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Synthetic Methods

A Different Approach to Enantioselective Organic Synthesis: Absolute Asymmetric Synthesis of Organometallic Reagents**

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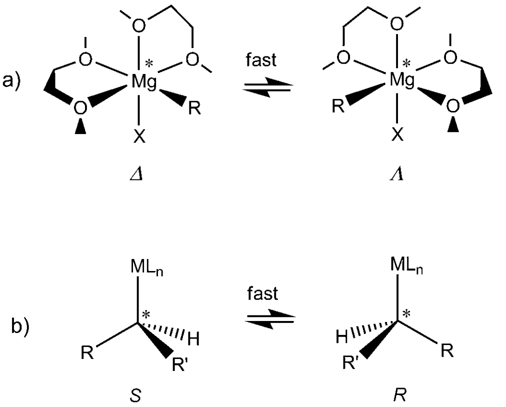
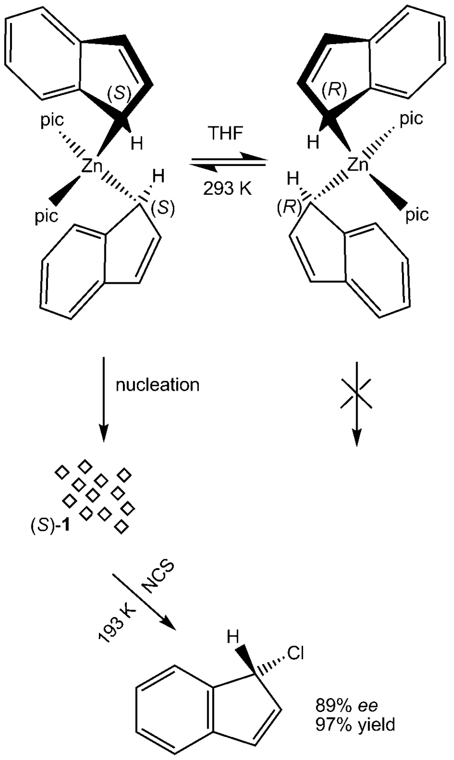
Homochirality is the signature of life (at least as we know it). The origin of biomolecular homochirality is still somewhat of a mystery, and additional knowledge on how optical activity can be created is necessary. Reactions that create enantiomerically enriched products from achiral or racemic precursors, without the intervention of chiral catalysts or solvents, constitute examples of absolute asymmetric synthesis (AAS).[1] There are only a few genuine examples of AAS known today; one route goes by the transformation of achiral substrates in a chiral crystal.[2] Although ingenious intracrystal photochemical reactions have been designed,[3] which can give very high enantiomeric excess (*ee*), they are restricted to special substrates and thus, so far, are of limited use in organic synthesis. In contrast, AAS of generic organometallic reagents may yield enantiopure crystal batches,[4] which can be used in intercrystal reactions with many different substrates to give a wide range of organic products with potentially 100% *ee* and yield. Apart from the theoretical implications of new symmetry-breaking reactions, this AAS approach would have several advantages over traditional methods: 1) equal access to both enantiomers, 2) solvent-free reactions with new selectivity attainable, 3) easy workup and scaleup, 4) no need for noble metals or enantiopure ligands, and 5) good atom economy.

We have previously reported AAS of chiral-at-metal Grignard reagents[4b] (Scheme 1a). Subsequent nucleophilic addition of these Grignard reagents to different aldehydes yielded the corresponding alcohols in good yields, but with only 22% *ee*. It is still unclear whether the helical Grignard reagents have low inherent selectivity, or if the crystals simply decompose during reaction. We are now instead synthesizing labile organometallic reagents bearing stereogenic α-carbon atoms (Scheme 1b), with the intention of identifying a conglomerate[5] phase of such a reagent, which can then be subjected to total spontaneous resolution.[6]

Our method for finding conglomerates is still basically trial and error; after synthesizing a long series of racemic phases we can now report AAS (Scheme 2) of a new diindenylzinc reagent, $[Zn(ind)_2(pic)_2]$ (**1**), (ind = η^1-indenyl and pic = 3-methylpyridine). Chiral crystals of this reagent are easy to handle and react rapidly with *N*-chlorosuccinimide (NCS) at low temperatures to give 1-chloroindene with 87–89% *ee* and 78–97% yield. We believe that this constitutes a first proof-of-concept for the AAS approach.



