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Stereoarrayed 2,3-Disubstituted 1-Indanols via Ruthenium(II)-Catalyzed Dynamic Kinetic Resolution−Asymmetric Transfer Hydrogenation

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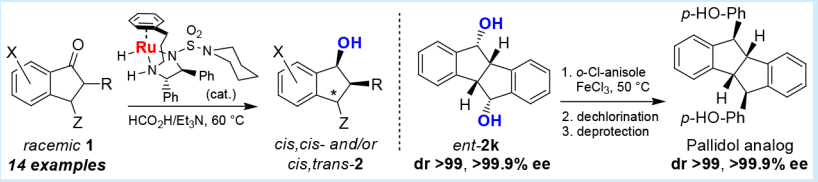
Supporting Information



ABSTRACT: Activated racemic 2,3-disubstituted 1-indanones **1** possessing two stereolabile centers were stereoselectively reduced to the corresponding chiral 2,3-disubstituted-1-indanols **2** by ruthenium(II)-catalyzed dynamic kinetic resolution−asymmetric transfer hydrogenation. In particular, this route offers a practical access to a new class of conformationally rigid enantiopure 1,4-diols **2k−m** having four contiguous chiral centers. Transformation of *ent*-**2k** into a Pallidol analogue via a highly diastereo- and regioselective Friedel−Crafts benzylation of *o*-chloroanisole is presented.

Stereogenic indanones, indanols, and closely related compounds have attracted much attention due to their relevance and wide synthetic application toward numerous natural compounds or medicinal molecules.[1−4] For example, the naturally occurring resveratrol-based oligomers caraphenol C and pallidol displayed antiosteoporosis and neuroprotective activities[2] as the polycyclic Incarviatone A,[3] while tetrapetalone was found to possess an anti-inflammatory property[4] (Figure 1).

As interesting high-potential targets having a wide-range of molecular complexity, the diversification of efficient synthetic accesses toward their stereopure indan-based scaffolds is therefore beneficial. Various approaches such as chiral pool,[5] biotransformation,[2c] and organo- or metal-mediated catalysis[6] were particularly highlighted in the literature. Surprisingly, however, only a few methods exist for the stereoselective construction of 2,3-disubstituted 1-indanols.[7]

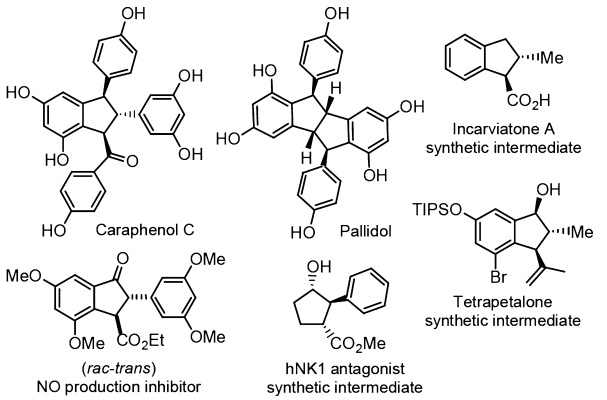


Figure 1. Examples of bioactive stereogenic indanones, indanols, and related compounds.

In the framework of our research work on asymmetric ketones reduction catalyzed by enantiopure Ru(II) complexes,[8] we present here an entry to indanols possessing multiple contiguous stereocenters via dynamic kinetic resolution−asymmetric transfer hydrogenation (DKR−ATH).[9]

Indeed, *rac*-2-substituted 1-indanones are well-known to undergo efficient Ru(II)-catalyzed DKR−ATH in HCO_2H/Et_3N mixtures leading preferentially to the enantiomeric *cis*-2-substituted 1-indanols (Scheme 1).[10] Moreover, we were first to report the efficient DKR−ATH of *rac*-3-(methoxycarbonyl)-1-indanone with excellent stereoinduction.[11]

These advances prompted us to investigate the DKR−ATH of activated *rac*-2,3-disubstituted 1-indanones (Scheme 1 and Figure 2), which were envisaged to possess two stereolabile centers. The potential of generating multiple stereodefined contiguous chiral centers in one pot under a controlled reductive process is clearly advantageous. For instance, 1-indanone-derived substrates **1a−j** and **1k−m** would lead ideally to a single stereoisomer out of 2^3 and 2^4 possible isomers, respectively.

