3,4-Dimethylphenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1r



Yield 49.6% (58.6 mg, pale yellow solid); mp 103.9–105.0 °C; >99% ee (Chiralpak IB, 0 to 2% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 17.0 min, t_R(minor) = 17.8 min); $[\alpha]_D^{24} = +58.7$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, 1H, J = 7.7 Hz), 7.55 (t, 1H, J = 7.5 Hz), 7.40 (t, 1H, J = 7.4 Hz), 7.27 (d, 1H, J = 7.7 Hz), 7.07 (d, 1H, J = 7.6 Hz), 6.93–6.81 (m, 2H), 4.50 (dd, 1H, J = 8.0, 3.8 Hz), 3.20 (dd, 1H, J = 19.2, 8.0 Hz), 2.67 (dd, 1H, J = 19.2, 3.8 Hz), 2.23 (s, 3H), 2.21 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 206.3, 158.3, 141.1, 137.1, 136.7, 135.2, 135.0, 130.1, 128.8, 127.7, 126.9, 125.0, 123.3, 46.9, 44.1, 19.8, 19.3; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{17}H_{16}O$ 236.1201; found 236.1201.

(1*R*,3*R*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (2s)



Yield 42% (58 mg as white solid); mp 91.7–93.1 °C; 99% ee (Chiralpak IB, 0 to 4.5% IPA for 10 min in *n*-hexane, 0.8 mL min^{-1},

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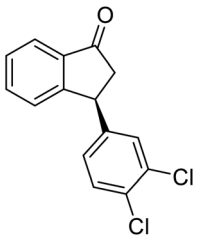
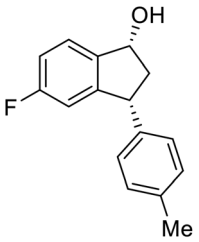
270 nm, t_R(major) = 20.9 min, t_R(minor) = 22.0 min); $[\alpha]_D^{29} = -18.3$ (*c* 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, 1H, *J* = 7.4 Hz), 7.38 (d, 1H, *J* = 8.3 Hz), 7.35–7.25 (m, 3H), 7.07 (dd, 1H, *J* = 8.3, 2.0 Hz), 6.94 (d, 1H, *J* = 7.4 Hz), 5.30 (s, 1H), 4.15 (t, 1H, *J* = 8.3 Hz), 3.01 (dt, 1H, *J* = 13.1, 7.3 Hz), 2.01 (s, 1H), 1.89 (ddd, 1H, *J* = 13.0, 8.8, 7.3 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 145.1, 144.7, 144.5, 132.6, 130.6, 130.6, 130.2, 128.7, 127.7, 127.7, 124.9, 123.9, 74.9, 47.6, 46.7; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{12}Cl_2O$ 278.0265; found 278.0263.

(*S*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1s



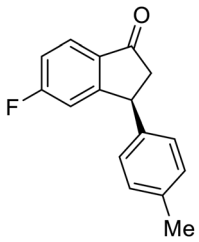
Yield 46.8% (64.8 g, white solid); mp 114.1–114.5 °C; >99% ee (Chiralpak IB, 0 to 4.5% IPA for 10 min in *n*-hexane, 0.8 mL min^{-1}, 270 nm, t_R(major) = 23.7 min, t_R(minor) = 22.8 min); $[\alpha]_D^{25} = +35.5$ (*c* 2.4, CH_2Cl_2). Literature values: $[\alpha]_D^{23} = +48$ (*c* 1.0, $CHCl_3$ for 92% ee).[7] $[\alpha]_D^{25} = +38.2$ (*c* 0.5, CH_2Cl_2 for 90% ee).[23] $[\alpha]_D^{24} = +49.5$ (*c* 1.33, $CHCl_3$, for 98% ee);[19] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, 1H, *J* = 7.7 Hz), 7.61 (t, 1H, *J* = 7.4 Hz), 7.46 (t, 1H, *J* = 7.4 Hz), 7.38 (d, 1H, *J* = 8.3 Hz), 7.26 (d, 1H, *J* = 7.7 Hz), 7.23 (d, 1H, *J* = 2.1 Hz), 6.95 (dd, 1H, *J* = 8.3, 2.1 Hz), 4.55 (dd, 1H, *J* = 8.1, 3.8 Hz), 3.23 (dd, 1H, *J* = 19.2, 8.1 Hz), 2.62 (dd, 1H, *J* = 19.2, 3.8 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.9, 156.5, 144.0, 136.8, 135.4, 133.0, 131.1, 130.9, 129.7, 128.4, 127.0, 126.7, 123.7, 46.5, 43.6; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{10}Cl_2O$ 276.0109; found 276.0104.

(1*R*,3*R*)-5-Fluoro-3-(*p*-tolyl)-2,3-dihydro-1*H*-inden-1-ol (2t)



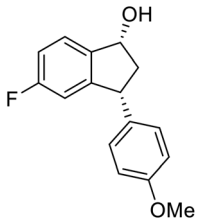
Yield 42% (50 mg as white solid); mp 87.3–88.1 °C; 99% ee (Chiralpak IB, 0 to 3% IPA for 8 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 25.2 min, t_R(minor) = 22.4 min); $[\alpha]_D^{29} = -33.7$ (*c* 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (dd, 1H, *J* = 8.3, 5.2 Hz), 7.14 (d, 2H, *J* = 8.1 Hz), 7.10 (d, 2H, *J* = 8.1 Hz), 6.96 (t, 1H, *J* = 8.7 Hz), 6.62 (d, 1H, *J* = 9.0 Hz), 5.23 (t, 1H, *J* = 7.2 Hz), 4.11 (t, 1H, *J* = 8.4 Hz), 3.01 (dt, 1H, *J* = 12.9, 7.3 Hz), 2.34 (s, 3H), 2.13–1.88 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.4 (d, J_{C-F} = 245.5 Hz), 148.2 (d, J_{C-F} = 8.0 Hz), 140.8 (d, J_{C-F} = 2.3 Hz), 140.5, 136.4, 129.4, 128.0, 125.0 (d, J_{C-F} = 9.0 Hz), 114.4 (d, J_{C-F} = 22.9 Hz), 111.9 (d, J_{C-F} = 22.3 Hz), 74.4, 47.8, 47.5, 21.0; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{15}FO$ 242.1107; found 242.1116.