Scheme 1. a) Chiral-at-metal and b) α-stereogenic reagents are stereochemically labile and thus suitable for the AAS approach.



Scheme 2. Proof-of-concept for the AAS approach.

When two equivalents of 3-picoline are added to a solution of diindenylzinc (prepared from indene, potassium,

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and zinc chloride) in THF, crystals of [Zn(ind)$_2$(pic)$_2$] are deposited after a few hours. At ambient temperature both a chiral and a racemic phase crystallize concomitantly unless special precautions are taken. The careful layering of a viscous hydrocarbon on top of the THF solution typically results in large chiral crystals of either (*R,R*)-[Zn(ind)$_2$(pic)$_2$] ((*R*)-**1**) or (*S,S*)-[Zn(ind)$_2$(pic)$_2$] ((*S*)-**1**). At lower concentrations racemic crystals (*rac*-**1**) are preferentially formed. The *meso*-complex (*R,S*)-[Zn(ind)$_2$(pic)$_2$] has not been observed.

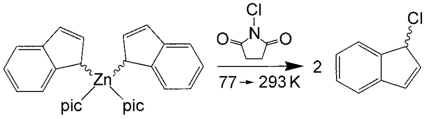
A preliminary screening of the reactivity of single crystals of **1** towards different electrophiles suggested enantioselective chlorination with NCS as a promising test reaction for optimization. Moreover, organic compounds having a C−Cl bond attached to a chiral stereocenter are versatile building blocks in synthesis.[7] Surprisingly, as seen in entry 5 in Table 1, both indenyl groups in [Zn(ind)$_2$(pic)$_2$] react selectively with NCS to give a total *ee* value of 89 % with up to 97 % yield. We feared that once the first indenyl group had reacted, the second indenyl group would easily reorganize (e.g., to pentahapto coordination) with loss of enantioselectivity, which should give a maximum *ee* value of 50 %. These results indicate that conglomerates containing only one indenyl group, that is [Zn(ind)XL$_2$] where X is an inert anionic ligand, would exhibit excellent selectivity.

Table 1 shows that the selectivity depends strongly on both the choice of the solvent and the existence of a radical inhibitor (benzoquinone), which could indicate that the reagent crystals actually dissolve and that the reaction with NCS takes place in solution. Clearly, the reaction with NCS would then have to be very fast since it is competing with racemization and side reactions with methanol and radicals. Indeed, stopping the reaction at 223 K still gives good yields (with similar *ee* values), indicating a high reaction rate even at this temperature.

If the reaction between **1** and NCS does take place in solution, we have created optical activity by AAS of a reagent (**1**) that racemizes rapidly in one solvent. We have then, by changing to another solvent, been able to trap the optical activity to yield an inert optically active product (Scheme 3). To the best of our knowledge, this is the first report of such an experiment.