In the present work, four subcategories of activated *rac*-2,3-disubstituted-1-indanone substrates were investigated having either an ester, cyano, keto, or amide functionality on C3 and some varied substituents on C2. These racemic indanones are readily prepared via Lewis acid catalyzed Friedel−Crafts intramolecular acylation of 3-substituted 2-phenylsuccinic acids

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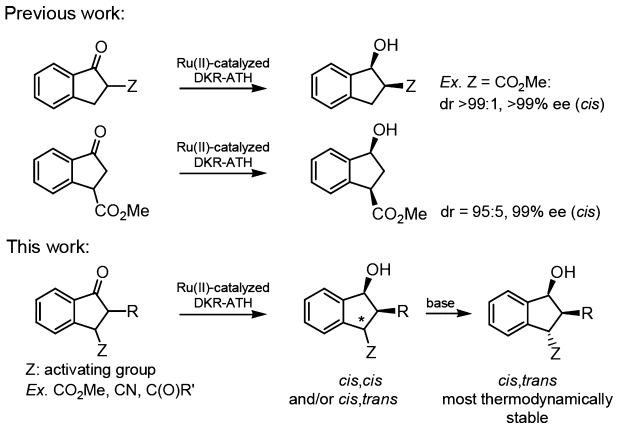
Scheme 1. Ru(II)-Catalyzed DKR–ATH Strategies to Highly Stereopure 2- and/or 3-Substituted 1-Indanols



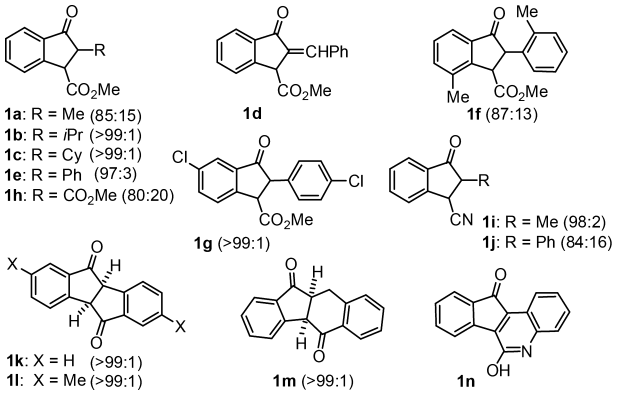


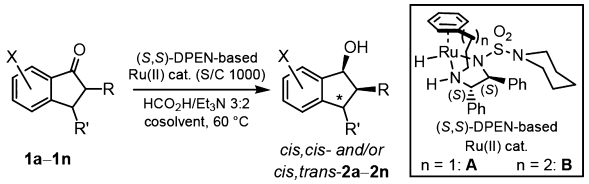
Figure 2. Various functionalized racemic 2,3-disubstituted 1-indanones explored herein in Ru(II)-catalyzed DKR–ATH (dr of starting substrate mixture in parentheses).

(for **1a–l**)[12] or 2-hydroxy-3-phenyl-4-quinolinecarboxylic acid (for **1n**).[13]

For this purpose, we initially surveyed our laboratory-developed *ansa*-Ru(II)-type catalysts **A** and **B** (Table 1) for their suitability in DKR–ATH of the basic substrate *rac*-2-methyl-3-methoxycarbonyl-1-indanone (**1a**: R = Me). This racemic indanone, prepared with a dr = 85:15, revealed by ^{1}H NMR a fast deuterium exchange (within 10 min) at C2 and C3 upon exposure to DCO_2D/Et_3N 3:2 at 60 °C. Thus, under our standard ATH conditions with an S/C (substrate/catalyst) = 1000 in neat HCO_2H/Et_3N 3:2 at 60 °C, the reduction proceeded quantitatively within 2 h with cat. **A** or **B** affording the alcohol product **2a** with a dr = 44:50:6:0 (by ^{1}H NMR)[14] and excellent ee's (>99.9% each).[15] Hence, the occurrence of a DKR was validated. A prolonged reaction time (7 days) favored the epimerization at C3 leading in majority to the most thermodynamically stable *cis,trans*-(1*S*,2*S*,3*S*)-**2a** (dr = 86:8:6:0). Silica gel chromatography of the crude afforded the diastereomerically enriched *cis,trans*-(1*S*,2*S*,3*S*)-**2a** as an oil (dr = 95:0:5:0, 74% yield). Its absolute configuration was assigned by extension from the X-ray crystal structures of **2f** and **2h**.