(*S*)-5-Fluoro-3-(*p*-tolyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1t



Yield 43% (51.6 mg, pale brown solid); mp 82.7–83.3 °C; 99% ee (Chiralpak IB, 0 to 3% IPA for 8 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 16.4 min, t_R(minor) = 17.2 min); $[\alpha]_D^{26} = +60.2$ (*c* 2.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (dd, 1H, *J* = 8.5, 5.3 Hz), 7.19–7.06 (m, 3H), 7.01 (d, 2H, *J* = 8.1 Hz), 6.91 (d, 1H, *J* = 8.3 Hz), 4.51 (dd, 1H, *J* = 8.1, 3.9 Hz), 3.23 (dd, 1H, *J* = 19.2, 8.1 Hz), 2.70 (dd, 1H, *J* = 19.2, 3.9 Hz), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.1, 167.4 (d, J_{C-F} = 256.8 Hz), 161.1 (d, J_{C-F} = 9.6 Hz), 139.9, 137.0, 133.1 (d, J_{C-F} = 1.8 Hz), 129.7, 127.4, 125.7 (d, J_{C-F} = 10.4 Hz), 116.3 (d, J_{C-F} = 24.0 Hz), 113.4 (d, J_{C-F} = 22.4 Hz), 47.0, 43.9, 21.0; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{13}FO$ 240.0950; found 240.0961.

(1*R*,3*R*)-5-Fluoro-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-ol (2u)



Yield 42% (53 mg as white solid); mp 86.5–87.0 °C; 95% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 23.7, t_R(minor) = 21.2 min); $[\alpha]_D^{29} = -34.1$ (*c* 1.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (dd, 1H, *J* = 8.3, 5.2 Hz), 7.14 (d, 2H, *J* = 8.7 Hz), 7.04–6.92 (m, 1H), 6.87 (d, 2H, *J* = 8.7 Hz), 6.66–6.59 (m, 1H), 5.24 (t, 1H, *J* = 6.8 Hz), 4.11 (t, 1H, *J* = 8.4 Hz), 3.81 (s, 3H), 3.02 (dt, 1H, *J* = 12.9, 7.2 Hz), 2.02–1.88 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.4 (d, J_{C-F} = 245.5 Hz), 158.5, 148.4 (d, J_{C-F} = 7.9 Hz), 140.7 (d, J_{C-F} = 2.2 Hz), 135.6, 129.1, 125.0 (d, J_{C-F} = 9.1 Hz), 114.4 (d, J_{C-F} = 22.8 Hz), 114.1, 111.8 (d, J_{C-F} = 22.3 Hz), 74.4, 55.3, 47.6, 47.4; HRMS (EI, double

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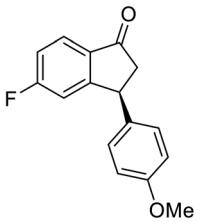
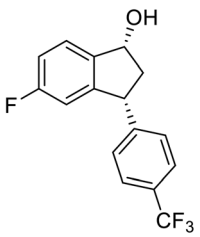
focusing) m/z: $[M]^+$ calcd for $C_{16}H_{15}FO_2$ 258.1056; found 258.1056.

(*S*)-5-Fluoro-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1u



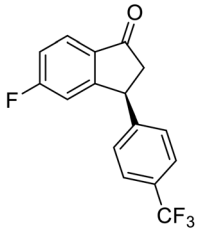
Yield 44.8% (57.4 mg, pale brown solid); mp 112.3–112.9 °C; 98% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 18.2 min, t_R(minor) = 17.7 min); $[\alpha]_D^{27}$ = +55.5 (*c* 2.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (dd, 1H, J = 8.5, 5.3 Hz), 7.10 (td, 1H, J = 8.5, 1.8 Hz), 7.04 (d, 2H, J = 8.7 Hz), 6.91 (dd, 1H, J = 8.5, 1.8 Hz), 6.86 (d, 2H, J = 8.7 Hz), 4.50 (dd, 1H, J = 8.0, 3.9 Hz), 3.80 (s, 3H), 3.23 (dd, 1H, J = 19.2, 8.1 Hz), 2.68 (dd, 1H, J = 19.2, 3.9 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.1, 167.4 (d, J_{C-F} = 256.8 Hz), 161.2 (d, J_{C-F} = 9.6 Hz), 158.8, 134.9, 133.1 (d, J_{C-F} = 1.8 Hz), 128.6, 125.7 (d, J_{C-F} = 10.3 Hz), 116.3 (d, J_{C-F} = 24.0 Hz), 114.4, 113.4 (d, J_{C-F} = 22.4 Hz), 55.3, 47.1, 43.6; HRMS (EI, double focusing) m/z: $[M]^+$ calcd for $C_{16}H_{13}FO_2$ 256.0900; found 256.0903.

