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Enantioselective Synthesis of Vicinal Halohydrins via Dynamic Kinetic Resolution

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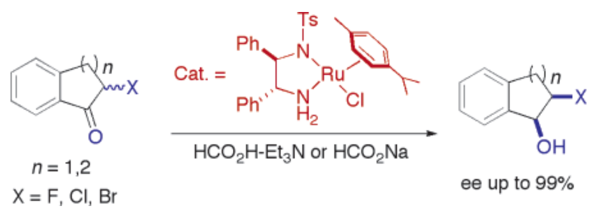
ABSTRACT



Expanding the scope of enantioselective catalysis via DKR, transfer hydrogenation of a variety of cyclic α-halo ketones was accomplished using the Noyori/Ikariya (*R*,*R*)- or (*S*,*S*)-I catalysts and either HCO_2H/Et_3N or HCO_2Na/*n*-Bu_4NBr in H_2O/CH_2Cl_2 as the hydrogen sources. Good yields of vicinal bromo-, chloro-, and fluorohydrins with excellent de and ee levels were achieved in most cases after a simple tuning of reaction conditions.

Vicinal halohydrins are versatile building blocks and key intermediates for the synthesis of many bioactive compounds, and the development of methods for their asymmetric synthesis has therefore attracted much attention.[1] Though a number of methods are known, there is still need of a general approach to the enantioselective synthesis of cyclic *cis* vicinal halohydrins.

On the other hand, dynamic kinetic resolution (DKR),[2] not limited by the theoretical 50% maximum yield associated with conventional separation techniques or classical kinetic resolutions, is established as the most efficient technique for the resolution of racemates. The seminal work by the Noyori[3] and Genêt[4] groups on the catalytic hydrogenation of β-ketoesters via DKR has found a number of applications[2] and stimulated the development of related reactions such as the transfer hydrogenation of 1,2-diketones[5] and of several types of 2-substituted ketones.[6] Recently, we have reported on the transfer hydrogenation of α-alkyl(aryl) cyclic ketimines as the first process involving reduction of C═N bond via DKR.[7] Additionally, DKR techniques have also been applied to

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(1) Halohydrins and derivatives. In *Fiesers' Reagents for Organic Synthesis*; Smith, J. G., Fieser, M., Eds.; Wiley: New York, 1990. (b) Bonini, C.; Righi, G. *Synthesis* **1994**, 225. (c) Haufe, G. *J. Fluor. Chem.* **2004**, *125*, 875−894.

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(4) (a) Genêt, J. P.; Mallart, S.; Jugé, S. French patent 8,911,159, 1989. (b) Genêt, J. P.; Pinel, C.; Mallart, S.; Jugé, S.; Thorimbert, S.; Laffite, J. A. *Tetrahedron: Asymmetry* **1991**, *2*, 555.

(5) (a) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *7*, 1119−1121. (b) Koike, T.; Murata, K.; Ikariya, T. *Org. Lett.* **2000**, *7*, 3833−3836.

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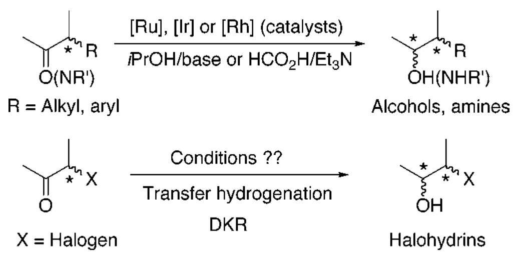
diastereoselective nucleophilic substitutions of α-iodo- and α-bromoesters and amides[8] and to the hydrogenation of α-chloro-β-ketoesters by Ru(II)-diphosphine catalysts.[9]

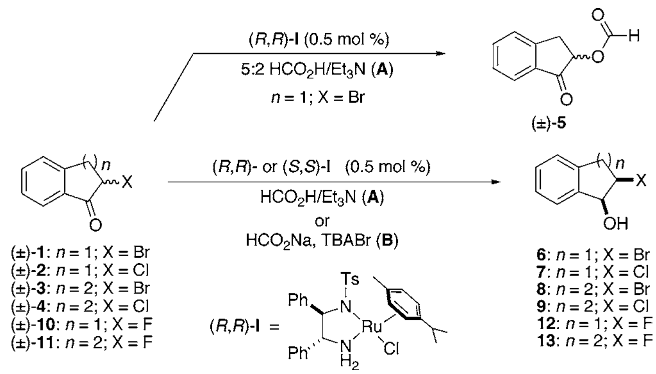
Even considering the sensibility of α-halo ketones toward substitutions and/or eliminations, a global analysis of the above information suggests that hydrogenation of haloketones via DKR under appropriate conditions should provide a valuable tool for the synthesis of the title compounds (Scheme 1).