Next, the branched higher homologues **1b** (R = *i*Pr) and **1c** (R = Cy) (dr >99:1) were profiled in this transformation using Ru(II) cat. **B**. To our delight, these indanones underwent full conversion within 24 h to the *cis,trans*-configured alcohols in excellent stereoselectivity (dr = 95:5:0:0, >99.5% ee). Facile single recrystallization afforded the stereopure *cis,trans*-(1*S*,2*S*,3*S*)-**3b** or *cis,trans*-(1*S*,2*S*,3*S*)-**3c**. Such a high level of attained *cis,trans* selection is the result of the high chiral recognition ability of the Ru(II) cat. in the reduction step delivering a 1,2-*cis* geometry, while the configuration at C3 is thermodynamically driven.

Table 1. Ru(II)-Catalyzed DKR–ATH of the Various Racemic 2,3-Disubstituted 1-Indanones 1 of Figure 2[a]



indanone	time (h)	conv[a,b] (%)	dr[a,b]	ee[a,b] (%)
1a	2	100	44:50:6:0	
	24	100	59:35:6:0	
	170	100 (74)	86:8:6:0 (95:0:5)	>99.9 (>99.9)
1b	24	100 (85)	95:5:0:0 (>99)	>99.5 (>99.9)
1c	24	100 (81)	95:5:0:0 (>99)	>99.5 (>99.9)
1d	5	100	65:25:10:0	
	48	100 (88)	87:3:10:0 (89:0:11)	>99.5
1e	24	100 (93)	98:2:0:0 (>99)	>99.9 (>99.9)
1f[c]	24	100 (85)	92:8:0:0 (>99)	>99.5 (>99.9)
1g	24	100	97:3:0:0	99.9
1h	18	100 (70)	92:2:2:4 (>99)	>99.5 (>99.9)
1i	1.5	100 (80)	8:92:0:0 (>99)	>99.5 (>99.9)
1k[d]	10	100	>99	>99.9
1k[c,e]	10	92 (42)	>99 (>99)	>99 (>99)
1l[c,d]	10	100 (97)	>99 (>99)	>99 (>99)
1m[f]	3.5	100[g] (45)	95:5 (>99)	>99.9 (>99.9)
1n[h,i]	18	100[j] (35)	>99	>99.9

[a]ATH of indanones **1** (1.0 mmol) was carried out at 60 °C using (*S,S*)-DPEN-based Ru(II) cat. **B** with HCO_2H/Et_3N 3:2 (1 mL). Conversion and dr were determined by ^{1}H NMR, and ee of the major diastereomer was determined by chiral HPLC; dr corresponds to *cis,trans*-, *cis,cis*-, *trans,trans*-, and *trans,cis*-diastereomers. The major products formed are presented in Figure 3. [b]Isolated yields and the corresponding dr and ee values obtained after upgrading by chromatography and/or recrystallization are shown in parentheses; for more details, see the SI. [c]Cat. **A** used. [d]PhCl used as cosolvent. [e]Reaction was carried out at 50 °C with EtOAc as cosolvent; monoreduced **2k′** isolated. [f]S/C = 100. [g]45% of side product **3m** was also formed. [h]DMF used as cosolvent. [i]S/C = 200. [j]63% of side product **3n** was also formed.

