# Zirconium-Catalyzed Kinetic Resolution of Pyrans

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Methods that allow for the enantioselective preparation of chiral pyrans are of great value, since six-membered cyclic ethers are common constituents of medicinally important agents. We recently reported that, in the presence of catalytic amounts of (EBTHI)ZrCl$_2$[2] and an alkylmagnesium halide, cyclic ethers undergo carbomagnesation[3] with excellent enantiofacial selectivity.[4] The levels of regiocontrol and π-facial selectivity in these carbon–carbon bond forming reactions imply highly ordered catalyst–substrate association. If metallacyclopentane formation is the product-determining step,[3h] it follows that reaction of one enantiomer of a 2-substituted pyran should proceed rapidly through mode I, where the small substituent at the stereogenic center (R$_1$ = H) is positioned proximal to the catalyst structure. The corresponding enantiomer should react relatively slowly, as neither of the available reaction pathways is attractive: mode II situates the alkyl group into the metallocene unit, and III bears severe steric interactions.[5] That is, with chiral pyrans, the preexisting stereogenic center should influence the reaction outcome, affording differential rates of carbomagnesation of the two substrate enantiomers.[6] Herein, we report the results of our

I   R$_1$ = H, R$_2$ = alkyl   III   R = alkyl
II   R$_1$ = alkyl, R$_2$ = H
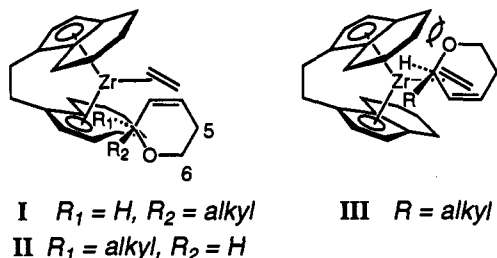
investigation in connection to the kinetic resolution of chiral pyrans.

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(5) The alternative regiochemical modes such as IV are not considered, since products resulting from the derived metallacycle are not observed with achiral pyrans (ref 4); this is presumably due to the preference for formation of C–Zr α to C–O bond (ref 3h). It is also possible that mode IV is operative but, because subsequent elimination is slow and addition reversible, product only arises from modes I–III. Related mechanistic studies are in progress.

IV
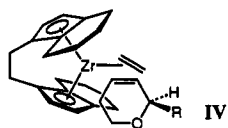
Table 1. Zirconium-Catalyzed Kinetic Resolution of Pyrans[a]

entry	racemic substrate		conversion[b] (%)	mol% cat.	temp (°C)	time (h)	unreacted subs. config., ee(%)[c]
1			60	10	25 °C	10	R, 94
			60	10	70 °C	0.5	R, >99
			60	5	70 °C	1	R, 93
2			58	10	25 °C	24	R, 88
			63	10	70 °C	2	R, >99
3			59	10	70 °C	0.5	R, >99
4			60	10	25 °C	40	R, 41
5	*anti*-5	a R = MgCl	56	10	70 °C	2.5	2R, 6R, >99
		b R = TBS	60	10	70 °C	2	2R, 6R, >99
6			58	20	70 °C	6	S, 99
7	*syn*-7	a R = MgCl	63	10	70 °C	1.5	2R, 5S, >99
		b R = TBS	61	10	70 °C	2.5	2R, 5S, 94

[a] Reaction conditions: indicated mol % catalyst, 5.0 equiv of EtMgCl, THF. [b] Conversions determined by GLC analysis in comparison with an internal standard, by analysis of ¹H NMR spectrum of the reaction mixture, and through isolation (silica gel chromatography). [c] The identity of recovered starting materials was determined through comparison with authentic enantiomers (see supplementary material for details). Enantiomeric excess determined by chiral GLC (BETA-DEX 120 chiral column by Supelco, entries 1, 2, 4, 5, and 7b; CHIRALDEX-GTA by Alltech, entries 3, 6, and 7a). Mass recovery in all reactions is >90%.

As illustrated in Table 1, when racemic pyrans are treated with 5 equiv of EtMgCl and 5–10 mol % (R)-(EBTHI)ZrCl$_2$, at about 60% conversion the unreacted starting material is recovered with excellent enantiopurity.[7] Resolution of (±)-1 under the above conditions provides starting material with 94% ee (chiral GLC). *Whereas the procedure at 25 °C requires 12 h, when the reaction mixture is heated to 70 °C, the resolution process is complete within 30 min and the unreacted pyran is obtained in >99% ee* (minor enantiomer could not be detected by chiral GLC).[8] A similar effect is observed in the kinetic resolution of 2 (entry 2); at 70 °C, faster reaction rates and more effective resolution is observed (88% ee vs >99% ee at 58% and 63% conversion; k_{fast}/

(6) Kinetic resolution has an important advantage over asymmetric synthesis: a few additional percent conversion can provide materials of significantly higher enantiomeric purity (in contrast, ee's are constant in the course of an asymmetric synthesis). See: Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981,** *103,* 6237–6240. For a review of kinetic resolution, see: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988,** *18,* 249–330. For recent advances in catalytic kinetic resolution, see: (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; pp 247–308. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987,** *109,* 5765–5780. (c) Carlier, P. R.; Mungall, W. S.; Shroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988,** *110,* 2978–2979. (d) VanNieuwenhze, M. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993,** *115,* 7864–7865. (e) Lohray, B.; Bhushan, V. *Tetrahedron Lett.* **1993,** *34,* 3911–3914. (f) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988,** *53,* 708–710.