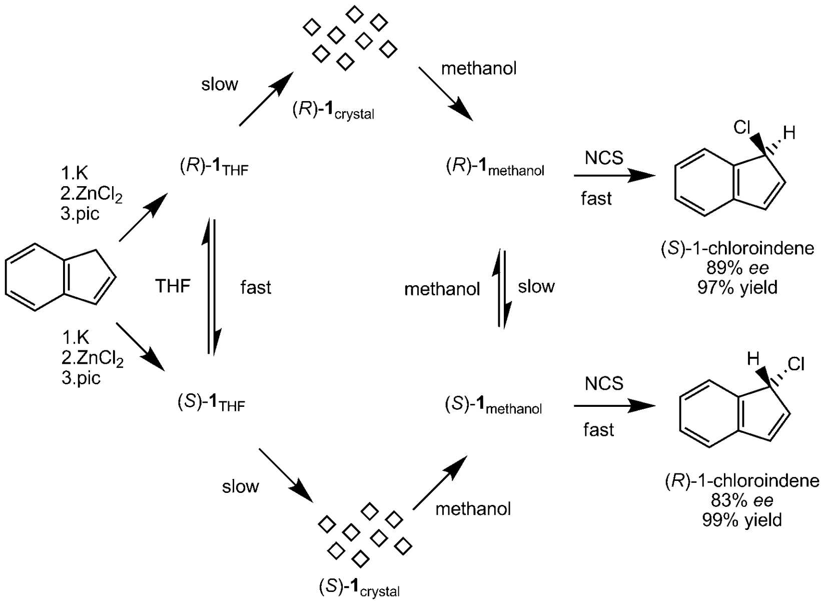
That a hand-picked single crystal reacts to give an optically active product does not qualify as AAS. It is necessary to use a full crystal batch to demonstrate preferential crystallization and total spontaneous resolution. Indeed, as shown in entries 8–9 of Table 1, AAS has been demonstrated. Attaining the same selectivity (ca. 90 % *ee*) for a whole batch as for a single crystal should simply be a matter of additionally optimizing the crystallization conditions (see the Experimental Section). Notably, the NCS reaction with *rac*-**1** is a more convenient route to racemic 1-chloroindene, compared to literature methods.[8]

Table 1: Reactions between chiral crystals of **1** and NCS.



Entry[a]	Reagent	Solvent	Product rotation	Yield[b] [%]	*ee*[b] [%]
1	(*S*)-**1**[c]	none	(+)	60–70	17–22
2	(*R*)-**1**[c]	H_2O	(−)	86–91	13–14
3	(*S*)-**1**[c]	CH_3OH	(+)	89–95	26–29
4	(*S*)-**1**[c]	CH_3OH[d]	(+)	85–99	82–83
5	(*R*)-**1**[c]	CH_3OH[d]	(−)	78–99	87–89
6	(*S*)-**1**[c]	CH_3CN	(+)	97–98	19–23
7	(*S*)-**1**[c]	THF	(+)	91–97	0–3
8	(*S*)-1[e]	CH_3OH[d]	(+)	60–80	0–71[f]
9	(*R*)-**1**[e]	CH_3OH[d]	(−)	60–80	0–56[f]

[a] Each entry summarizes more than10 experiments, in total more than 500 experiments. [b] Determined by HPLC analysis (for the yield of the isolated product, see Experimental section). [c] Single crystal. [d] Benzoquinone added. [e] Dominant enantiomer, full batch. [f] See the experimental section for optimal conditions.



Scheme 3. Creating optical activity by crystallizing **1** in THF, redissolving it, and then trapping it with NCS in methanol.

The crystal structures of (*R*)-**1**, (*S*)-**1**, and *rac*-**1** have been determined.[9] The molecular structure is essentially the same in both the chiral and racemic phases; zinc exhibits an approximate tetrahedral coordination geometry (Figure 1), with both indenyl groups bound in a monohapto mode (as opposed to most transition-metal indenyl complexes, which display pentahapto coordination) rendering the α-carbon atoms stereogenic.

Interestingly, the two picoline ligands adopt a helical conformation around zinc (Figure 2), thus adding an extra element of chirality to the complex. Right-handed helicity is exclusively found in (*R*)-**1** and left-handed in (*S*)-**1**. The assignment of the absolute structure in the chiral crystals is