(1*R*,3*R*)-5-Fluoro-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-inden-1-ol (2v)



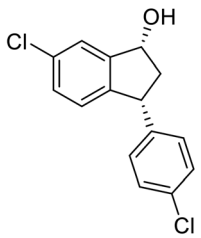
Yield 43% (48 mg as white solid); mp 86.1–86.5 °C; 92% ee (Chiralpak IB, 0 to 2% IPA for 60 min in *n*-hexane, 0.6 mL min^{-1}, 270 nm, t_R(major) = 48.3 min, t_R(minor) = 46.1 min); $[\alpha]_D^{29}$ = −21.9 (*c* 2.6, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, 2H, J = 8.1 Hz), 7.44 (dd, 1H, J = 8.3, 5.2 Hz), 7.35 (d, 2H, J = 8.1 Hz), 7.01 (t, 1H, J = 8.6 Hz), 6.60 (d, 1H, J = 8.8 Hz), 5.29 (s, 1H), 4.24 (t, 1H, J = 8.3 Hz), 3.06 (dt, 1H, J = 13.1, 7.3 Hz), 1.98 (ddd, 2H, J = 13.1, 8.9, 7.1 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.4 (d, J_{C-F} = 246.4 Hz), 147.7–147.6 (m), 147.0 (d, J_{C-F} = 7.9 Hz), 140.8 (d, J_{C-F} = 2.4 Hz), 129.2 (d, J_{C-F} = 32.4 Hz), 128.6, 125.7 (q, J_{C-F} = 3.8 Hz), 125.4, 125.3, 114.9 (d, J_{C-F} = 22.9 Hz), 111.8 (d, J_{C-F} = 22.4 Hz), 74.3, 48.1, 47.1; HRMS (EI, double focusing) m/z: $[M]^+$ calcd for $C_{16}H_{12}F_4O$ 296.0824; found 296.0824.

(*S*)-5-Fluoro-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1v



Yield 43.2% (63.5 mg, pale brown solid); mp 112.0–112.4 °C; 99% ee (Chiralpak IB, 0 to 2% IPA for 60 min in *n*-hexane, 0.6 mL min^{-1}, 270 nm, t_R(major) = 44.6 min, t_R(minor) = 43.7 min); $[\alpha]_D^{27}$ = +29.9 (*c* 2.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 (dd, 1H, J = 8.5, 5.3 Hz), 7.60 (d, 2H, J = 8.1 Hz), 7.25 (d, 2H, J = 8.1 Hz), 7.15 (td, 1H, J = 8.6, 2.1 Hz), 6.89 (dd, 1H, J = 8.4, 1.7 Hz), 4.62 (dd, 1H, J = 8.2, 3.9 Hz), 3.28 (dd, 1H, J = 19.2, 8.2 Hz), 2.69 (dd, 1H, J = 19.2, 3.9 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 203.1, 168.7, 166.2, 159.7 (d, J_{C-F} = 9.5 Hz), 146.9, 133.2 (d, J_{C-F} = 1.9 Hz), 129.7 (q, J_{C-F} = 32.6 Hz), 128.0, 126.1 (q, J_{C-F} = 3.8 Hz), 124.0 (d, J_{C-F} = 271.9 Hz), 116.8 (d, J_{C-F} = 23.9 Hz), 113.4 (d, J_{C-F} = 22.5 Hz), 46.7, 44.0; HRMS (EI, double focusing) m/z: $[M]^+$ calcd for $C_{16}H_{10}F_4O$ 294.0668; found 294.0674.

(1*R*,3*R*)-6-Chloro-3-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (2w)



Yield 49.6% (68.7 mg as white solid); mp 100.5–101.1 °C; 98% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 21.8 min, t_R(minor) = 20.1 min); $[\alpha]_D^{29}$ = −42.4 (*c* 3.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, 1H, J = 1.8 Hz), 7.30 (d, 2H, J = 8.4 Hz), 7.21 (dd, 1H, J = 8.1, 1.8 Hz), 7.14 (d, 2H, J = 8.4 Hz), 6.84 (d, 1H, J = 8.1 Hz), 5.26 (q, 1H, J = 7.0 Hz), 4.12 (d, 1H, J = 8.3 Hz), 3.03 (dt, 1H, J = 13.0, 7.2 Hz), 2.0–1.8 (m, 2H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 147.1, 143.5, 142.2, 133.3, 132.6, 129.5, 128.9, 128.7, 126.2, 124.2, 47.3, 47.3; HRMS (EI, double focusing) m/z: $[M]^+$ calcd for $C_{15}H_{12}Cl_2O$ 278.0265; found 296.0268.

(*S*)-6-Chloro-3-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1w

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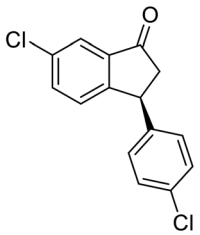
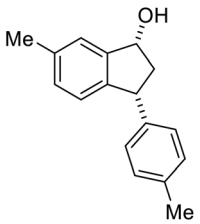


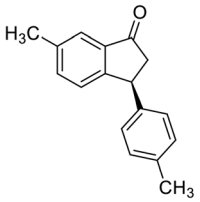
Yield: 45.3% (62.7 mg, white solid); mp 81.6–82.1 °C; >99% ee (Chiralpak IB, 0 to 4% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 17.9 min, t_R(minor) = 16.9 min); $[\alpha]_D^{28}$ = +44.9 (*c* 2.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, 1H, J = 2.0 Hz), 7.54 (dd, 1H, J = 8.2, 2.0 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.19 (d, 1H, J = 8.2 Hz), 7.04 (d, 2H, J = 8.4 Hz), 4.53 (dd, 1H, J = 8.1, 3.9 Hz), 3.26 (dd, 1H, J = 19.3, 8.1 Hz), 2.66 (dd, 1H, J = 19.3, 3.9 Hz) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 203.9, 155.3, 141.6, 138.2, 135.2, 134.7, 133.1, 129.2, 128.9, 128.0, 123.4, 47.0, 43.4 ppm; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{15}H_{10}Cl_2O$ 276.0109; found 276.0108.