(7) It is imperative that the chiral catalyst be freshly prepared (less than 2 weeks old) and kept under a strict atmosphere of argon. Inferior quality catalyst batches afford little resolution.

(8) The exact origin of the temperature effect is the subject of ongoing mechanistic studies.

k_{slow} = 13 and >20, respectively).[9] Since catalytic resolution can be effected at elevated temperatures, lower quantities of the catalyst might be used without significant reduction in enantioselectivity: reaction of **1** with 5 mol % (*R*)-(EBTHI)-ZrCl$_2$ at 70 °C yields the recovered starting material in 93% ee (60% conversion). As expected from models I–III, a C5-substituted cyclic ether is resolved effectively (entry 6, presumably due to interaction of C5 alkyl with metal-bound ethylene).[10] However, differences in rates of reactions of enantiomeric pyrans substituted at C6 are significantly lower (entry 4; no notable improvement observed at 70 °C). Nonetheless, as the kinetic resolution of *anti*-**5**[11] illustrates, with a C2 side chain also present, multisubstituted six-membered ethers that contain a moiety at C6 can be resolved with exceptional enantioselectivity (>99% ee). Entries 3, 5, and 7[12] indicate that unprotected alcohols are suitable to the resolution conditions; these examples demonstrate that the versatile protecting group *tert*-butyldimethylsilyl (TBS) ether survives catalytic carbomagnesation at 70 °C without any complications.

The Zr-catalyzed resolution procedure is attractive because racemic pyrans can be prepared easily in large scale through metal-catalyzed diene metathesis. Noteworthy are recent reports from Grubbs's laboratories[13] which describe the chemistry of metathesis catalyst (PCy$_3$)$_2$Cl$_2$Ru=CHCH=CPH$_2$ (**9**). We have employed **9** in the preparation of a number of substrates shown in Table 1. Importantly, *metathesis and resolution processes can be carried out in a single pot*. The example shown in eq 1 is illustrative. Treatment of (±)-**8** with 1 mol % **9** in THF for 5 h, followed by the addition of 5 equiv of EtMgCl and 10 mol % (*R*)-(EBTHI)ZrCl$_2$ and stirring at 70 °C for 2 h, affords (*R*)-**1** in >99% ee (60% conversion by GLC; 35% yield). The sequential metathesis–carbomagnesation is therefore a fruitful collaboration among Ru- and Zr-based catalysts and a Mg-based reagent.

In summary, asymmetric catalytic carbomagnesation is an effective method for the kinetic resolution of various unsaturated

(9) Relative rates were calculated by an equation reported previously. See ref 6.

(10) An increase in the amount of catalyst is needed (20 vs 10 mol %) to avoid prolonged reaction times at 70 °C; otherwise, ~10% substrate decomposition occurs, diminishing the effectiveness of the resolution procedure.

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>99% ee at 60% conversion
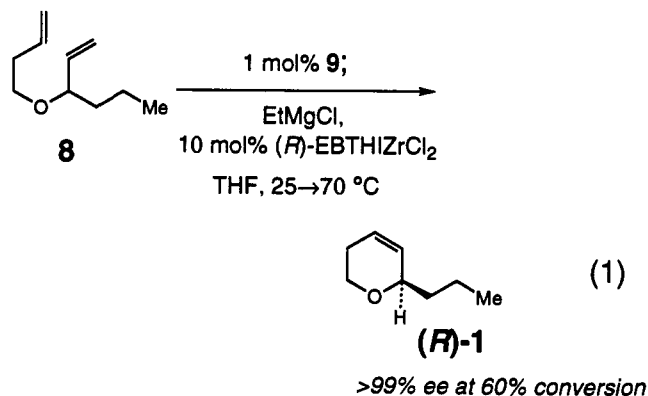
pyrans. With the exception of substrates singly-functionalized at C6, other substituted pyrans are resolved with excellent enantioselectivity through zirconium-catalyzed carbomagnesation. Since the alkene site in the resolved substrates is amenable to various functionalization procedures and the racemic starting materials are prepared readily through diene metathesis, the chemistry reported herein should prove to be of significant utility in modern enantioselective synthesis. Further studies on catalytic asymmetric carbonmagnesation are in progress and will be the subject of future reports.

Supplementary Material Available: Experimental procedures and spectral and analytical data for all recovered starting materials and reaction products (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.