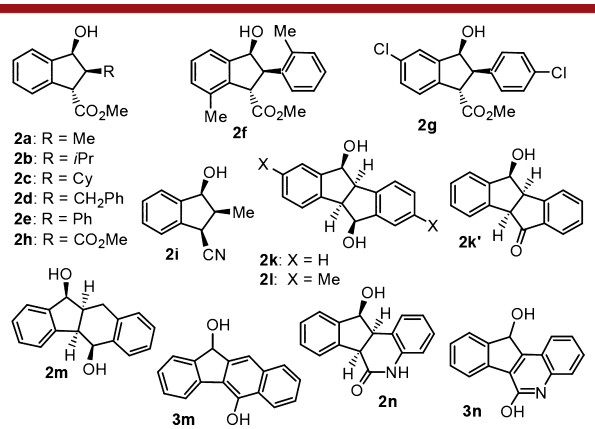


Figure 3. DKR–ATH alcohol products **2** derived from *rac*-2,3-disubstituted 1-indanones **1**.

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In the case of 2-benzylidene-3-(methoxycarbonyl)-1-indanone (**1d**), the C=C bond was reduced first (within 1 h) followed by the keto function (5 h), culminating in a dr = 65:25:10:0 with the *cis,trans*-(1*S*,2*S*,3*S*)-**2d** as major product. A prolonged reaction time (3 days) resulted in a dr = 87:3:10:0 (>99.5% ee for the *cis,trans*). Accordingly, a series of *rac*-2-*R*-3-(methoxycarbonyl)-1-indanones wherein R = Ph (**1e**),[16] *o*-Tol (**1f**), *p*-Cl-Ph (**1g**), and CO_2Me (**1h**) was subjected to DKR–ATH. The corresponding *cis,trans*-indanols **2e–h** were obtained as the major diastereomers, and these were upgraded by silica gel chromatography and/or recrystallization to dr >97:3 and >99.9% ee. Noteworthy, the reduction of **1f** was slightly more enantioselective with cat. **A**.

Switching to *rac*-2-methyl-3-cyano-1-indanone (**1i**), *cis,cis*-**2i** was obtained as the major diastereomer (*cis,trans*/*cis,cis* = 8:92, >99.5% ee for the *cis,cis*) by quenching the reaction just after complete conversion (1.5 h). Further heating of the mixture at 60 °C for 2 days led to partial epimerization at C3 (*cis,trans*/*cis,cis* = 17:83), and this gradually progressed to a ~50:50 ratio within 14 days. However, recrystallization of the mixture with dr = 92:8 afforded the stereomerically pure *cis,cis*-(1*S*,2*S*,3*R*)-**2i** (dr >99, >99.9% ee) in 80% yield. By contrast, the structurally related *rac*-2-phenyl-3-cyano-1-indanone (**1j**) was practically inert under the adopted reaction conditions (<1% conversion).

Exploring the substrate scope, we shifted to the rigid indanoindandiones **1k** and **1l**. Thus, when the reduction was performed at 60 °C in the presence of PhCl as cosolvent (in order to solubilize the starting material), the single stereomeric diols *cis,cis,cis*-**2k** and *cis,cis,cis*-**2l** (dr >99, >99.9% ee) possessing four contiguous stereocenters were quantitatively formed. The (4b*R*,5*S*,9b*R*,10*S*) absolute configuration of **2k** was unambiguously confirmed by X-ray crystallographic analysis (Figure 4, left). It is worth noting that the reduction of **1k** under milder conditions (50 °C for 10 h) with EtOAc as cosolvent led to the stereopure monoalcohol *cis,cis*-**2k′** in 42% isolated yield. This protocol was also extended to the indanotetralindione **1m** and the indenono-(2-hydroxyquinoline) **1n**. The former was exposed to HCO_2H/Et_3N 3:2 at 60 °C with S/C = 100 leading to 55% of diol **2m** (dr = 95:5, > 99.9% ee) along with 45% of racemic **3m**.[17] The poorly soluble **3m** precipitated quantitatively in CH_2Cl_2 and was filtered off, and the diol *cis,cis,cis*-**2m** was recrystallized from CH_2Cl_2/hexane (45% isolated yield; dr >99, > 99.9% ee). Indenono-2-hydroxyquinoline **1n** was best reduced at 60 °C within 18 h with S/C = 200 in the presence of DMF as cosolvent, yielding 37% of the stereopure alcohol **2n** (dr >99, >99.9% ee) along with 67% of the partially reduced racemic product **3n**. The poorly soluble **3n** was eliminated by filtration, and the alcohol *cis,cis*-**2n** was isolated in stereopure form (dr >99, > 99.9% ee). The absolute configurations of **2m** (Figure 4, right) and **2n** were determined by X-ray crystallographic analysis.