(1*R*,3*R*)-6-Methyl-3-(*p*-tolyl)-2,3-dihydro-1*H*-inden-1-ol (2x)



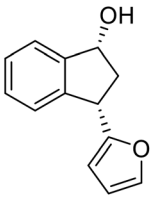
Yield: 42.3% (50.0 mg, white solid); mp 100.8–101.8 °C; 98% ee (Chiralpak IB, 0 to 3% IPA for 8 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 31.6 min, t_R(minor) = 21.6 min); $[\alpha]_D^{29}$ = −32.4 (*c* 3.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (s, 1H), 7.17–7.08 (m, 4H), 7.05 (d, 1H, J = 7.8 Hz), 6.84 (d, 1H, J = 7.8 Hz), 5.25 (d, 1H, J = 7.2 Hz), 4.12 (t, 1H, J = 8.4 Hz), 3.00 (dt, 1H, J = 12.8, 7.2 Hz), 2.38 (s, 3H), 2.34 (s, 3H), 1.95–1.83 (m, 2H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ = 145.4, 142.9, 141.5, 136.9, 136.1, 129.3, 129.3, 128.1, 124.8, 124.2, 75.1, 47.6, 47.5, 21.3, 21.0 ppm; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{17}H_{18}O$ 238.1358; found 238.1371.

(*S*)-6-Methyl-3-(*p*-tolyl)-2,3-dihydro-1*H*-inden-1-one, (*S*)-1x



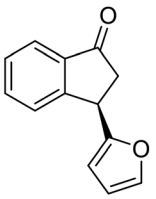
Yield: 46.1% (54.4 mg, white solid); mp 77.7–78.4 °C; 99% ee (Chiralpak IB, 0 to 3% IPA for 8 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 17.6 min, t_R(minor) = 17.3 min); $[\alpha]_D^{28}$ = +56.9 (*c* 2.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.60 (s, 1H), 7.38 (d, 1H, J = 8.0 Hz), 7.15 (d, 1H, J = 8.0 Hz), 7.11 (d, 2H, J = 8.0 Hz), 7.00 (d, 2H, J = 8.0 Hz), 4.50 (dd, 1H, J = 8.0, 3.8 Hz), 3.21 (dd, 1H, J = 19.2, 8.0 Hz), 2.65 (dd, 1H, J = 19.2, 3.8 Hz), 2.42 (s, 3H), 2.32 (s, 3H) ppm; ^{13}C{^{1}H} ($CDCl_3$, 101 MHz): δ 206.3, 155.6, 140.9, 137.8, 136.9, 136.5, 136.3, 129.5, 127.5, 126.5, 123.2, 76.7, 47.3, 43.7, 21.1, 21.0 ppm; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{17}H_{16}O$ 236.1201; found 236.1206.

(1*R*,3*S*)-3-(Furan-2-yl)-2,3-dihydro-1*H*-inden-1-ol (2y)



Yield 40% (40 mg, pale brown solid); mp 109.9–111.0 °C; 98% ee (Chiralpak IB, 0 to 5% EtOH for 3 min in *n*-hexane, 0.8 mL min^{-1}, 270 nm, t_R(major) = 18.8 min, t_R(minor) = 15.4 min); $[\alpha]_D^{20}$ = −39.6 (*c* 1.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, 1H, J = 6.8 Hz), 7.36–7.26 (m, 3H), 7.23–7.17 (m, 1H), 6.31 (t, 1H, J = 3.0, 1.8 Hz), 6.13 (d, 1H, J = 3.1 Hz), 5.24 (t, 1H, J = 6.3 Hz), 4.34 (t, 1H, J = 7.5 Hz), 2.91 (ddt, 1H, J = 1350.7, 13.4, 7.9, 6.9 Hz), 2.21–2.03 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.9, 144.7, 143.0, 141.7, 128.6, 127.7, 124.9, 124.4, 110.2, 105.3, 75.1, 42.3, 41.5; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{13}H_{12}O_2$ 200.0837; found 200.0846.

(*R*)-3-(Furan-2-yl)-2,3-dihydro-1*H*-inden-1-one, (*R*)-1y



tYield 41.3% (41.0 mg, brown oil); 95% ee (Chiralpak IB, 0 to 5% EtOH for 3 min in *n*-hexane, 0.8 mL min^{-1}, 270 nm, t_R(major) = 14.1 min, t_R(minor) = 14.4 min); $[\alpha]_D^{19}$ = −7.8 (*c* 1.5, CH_2Cl_2) Literature values: $[\alpha]_D^{25}$ = −4.3 (*c* 0.6, $CHCl_3$ for 50% ee).[26] $[\alpha]_D^{25}$ = −7.4 (*c* 0.3, $CHCl_3$ for 58% ee);[23] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, 1H, J = 7.6 Hz), 7.65–7.59 (m, 2H), 7.52 (d, 1H, J = 7.8 Hz), 7.44 (t, 1H, J = 7.4 Hz), 7.35 (d, 1H, J = 1.8 Hz), 6.31 (t, 1H, J = 3.2, 1.8 Hz), 6.11 (d, 1H, J = 3.2 Hz), 4.69 (dd, 1H, J = 8.1, 4.1 Hz), 3.13 (dd, 1H, J = 19.0, 8.1 Hz), 2.88 (dd, 1H, J = 19.0, 4.1 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 205.0, 155.2, 154.7, 142.2, 136.4, 135.0, 128.3, 126.6, 123.7, 110.3, 105.8, 42.8, 37.7; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{13}H_{10}O_2$ 198.0681; found 198.0677.