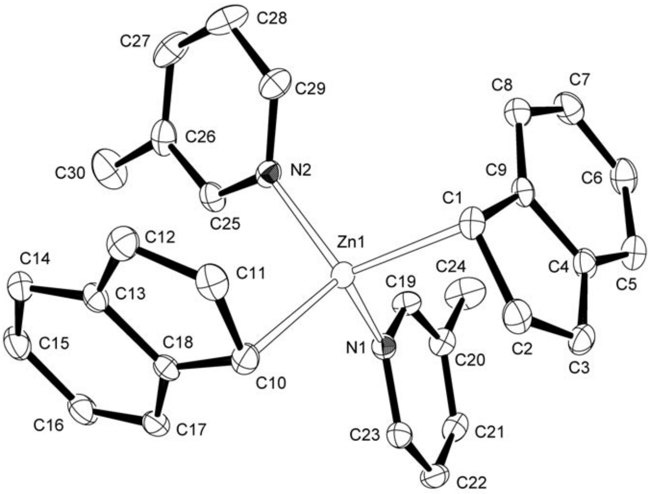


Figure 1. ORTEP view of (*S*,*S*)-[Zn(ind)$_2$(pic)$_2$] (S-**1**) showing the crystallographic numbering. Selected bond distances [Å] and angles [°]: Zn1–C1 2.102(2), Zn1–C10 2.111(2), Zn1–N1 2.080(1), Zn1–N2 2.078(1), C1–C2 1.462(2), C1–C9 1.460(2), C2–C3 1.368(2), C3–C4 1.438(2), N2-Zn1-N1 99.37(5), N2-Zn1-C1 112.60(6), N1-Zn1-C1 104.14(6), N2-Zn1-C10 107.75(6), N1-Zn1-C10 110.18(6), C1-Zn1-C10 120.65(6), C9-C1-Zn1 105.86(9), C2-C1-Zn1 98.06(9).

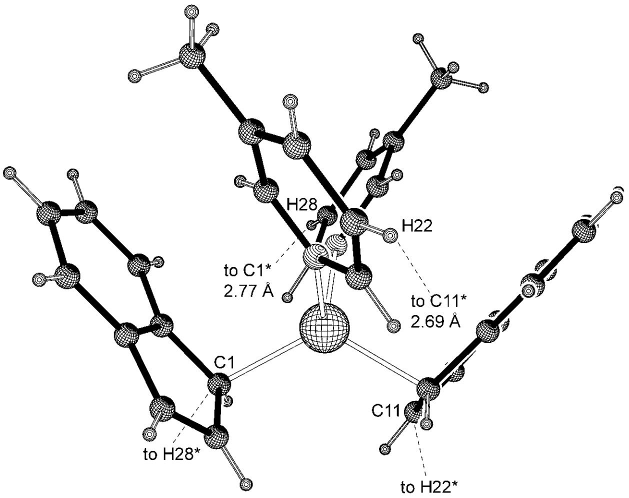


Figure 2. Showing the helical arrangement of picoline ligands in (*S*)-**1**, and the CH–π interactions involved in supramolecular helix formation.

unambiguous, and a Flack parameter of 0.006(6) is indicative of enantiopurity.[10] The chiral and racemic phases have similar densities (1.319 and 1.336 g cm^{-3}, respectively) and the most notable difference in packing is perhaps that the chiral phase exhibits formation of supramolecular helices through CH–π interactions[11] involving a picoline ring hydrogen atom and an indenyl ligand in a different molecule (Figure 2).

In conclusion, we have synthesized both enantiomers of 1-chloroindene with high selectivity from solely achiral starting materials, and without using optically active catalysts or auxiliaries. This constitutes a first proof-of concept for the usefulness of the organometallic AAS approach in enantioselective organic synthesis. By using a full range of electrophilic substrates, a single crystalline reagent could give a multitude of enantiopure organic products. Moreover, many more new conglomerate reagents can be prepared since the indenyl group may be replaced by other functional groups, and zinc may be exchanged for another metal. The potential of this AAS approach is thus very high.

Experimental Section

[Zn(ind)$_2$(pic)$_2$] (**1**): In a typical experiment, 3-picoline (0.28 mL, 3.0 mmol) was added, at ambient temperature, to a solution of diindenylzinc[12] (0.44 g, 1.5 mmol) in 3.0 mL THF. (Addition of a small quantity of indenylpotassium at this stage seems to improve crystal quality in the subsequent step.) A sample of 0.2 mL was withdrawn and layered with dry kerosene. After a few hours, chiral single crystals of exclusively (*R*)-**1** and/or (*S*)-**1** had formed in 90% yield. The identity of all crystalline material in such a batch was established by X-ray diffraction analysis. Crystallization from more dilute solutions gives predominantly *rac*-**1**.