Scheme 1. Transfer Hydrogenation of α-Halo Ketones via DKR; A Synthetic Route to Halohydrins



Experiments were initally performed with 2-bromo- and 2-chloro- indanones and tetralones (±)-**1**−**4** as substrates, using the Noyori/Ikariya [RuCl(TsDPEN)(*p*-cymene)] catalysts (*R*,*R*)- or (S,S)-**I** (Scheme 2) in 5:2 HCO_2H/Et_3N azeotropic mixture as the solvent and hydrogen donor[10] (conditions **A**). The alternative transfer hydrogenations from 2-propanol require a basic medium that would result in the above-mentioned side reactions at the sensitive α-halogenated center. On the other hand it was foreseen that the HCO_2H/Et_3N system should enable the required enolization of the substrates by bifunctional acid-basic catalysis under mild conditions. When this strategy was applied to 2-bromoindan-1-one **1**, however, nucleophilic substitution by formate took place to afford the undesired product **5** (Scheme 2). Based in a recent report by Deng and co-workers,[11] we performed the reaction using aqueous HCO_2Na as the hydrogen donor in a biphasic system and *n*-Bu_4NBr (2%) as a phase transfer catalyst. Under these conditions (**B**), the desired reduction takes place smoothly to afford *cis*-2-bromo-1-indanol **6** in 84% yield and with excellent ee >99% (Table 1, entry 1). The chlorinated analogue **2** resisted even conditions **A**,[12] leading to the desired product **7** in 88% yield, again with excellent de and ee levels (entry 2). For comparison purposes, conditions **B** were applied with similar results (entry 3).

Scheme 2. Asymmetric Transfer Hydrogenation of α-Halo Indanones and Tetralones



A slow racemization of the halogen-containing stereocenter was initially considered as a possible explanation for the long reaction times required for completion. Though highly basic conditions cannot be used, it was found that a slight modification of the HCO_2H/Et_3N ratio has a strong influence in the reaction rate. After a short screening, an optimum 2:1 HCO_2H/Et_3N ratio was found to accelerate strongly[13] the reduction of **2**, affording *cis* chlorohydrin **7** in 83% yield and 99% ee (entry 4).

The method was also extended to halogenated tetralones: conditions **B** were applied to 2-bromotetralone **3**, leading to bromohydrine **8** with excellent diastero- and enantioselectivity, but in a poor 22% yield (entry 5). Fortunately, a satisfactory 64% yield with comparable de and ee was achieved by increasing the amount of *n*-Bu_4NBr to 30 mol % (entry 6). For the chlorinated analogue **4**, both the "standard" conditions **A** and the modified phase transfer conditions **B** afforded chlorohydrin **9** efficiently (entries 7 and 9), but best results were again observed by decreasing the HCO_2H/Et_3N ratio to an optimum of 1.2:1, maintaining excellent de and ee values in a much faster reaction[13] (entry 10).

The specific interest in fluorohydrins[1c,14] prompted us to study also α-fluoro ketones as substrates. Despite the singular

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(8) (a) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700−7706. (b) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K.-i. *J. Org. Chem.* **1997**, *62*, 5830−5837. (c) Camps, P.; Pérez, F.; Soldevilla, N. *Tetrahedron: Asymmetry* **1998**, *9*, 2065−2079. (d) Caddick, S.; Afonso, C. A. M.; Candeias, S. X.; Hitchcock, P. B.; Jenkins, K.; Murtagh, L.; Pardoe, D.; Gil Santos, A.; Treweeke, N.; Weaving, R. *Tetrahedron* **2001**, *57*, 6589−6605.

(9) (a) Genêt, J. P.; Cano de Andrade, M. C.; Ratovelomanana-Vidal, V. *Tetrahedron Lett.* **1995**, *36*, 2063−2066. (b) Sayo, N.; Sano, N.; Kumobayashi, H. EP 519763A2, 1992.

(10) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522.

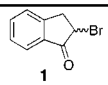
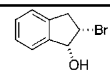
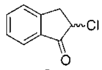
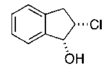
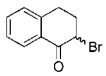
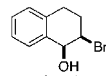
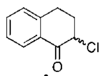
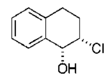
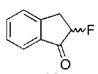
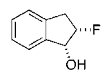
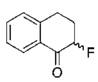
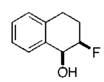
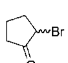
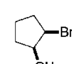
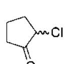
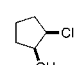
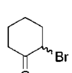
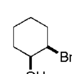
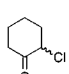
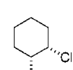
(11) Ma, Y.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. *Org. Lett.* **2003**, *12*, 2103−2106.