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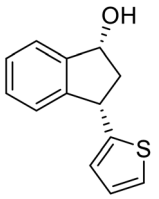
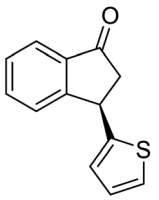
(1*R*,3*S*)-3-(Thiophen-2-yl)-2,3-dihydro-1*H*-inden-1-ol (2z)



Yield 42% (50 mg, pale brown solid); mp 75.9–76.2 °C; 98% ee (Chiralpak IB, 0 to 5% EtOH for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 14.7 min, t_R(minor) = 14.2 min); $[\alpha]_D^{22} = -5.2$ (*c* 2.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, 1H, J = 7.3 Hz), 7.34–7.24 (m, 2H), 7.18 (dd, 1H, J = 5.1, 1.2 Hz), 7.14 (d, 1H, J = 7.4 Hz), 6.96 (dd, 1H, J = 5.1, 3.5 Hz), 6.92 (d, 1H, J = 3.1 Hz), 5.23 (t, 1H, J = 7.0 Hz), 4.49 (t, 1H, J = 8.2 Hz), 3.06 (dt, 1H, J = 12.9, 7.2 Hz), 2.15–1.96 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.0, 144.9, 144.6, 128.5, 127.6, 126.8, 124.9, 124.6, 123.9, 123.9, 74.8, 47.5, 43.1; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{13}H_{12}OS$ 216.0609; found 216.0617.

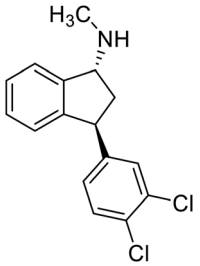
(*R*)-3-(Thiophen-2-yl)-2,3-dihydro-1*H*-inden-1-one, (*R*)-1z



Yield 49.7% (53.2 mg, brown solid); mp 54.8–55.0 °C; 94% ee (Chiralpak IB, 0 to 5% EtOH for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 34.5 min, t_R(minor) = 16.4 min); $[\alpha]_D^{21} = -3.0$ (*c* 2.4, CH_2Cl_2). Literature value for (*S*)-**1z**: $[\alpha]_D^{23} = +8$ (*c* 1.0, $CHCl_3$ for 93% ee);[27] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, 1H, J = 7.6 Hz), 7.61 (t, 1H, J = 7.5 Hz), 7.51–7.40 (m, 2H), 7.19 (d, 1H, J = 5.1 Hz), 6.95 (dd, 1H, J = 5.1, 3.5 Hz), 6.88 (d, 1H, J = 3.5 Hz), 4.89 (dd, 1H, J = 8.0, 4.0 Hz), 3.27 (dd, 1H, J = 19.1, 8.0 Hz), 2.80 (dd, 1H, J = 19.1, 4.0 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.8, 156.7, 146.8, 136.1, 135.1, 128.3, 126.9, 126.7, 124.7, 124.3, 123.5, 47.2, 39.4; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{13}H_{10}OS$ 214.0452; found 214.0457.

Synthesis of (1*R*,3*S*)-3-(3,4-dichlorophenyl)-*N*-methyl-2,3-dihydro-1*H*-inden-1-amine, (+)-indatraline[7]

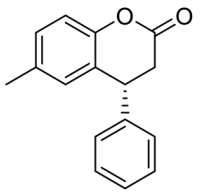
A solution of (1*S*,3*S*)-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (**2s**) (87 mg, 0.3 mmol) and triethylamine (210 μL, 1.5 mmol) dissolved in anhydrous THF (3.0 mL) was cooled to −20 °C and methananesulfonyl chloride (70 μL, 0.9 mmol) was added dropwise. The reaction mixture was stirred at −20 °C for 1 h. Then 2 M solution of methylamine in THF (3.75 mL 7.5 mmol) was added slowly over 30 min. The reaction mixture was allowed to warm to rt and stirred 18 hours. The solvent was removed by rotary evaporation, and EtOAc (10 mL) and water (10 mL) were added. The phases were separated and the aqueous layer was re-extracted with EtOAc (20 mL × 3) and the combined organic layers were washed with brine (40 mL), dried over anhydrous $MgSO_4$, concentrated by rotary evaporation. The crude residue was purified by silica-gel column chromatography (EtOAc : Et_3N = 95 : 5) to give (+)-indatraline (56.6 mg, 65%) as a yellow oil.