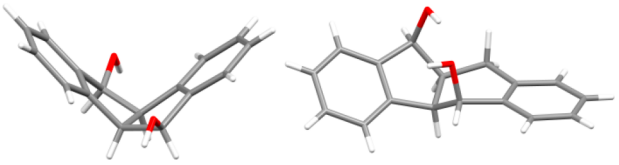
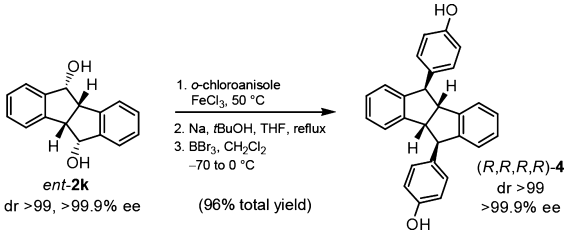


Figure 4. Crystal structures of 1,4-diols (4b*R*,5*S*,9b*R*,10*S*)-**2k** (left) and (4b*R*,5*S*,10a*S*,11*S*)-**2m** (right).

Aiming to demonstrate further the synthetic usefulness of our route, the enantiopure 1,4-diol *ent*-**2k** was prepared on a 2-g scale employing (*R*,*R*)-DPEN-based Ru(II) cat. **B** and was subjected to $FeCl_3$-catalyzed Friedel–Crafts regioselective benzylation of *o*-chloroanisole[18] (Scheme 2). Due to its inherent butterfly molecular structure, the benzylation was totally diastereoselective (dr >99) with full inversion of configuration at the benzylic carbons. Dechlorination using Na/*t*BuOH[19] followed by demethylation with BBr_3 afforded the pallidol[20] analogue (*R*,*R*,*R*,*R*)-**4** in 96% yield for three steps.

Scheme 2. Transformation of the 1,4-Diol *ent*-2k into the Pallidol Analogue 4



In conclusion, we have successfully established the first highly stereoselective Ru(II)-catalyzed asymmetric-transfer hydrogenation relying upon the kinetic conversion of stereolabile activated 2,3-disubstituted 1-indanones **1**. A series of alcohol products **2** possessing multiple contiguous chiral centers were obtained in stereopure forms. This practical protocol served as the key step toward the synthesis of a pallidol analog **4** having four contiguous stereogenic carbons. We believe that the present methodology will be attractive to other chemists when elaborating chiral compounds with high molecular complexity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00980.

Experimental data, chiral HPLC chromatograms, and NMR spectra for prepared compounds (PDF)

Accession Codes

CCDC 1829925–1829929 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(13) See the Supporting Information for their concise synthesis.

(14) dr's correspond to the respective ratios of *cis,trans-*, *cis,cis-*, *trans,trans-*, and *trans,cis*-**2a** (*trans,cis*-**2a** not formed). For their characteristic ^1H NMR signals, see the Supporting Information.

(15) Though identical diastereo- and enantioselectivities were obtained using either cat. **A** or **B**, the reduction was somewhat faster with **B**.

(16) Similarly as for the substrate **1a**, exposing **1e** (dr = 97:3) to DCO_2D/Et_3N 3:2 in $CDCl_3$ at 60 °C revealed by ^1H NMR a fast deuterium exchange (within 10 min) at C2 and C3.

(17) Noteworthy, exposure of **1m** to HCO_2H/Et_3N 3:2 at 60 °C (without catalyst) resulted in its complete isomerisation to **3m** within 2 h.

(18) The reaction conditions were adopted from: Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913−3917.

(19) For dechlorination of an aromatic ring using Na/*t*BuOH, see: Yoshida, H.; Asatsu, Y.; Mimura, Y.; Ito, Y.; Ohshita, J.; Takaki, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 9676−9679.

(20) For the synthesis of *rac*-pallidol, see ref 2b, and for its asymmetric synthesis via a Nazarov-type cyclization using chiral sulfoxides, see ref 5c.

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