(12) The asymmetric Rh-catalized transfer hydrogenation of chloromethyl ketones, unable to suffer β-eliminations, can also be performed in a similar reaction medium: (a) Hamada, T.; Torii, T.; Izawa, K.; Noyori, R.; Ikariya, T. *Org. Lett.* **2002**, *4*, 4373−4376. (b) Hamada, T.; Torii, T.; Izawa, K.; Ikariya, T. *Tetrahedron* **2004**, *60*, 7411−7417.

(13) Comparison with the results reported in ref 10 reveals that the reactions are even faster than for nonhalogenated analogues. Therefore, the results cannot be solely explained in terms of a faster enolization of the substrates. For a very recent study of the effect of pH in asymmetric transfer hydrogenation of ketones in aqueous media, see: Wu, X.; Li, X.; King, F.; Xiao, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3407−3411.

(14) (a) Maienfisch, P.; Hall, R. G. *Chimia* **2004**, *58*, 93−99. (b) Fluorine in the Life Sciences (Special issue). *ChemBioChem* **2004**, *5*, 557−726.

Table 1. Enantioselective Synthesis of Halohydrins via DKR

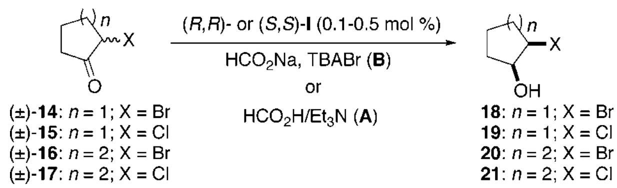
entry	substrate	*c*[a]	method	cat. **I**[b]	product	t (d)	yield[c]	de[d]	ee[e]
1	 **1**	1.0	**B**	(*S*,*S*)	 (1*R*,2*S*)-**6**	5	84	>98	>99
2	 **2**	2.0	**A**	(*S*,*S*)	 (1*R*,2*S*)-**7**	5	88	>98	98
3	**2**	1.0	**B**	(*R*,*R*)	(1*S*,2*R*)-**7**	6	85	>98	94
4	**2**	1.0	**A**[f]	(*R*,*R*)	(1*S*,2*R*)-**7**	1	83	>98	99
5	 **3**	1.0	**B**	(*R*,*R*)	 (1*S*,2*R*)-**8**	6	22	>98	>99
6	**3**	1.0	**B**[g]	(*S*,*S*)	(1*R*,2*S*)-**8**	6	64	>98	96
7	 **4**	2.0	**A**	(*S*,*S*)	 (1*R*,2*S*)-**9**	5	78	>98	92
8	**4**	1.0	**B**	(*R*,*R*)	(1*S*,2*R*)-**9**	6	25	>98	>99
9	**4**	1.0	**B**[g]	(*R*,*R*)	(1*S*,2*R*)-**9**	6	61	>98	96
10	**4**	1.0	**A**[h]	(*R*,*R*)	(1*S*,2*R*)-**9**	1	71	>98	>99
11	 **10**	2.0	**A**	(*S*,*S*)	 (1*R*,2*S*)-**12**	3	95	94	74
12	**10**	1.0	**A**	(*R*,*R*)	(1*S*,2*R*)-**12**	6	72	>98	93
13	**10**	1.0	**A**[h]	(*R*,*R*)	(1*S*,2*R*)-**12**	1	92	>98	92
14	 **11**	2.0	**A**	(*R*,*R*)	 (1*S*,2*R*)-**13**	3	98	50	98
15	**11**	1.0	**A**	(*S*,*S*)	(1*R*,2*S*)-**12**	5	40	>98	>99
16	**11**	1.0	**A**[h]	(*R*,*R*)	(1*S*,2*R*)-**13**	1	98	74	96
17	**11**	0.5	**A**[h]	(*R*,*R*)	(1*S*,2*R*)-**13**	1	98	94	97
18	 **14**	2.0	**B**	(*S*,*S*)[i]	 (1*S*,2*R*)-**18**	1	80	>98	45[j]
19	 **15**	1.0	**A**[h]	(*S*,*S*)	 (1*S*,2*R*)-**19**	1	80	80	60[j]
20	 **16**	2.0	**B**[g]	(*S*,*S*)[i]	 (1*S*,2*R*)-**20**	1	84	70	80[k]
21	 **17**	1.0	**A**[h]	(*R*,*R*)	 (1*R*,2*S*)-**21**	1	79	94	90[k]