Yield 65% (56.6 mg as a yellow oil); $[\alpha]_D^{27} = -18.6$ (*c* 0.1, $CHCl_3$). Literature value $[\alpha]_D^{22} = -18.9$ (*c* = 1.1, $CHCl_3$);[19] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, 1H, J = 6.3 Hz), 7.35 (d, 1H, J = 8.3 Hz), 7.31–7.26 (m, 2H), 7.21 (d, 1H, J = 2.0 Hz), 7.00–6.93 (m, 2H), 4.58 (t, 1H, J = 7.7 Hz), 4.35 (dd, 1H, J = 7.0, 2.7 Hz), 2.52 (m, 4H), 2.26 (t, 1H, J = 13.4, 7.3 Hz); ^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 146.1, 146.1, 145.0, 132.6, 130.5, 130.5, 129.9, 129.1, 127.5, 127.5, 125.4, 125.3, 63.2, 48.5, 42.0, 32.9; HRMS (EI, double focusing) *m*/*z*: [M]$^+$ calcd for $C_{16}H_{15}Cl_2N$ 291.0582; found 291.0613.

Synthesis of (*R*)-6-methyl-4-phenylchroman-2-one [(*R*)-5][27]

To a solution of (*R*)-**1c** (90 mg, 0.4 mmol) and *p*-toluenesulfonic acid (19.5 mg, 0.09 mmol) in CH_2Cl_2 (6 mL) was added *m*-CPBA (443 mg 1.76 mmol) portionwise. The solution was heated to reflux for 24 hours. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporator. The crude residue was purified by flash column chromatography on silica-gel (EtOAc : *n*-hexane 1 : 10) to provide (*R*)-**5** as a white solid (65%, 65 mg).



Yield 65% (65 mg, as white solid); mp 85.1–85.9 °C; 99% ee (Chiralpak IB, 0 to 6% IPA for 7 min in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 18.9 min, t_R(minor) = 17.9 min); $[\alpha]_D^{27.6} = -2.36$ (*c* 0.9, $CHCl_3$). Literature values $[\alpha]_D^{15.8} = -3.6$ (*c* 1.0, $CHCl_3$ for 99% ee).[55] $[\alpha]_D^{20} = -2.24$ (*c* 0.35, $CHCl_3$ for 98% ee);[56] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.4 (t, 2H, J = 7.4 Hz), 7.3 (d, 1H, J = 7.2 Hz), 7.2 (d, 2H, J = 7.2 Hz), 7.1–7.1 (m, 1H), 7.0 (d, 1H, J = 8.2 Hz), 6.8–6.7 (m, 1H), 4.3–4.2 (m, 1H), 3.1–2.9 (m, 2H), 2.3 (s,

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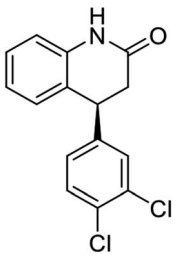
3H); ^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ 167.9, 149.7, 140.5, 134.3, 129.3, 129.1, 128.7, 127.6, 127.6, 125.3, 116.9, 40.8, 37.2, 20.8; HRMS (EI, double focusing) *m*/*z*: $[M]^+$ calcd for $C_{16}H_{14}O_2$ 238.0994; found 238.0991.

Synthesis[54] of (*S*)-7 and (*S*)-8

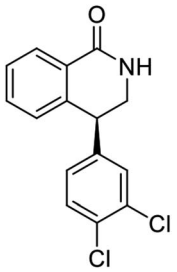
A suspension of hydroxylamine hydrochloride (144 mg, 2.1 mmol) and NaOAc (212 mg, 2.6 mmol) in 80% aqueous EtOH (20 mL) was stirred at rt for 30 min. (*S*)-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-inden-1-one ((*S*)-**1s**) (360 mg 1.3 mmol) was added and the reaction mixture was heated gently to reflux for 2 h. After cooling to rt, the solvent was evaporated under vacuum and the residue was diluted with EtOAc (60 mL) and washed with water (30 mL) and brine successively. The organic layer was dried over anhydrous $MgSO_4$, and concentrated by rotary evaporation. The crude oxime product (*ca.* 353 mg) was used in the next step without further purification. To a stirred solution of 1-indanone oxime (300 mg, *ca.*1.0 mmol) and *p*-toluenesulfonyl chloride (225 mg, 1.1 mmol) in 3 mL of acetone was added 4 N NaOH (0.5 mL) solution dropwise at −10 °C. After 5 min, the cooling bath was removed and the reaction mixture was stirred for 2 h at rt. Then the reaction mixture was poured into 50 g of ice and extracted with EtOAc (30 mL × 3). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated by rotary and the resulting residue was purified by flash chromatography (EtOAc : *n*-hexane 1 : 5) on silica-gel to give (*E*)-indanone oxime-*O*-tosylate ((*S*)-**6**, 360 mg, 78%) as a white solid. To a solution of (*E*)-indanone oxime-*O*-tosylate ((*S*)-**6**, 100 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) at −40 °C was added $AlCl_3$ (49 mg, 0.34 mmol) portionwise. The reaction mixture was stirred for 30 minutes at that temperature and allow to warm to rt. The reaction mixture was stirred for additional 2 h. Then, water (15 mL) was added carefully for quenching, and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. The crude residue was purified by flash column chromatography on silica-gel (EtOAc : *n*-hexane 1 : 3) to give (*S*)-**7** (26.8 mg, 41% yield), and (*S*)-**8** (23.1 mg, 35% yield). R_f for (*S*)-**7** = 0.2 and R_f for (*S*)-**8** = 0.1 (EtOAc : *n*-hexane 1 : 2).

(*S*)-4-(3,4-Dichlorophenyl)-3,4-dihydroquinolin-2(1*H*)-one (*S*-7).