1-Chloroindene (hand-picked single crystal reaction): A cube-shaped (volume approximately 1 mm^3) chiral crystal of [Zn(ind)$_2$(pic)$_2$] was selected at 173 K using a microscope.[13] The crystal was carefully powdered in a short test tube and immersed in liquid nitrogen. Methanol (0.2 mL) was slowly added at 77 K, followed by a mixture of NCS (65 mg) and freshly sublimated benzoquinone (9.0 mg). The mixture was then allowed to reach ambient temperature under careful grinding. Hydroquinone (0.10 g) was added to precipitate excess benzoquinone, whereafter the reaction mixture was extracted with hexane and washed with 2.5 M HCl. The NMR and HPLC data show that 1-chloroindene and indene are the only products. No strong bias for a specific enantiomer could be observed; 51 reactions yielded (−)-1-chloroindene and 70 reactions yielded (+)-1-chloroindene. See also Table 1.

1-Chloroindene (absolute asymmetric synthesis): The mother liquor from a complete crystal batch was withdrawn, the crystals washed with hexane, dried in vacuo and carefully powdered. (a high *ee* value is obtained when the crystal batch is prepared by layering a solution of **1** in THF with kerosene, followed by slow stirring). The reaction and work-up conditions were analogous to those used in single-crystal reactions. Yield: 60–80%, *ee*: 0–71% (HPLC). See Table 1.

1-Chloroindene (determination of isolated yield): Crystals of **1** (2.06 g) were powdered and treated with NCS (5.0 g), benzoquinone (0.5 g), and methanol (15 mL; as described above). Hydroquinone was then added, the reaction mixture was extracted with methanol, and then evaporated. The viscous remainder was extracted using hexanes, filtered through Celite and evaporated. Yield: 0.85 g (66%), not optimized.

Determination of *ee* value: A Varian model 9000 HPLC system combined with a PDR advanced laser polarimeter and a Daicel OD column was used.

X-ray diffraction: Crystals were selected and mounted under nitrogen in a glass capillary at low temperature[13] and transferred to a Rigaku R-AXIS IIc image plate system. Diffracted intensities were measured at 100(2) K, using graphite-monochromated Mo$_{K\alpha}$ radiation from a RU-H3R rotating anode. The structures were solved and refined using SHELX-97,[14] operating in the WinGX program suite.[15] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 711904 ((*S*)-**1**), 711905 ((*R*)-**1**) and 711906 (*rac*-**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The

Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[9] Crystal data for (*S*)-**1** (similar for (*R*)-**1**): 0.3 × 0.2 × 0.2 mm, $C_{30}H_{28}N_2Zn$, $M_r = 481.9$, orthorhombic, space group $P2_12_12_1$ (No.19), $a = 10.647(2)$, $b = 12.387(2)$, $c = 18.395(2)$ Å, $V = 2426.1(5)$ Å^3, $Z = 4$, $\rho_{\text{calcd}} = 1.319$ gcm^{-1}, $\mu = 1.032$ mm^{-1}. Refinement on F^2 for 308 parameters gave $R1 = 0.019$ and $wR2 = 0.047$ for all 4341 reflections. Crystal data for *rac*-**1**: 0.3 × 0.2 × 0.2 mm, $C_{30}H_{28}N_2Zn$, $M_r = 481.9$, monoclinic, space group $P2_1/c$ (No. 14), $a = 11.992(2)$, $b = 11.196(2)$, $c = 17.859(2)$ Å, $\beta = 91.953(6)°$, $V = 2396.5(5)$ Å^3, $Z = 4$, $\rho_{\text{calcd}} = 1.336$ g cm^{-1}, $\mu = 1.045$ mm^{-1}. Refinement on F^2 for 308 parameters gave $R1 = 0.032$ and $wR2 = 0.075$ for all 4122 reflections.

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