[a] Initial concentration of α-halo ketone. [b] 0.5 mol % unless otherwise stated. [c] Isolated yield. [d] Determined by ^{1}H NMR. [e] Determined by HPLC unless otherwise stated. [f] 2:1 HCO_2H/Et_3N used. [g] 30% of *n*-Bu_4NBr used. [h] 1.2:1 HCO_2H/Et_3N used. [i] 0.1 mol %. [j] Determined by ^{1}H and ^{19}F NMR analysis of the Mosher ester. [k] Determined by HPLC of the benzoate.

reactivity often exhibited by fluorinated compounds, a similar behavior was observed in this case: transfer hydrogenation of fluoroindanone **10** and fluorotetralone **11** proceeded via DKR under conditions **A** to afford fluorohydrins **12** and **13** in excellent yields. Some *trans* isomers were observed in 3% and 25%, respectively (entries 11 and 14), most probably due to the smaller steric repulsion by the fluorine atoms in the transition states leading to *trans* products. The ee was excellent for **13** (98% ee) but only moderate for **12** (74% ee), suggesting a screening for better results. Higher dilution resulted in better de and ee values, but much lower yields (entries 12 and 15). Once again, the 1.2:1 HCO_2H/Et_3N mixture afforded faster reactions[13] and better results for **12** (92% yield, >99:1 *cis*/*trans*, 92% ee) and **13** (98% yield, 87:13 *cis*/*trans*, 96% ee); this last result was further improved at higher dilution (0.5 M, 98% yield; 97:3 *cis*/*trans*, 97% ee) (entries 13, 16, and 17).

Finally, the reactions of monocyclic substrates such as cyclohexanone and cyclopentanone derivatives (±)-**14**−**17** were also investigated. Applying optimized conditions (**B** for bromo ketones **14** and **16**; **A** for chloro ketones **15** and **17**), halohydrins **18**−**21** were isolated in good yields and moderate to good ee's, though minor amounts (7−15%) of

Scheme 3. Transfer Hydrogenation of Monocyclic α-Halo Ketones



trans isomers (Scheme 3) were observed in some cases (entries 18−21).

The absolute configurations of (1*R*,2*S*)-**6** and (1*R*,2*S*)-**7** were assigned by comparison of their optical rotations with literature data [(1*R*,2*S*)-**6** had $[\alpha]^{20}_D$ +59.4 (*c* 0.75, $CHCl_3$), lit.[15] $[\alpha]^{25}_D$ −61.0 (*c* 0.62, $CHCl_3$. (1*R*,2*S*)-**7** had $[\alpha]^{20}_D$ −51.5 (*c* 0.8, $CHCl_3$), lit.[15] $[\alpha]^{25}_D$ −52.0 (*c* 0.6, $CHCl_3$)], and those of (1*S*,2*R*)-**8** and (1*R*,2*S*)-**20** were assigned by anomalous dispersion effects in their corresponding X-ray diffraction analysis (Figure 1).

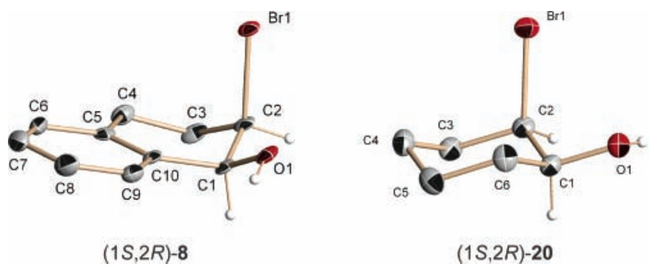


Figure 1. X-Ray structures of (1*S*,2*R*)-**8** and (1*S*,2*R*)-**20**.

In conclusion, the catalytic transfer hydrogenation of α-halo ketones via DKR appears as an efficient tool for the synthesis of halohydrins, including bromo-, chloro-, and even fluorohydrins. A simple tuning of the reaction conditions allows the isolation of the desired products in good-to-excellent yields and stereoselectivities in reasonable reaction times.

Acknowledgment. We thank the Spanish 'Ministerio de Ciencia y Tecnología' (grants CTQ2004-00290 and CTQ2004-00241) and the 'Junta de Andalucía' for financial support. A.R. and A.M. thank Bayer CropScience for predoctoral fellowships and the donation of chemicals.

Supporting Information Available: Experimental procedures, characterization data for new compounds, and crystal structures for (1*S*,2*R*)-**8** and (1*R*,2*S*)-**20** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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