Yield 41% (26.4 mg, as white solid); mp 131.1–131.9 °C; 99% ee (Chiralpak IB, 6% EtOH in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 17.5 min, t_R(minor) = 19.7 min); $[\alpha]_D^{26}$ = −86.8 (*c* 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.5 (s, 1H), 7.4 (d, 1H, *J* = 8.3 Hz), 7.3–7.2 (m, 1H), 7.1–7.0 (m, 2H), 6.9 (d, 2H, *J* = 7.9 Hz), 4.3 (t, 1H, *J* = 7.1 Hz), 3.0 (dd, 1H, *J* = 16.2, 6.3 Hz), 2.9 (dd, 1H, *J* = 16.2, 7.9 Hz); ^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 170.5, 141.9, 137.0, 132.9, 131.3, 130.9, 129.8, 128.6, 128.2, 127.1, 125.2, 123.6, 116.1, 41.2, 38.2; HRMS (EI, double focusing) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{11}Cl_2NO$ 291.0218; found 291.0210.

(*S*)-4-(3,4-Dichlorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (*S*-8).



Yield 35% (23.1 mg, as white solid); mp 176.8–177.2 °C; 98% ee (Chiralpak IA, 10% EtOH in *n*-hexane, 1 mL min^{-1}, 270 nm, t_R(major) = 19.6 min, t_R(minor) = 25.1 min); $[\alpha]_D^{26}$ = +21.2 (*c* 0.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.2 (d, 1H, *J* = 7.1 Hz), 7.5–7.4 (m, 3H), 7.0–7.0 (m, 3H), 6.7 (s, 1H), 4.3–4.2 (m, 1H), 3.8 (ddd, 1H, *J* = 12.5, 5.2, 2.7 Hz), 3.7 (ddd, 1H, *J* = 12.5, 7.1, 3.1 Hz); ^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 166.0, 141.0, 140.0, 132.9, 132.8, 131.6, 130.7, 130.4, 128.8, 128.4, 128.0, 127.9, 127.6, 46.9, 43.3; HRMS (EI, double focusing) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{11}Cl_2NO$ 291.0218; found 291.0218.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

1 B. Gabriele, R. Mancuso and L. Veltri, *Chem.–Eur. J.*, 2016, **22**, 5056–5094.
2 C. Borie, L. Ackermann and M. Nechab, *Chem. Soc. Rev.*, 2016, **45**, 1368–1386.
3 M. Turek, D. Szczęsna, M. Koprowski and P. Bałczewski, *Beilstein J. Org. Chem.*, 2017, **13**, 451–494.
4 S. Faiz, M. Yousaf, A. F. Zahoor, S. A. R. Naqvi, A. Irfan and G. Zaman, *Synth. Commun.*, 2017, **47**, 1121–1135.
5 S. A. Patil, R. Patil and S. A. Patil, *Eur. J. Med. Chem.*, 2017, **138**, 182–198.
6 M.-L. Tang, P. Peng, Z.-Y. Liu, J. Zhang, J.-M. Yu and X. Sun, *Chem.–Eur. J.*, 2016, **22**, 14535–14539.
7 X. Qin, M. W. Yao Lee and J. S. Zhou, *Org. Lett.*, 2019, **21**, 5990–5994.
8 H. Yu, I. J. Kim, J. E. Folk, X. Tian, R. B. Rothman, M. H. Baumann, C. M. Dersch, J. L. Flippen-Anderson,

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D. Parrish, A. E. Jacobson and K. C. Rice, *J. Med. Chem.*, 2004, **47**, 2624–2634.
9 M. Froimowitz, K.-M. Wu, A. Moussa, R. M. Haidar, J. Jurayj, C. George and E. L. Gardner, *J. Med. Chem.*, 2000, **43**, 4981–4992.
10 K. P. Bogeso, A. V. Christensen, J. Hyttel and T. Liljefors, *J. Med. Chem.*, 1985, **28**, 1817–1828.
11 K. P. Boegesoe, J. Arnt, V. Boeck, A. V. Christensen, J. Hyttel and K. G. Jensen, *J. Med. Chem.*, 1988, **31**, 2247–2256.
12 X.-D. Hao, J. Chang, B.-Y. Qin, C. Zhong, Z.-B. Chu, J. Huang, W.-J. Zhou and X. Sun, *Eur. J. Med. Chem.*, 2015, **102**, 26–38.
13 T. Atsumi, Y. Murakami, K. Shibuya, K. Tonosaki and S. Fujisawa, *Anticancer Res.*, 2005, **25**, 4029.
14 G. G. Bianco, H. M. C. Ferraz, A. M. Costa, L. V. Costa-Lotufo, C. Pessoa, M. O. de Moraes, M. G. Schrems, A. Pfaltz and L. F. Silva, *J. Org. Chem.*, 2009, **74**, 2561–2566.
15 S. B. Bhorkade, K. B. Gavhane and V. S. Shinde, *Tetrahedron*, 2016, **72**, 1954–1959.
16 S. H. Lee, S. J. Park, I. S. Kim and Y. H. Jung, *Tetrahedron*, 2013, **69**, 1877–1880.
17 G. Wang, C. Zheng and G. Zhao, *Tetrahedron: Asymmetry*, 2006, **17**, 2074–2081.
18 N. G. Nørager, L. L. R. Lorentz-Petersen, L. O. Lyngsø, J. Kehler and K. Juhl, *Synlett*, 2011, 1753–1755.
19 S. Roesner, J. M. Casatejada, T. G. Elford, R. P. Sonawane and V. K. Aggarwal, *Org. Lett.*, 2011, **13**, 5740–5743.
20 Q. Yan, D. Kong, M. Li, G. Hou and G. Zi, *J. Am. Chem. Soc.*, 2015, **137**, 10177–10181.
21 K. Yoo, H. Kim and J. Yun, *Chem.–Eur. J.*, 2009, **15**, 11134–11138.
22 W.-T. Wei, J.-Y. Yeh, T.-S. Kuo and H.-L. Wu, *Chem.–Eur. J.*, 2011, **17**, 11405–11409.
23 J. Yan, Y. Nie, F. Gao, Q. Yuan, F. Xie and W. Zhang, *Tetrahedron*, 2021, **84**, 132003.
24 W. M. Clark, A. J. Kassick, M. A. Plotkin, A. M. Eldridge and I. Lantos, *Org. Lett.*, 1999, **1**, 1839–1842.
25 B. H. Lee, Y. L. Choi, S. Shin and J.-N. Heo, *J. Org. Chem.*, 2011, **76**, 6611–6618.
26 A. Minatti, X. Zheng and S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 9253–9258.
27 G. Yue, K. Lei, H. Hirao and J. Zhou, *Angew. Chem., Int. Ed.*, 2015, **54**, 6531–6535.
28 S. Mannathan, S. Raoufmoghaddam, J. N. H. Reek, J. G. de Vries and A. J. Minnaard, *ChemCatChem*, 2017, **9**, 551–554.
29 Y.-N. Yu and M.-H. Xu, *J. Org. Chem.*, 2013, **78**, 2736–2741.
30 T. Ikariya and A. J. Blacker, *Acc. Chem. Res.*, 2007, **40**, 1300–1308.
31 T. Ikariya, K. Murata and R. Noyori, *Org. Biomol. Chem.*, 2006, **4**, 393–406.
32 R. Noyori, M. Yamakawa and S. Hashiguchi, *J. Org. Chem.*, 2001, **66**, 7931–7944.
33 R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97–102.
34 G. N. Hans, A. Zanotti-Gerosa and M. Wills, *Chem. Rec.*, 2016, **16**, 2623–2643.
35 F. Foubelo, C. Nájera and M. Yus, *Tetrahedron: Asymmetry*, 2015, **26**, 769–790.
36 T. Touge, T. Hakamata, H. Nara, T. Kobayashi, N. Sayo, T. Saito, Y. Kayaki and T. Ikariya, *J. Am. Chem. Soc.*, 2011, **133**, 14960–14963.
37 L.-S. Zheng, Q. Llopis, P.-G. Echeverria, C. Férard, G. Guillamot, P. Phansavath and V. Ratovelomanana-Vidal, *J. Org. Chem.*, 2017, **82**, 5607–5615.
38 A. E. Cotman, M. Lozinšek, B. Wang, M. Stephan and B. Mohar, *Org. Lett.*, 2019, **21**, 3644–3648.
39 S. Rast, B. Modec, M. Stephan and B. Mohar, *Org. Biomol. Chem.*, 2016, **14**, 2112–2120.
40 A. E. Cotman, B. Modec and B. Mohar, *Org. Lett.*, 2018, **20**, 2921–2924.
41 T. Touge, H. Nara, M. Kida, K. Matsumura and Y. Kayaki, *Org. Lett.*, 2021, **23**, 3070–3075.
42 I. Kaljurand, A. Kütt, L. Sooväli, T. Rodima, V. Mäemets, I. Leito and I. A. Koppel, *J. Org. Chem.*, 2005, **70**, 1019–1028.
43 R. Rendy, Y. Zhang, A. McElrea, A. Gomez and D. A. Klumpp, *J. Org. Chem.*, 2004, **69**, 2340–2347.
44 B. Venkat Ramulu, A. Gopi Krishna Reddy and G. Satyanarayana, *Synlett*, 2013, **24**, 868–872.
45 B. V. Ramulu, P. Niharika and G. Satyanarayana, *Synthesis*, 2015, **47**, 1255–1268.
46 A. Püschl, H. C. Rudbeck, A. Faldt, A. Confante and J. Kehler, *Synthesis*, 2005, 291–295.
47 N. Parveen and G. Sekar, *Adv. Synth. Catal.*, 2019, **361**, 4581–4595.
48 P. A. Dub and J. C. Gordon, *Dalton Trans.*, 2016, **45**, 6756–6781.
49 P. A. Dub and T. Ikariya, *J. Am. Chem. Soc.*, 2013, **135**, 2604–2619.
50 P. Van Kerrebroeck, K. Kreder, U. Jonas, N. Zinner and A. Wein, *Urology*, 2001, **57**, 414–421.
51 F. Ulgheri, M. Marchetti and O. Piccolo, *J. Org. Chem.*, 2007, **72**, 6056–6059.
52 B. D. Gallagher, B. R. Taft and B. H. Lipshutz, *Org. Lett.*, 2009, **11**, 5374–5377.
53 G. Chen, N. Tokunaga and T. Hayashi, *Org. Lett.*, 2005, **7**, 2285–2288.
54 B. S. Lee, I. Y. Lee, B.-S. Lee, C. E. Song and D. Y. Chi, *Bull. Korean Chem. Soc.*, 2000, **21**, 860.
55 T. Korenaga, R. Sasaki, T. Takemoto, T. Yasuda and M. Watanabe, *Adv. Synth. Catal.*, 2018, **360**, 322–333.
56 Y. Luo and A. J. Carnell, *Angew. Chem., Int. Ed.*, 2010, **49**, 2750–2754.