Catalytic asymmetric hydrogenation of aldehydes

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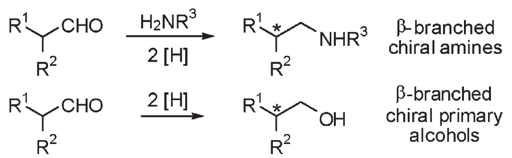
Racemic α-arylaldehydes provide the corresponding primary alcohols *via* dynamic kinetic resolution in excellent enantioselectivities and yields upon hydrogenation using a Noyori ruthenium catalyst; for example, the biologically active (*S*)-enantiomer of the non-steroidal anti-inflammatory drug ibuprofen could be synthesized *via* catalytic enantioselective hydrogenation of aldehyde 1f followed by oxidation with potassium permanganate in 76% isolated yield and 96 : 4 er.

The enantioselective transition metal-catalyzed hydrogenation and transfer hydrogenation of ketones has been developed into a powerful method for the synthesis of chiral secondary alcohols.[1] Remarkably, although both an asymmetric transfer hydrogenation of 1-*d*-benzaldehydes and a dynamic kinetic resolution of racemic ketones have been described by Noyori *et al.*,[2] the corresponding reactions of racemic α-branched aldehydes were unknown.[3] We have recently developed a catalytic asymmetric reductive amination of α-branched aldehydes *via* dynamic kinetic resolution [Eq. 1].[4] In this context, we reasoned that an analogous enantioselective hydrogenation of aldehydes to the corresponding β-branched chiral primary alcohols should also be feasible [Eq. 2].



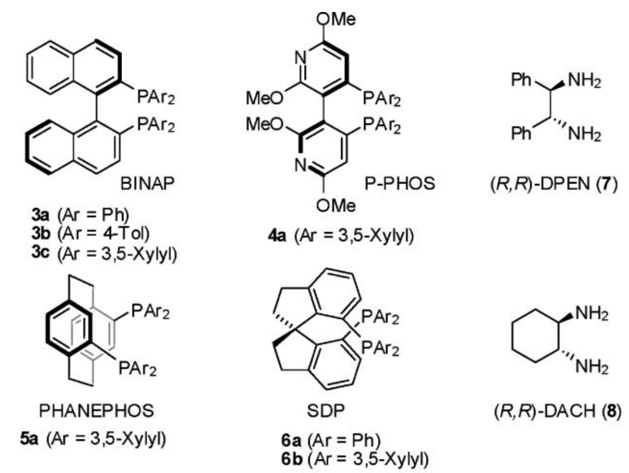
Initially considering transition metal-catalyzed, biocatalytic,[5] and organocatalytic variants, we quickly realized that the most efficient approach is the enantioselective Ru-catalyzed hydrogenation pioneered by Noyori *et al.* We found that racemic α-arylaldehydes provide the corresponding primary alcohols in excellent enantioselectivity in a dynamic kinetic resolution. During the preparation of this manuscript, Zhou *et al.* described a similar approach elegantly using a spirocyclic diphosphine ligand developed earlier in their laboratories.[6]

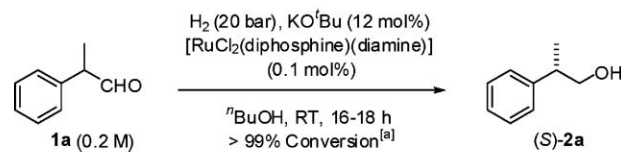
As a model reaction we studied the hydrogenation of 2-phenylpropanal (**1a**) in butanol with a selection of [$RuCl_2$(diphosphine)(diamine)] catalysts in the presence of KO^{t}Bu (Table 1). We anticipated that under the basic and protic conditions a rapid racemisation of the aldehyde should precede the asymmetric hydrogenation to give the desired chiral alcohol in complete conversion and high enantioselectivity. We were pleased to find that our reaction design indeed proved fruitful and in all cases > 99% conversion was observed. Of the studied diphosphines, (*R*)-xylyl-BINAP (**3c**, entry 3) provided the highest enantioselectivity in combination with diamines DPEN (**7**) or DACH (**8**). Other studied diphosphines were selected from the BINAP (**3**), P-PHOS (**4**), PHANEPHOS (**5**), and SDP (**6**) groups of ligands.[7]

With [$RuCl_2$(xylyl-BINAP **3c**)(DPEN **7** or DACH **8**)] as promising catalyst systems at hand we decided to explore the scope of our new dynamic kinetic resolution of aldehydes (Table 2).† Interestingly, the use of aldehyde **1a** as the model substrate turned out to be a good choice as many other substituted derivatives gave even higher enantioselectivities.

Similarly to the ketone hydrogenation the reaction is exceptionally efficient with quantitative conversion at very low catalyst loading in all cases studied. The enantioselectivity improved with increasing steric bulk of the alkyl substituent of the α-arylaldehyde

Table 1 Identification of an efficient catalyst system for the asymmetric hydrogenation of aldehyde **1a**





Entry	Diphosphine	Diamine	er[b] (ee)
1[c,d]	**3a**	**7**	78 : 22 (56%)
2[c,d]	**3b**	**7**	77 : 23 (54%)
3	**3c**	**7**	93 : 7 (86%)
4[e]	**3c**	**7**	93 : 7 (86%)
5[c]	**4a**	**7**	91 : 9 (82%)
6[f]	**5a**	**7**	53 : 47 (6%)
7	**6a**	**7**	74 : 26 (48%)
8	**6b**	**7**	86 : 14 (72%)
9[d]	**3c**	**8**	95 : 5 (90%)

[a] Determined by GC. [b] Determined by HPLC. [c] 1 mol% catalyst. [d] In ^{i}PrOH. [e] In ^{n}hexanol. [f] With (*S*,*S*)-DPEN.

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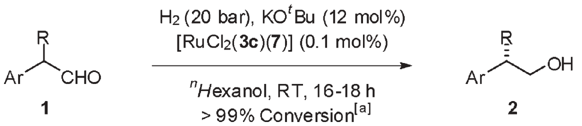
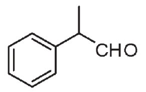
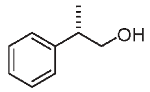
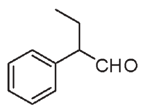
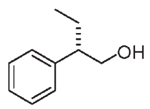
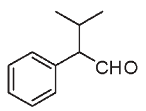
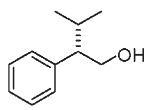
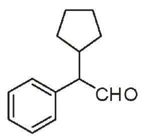
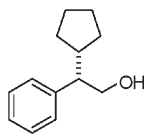
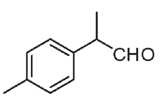
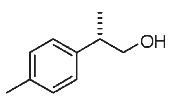
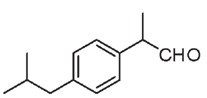
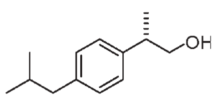
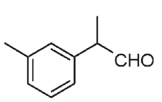
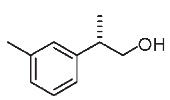
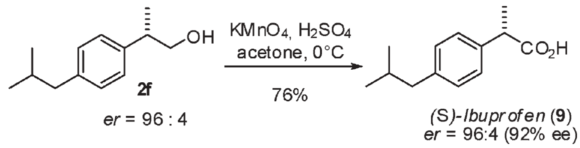
Table 2 Preliminary scope of the catalytic asymmetric aldehyde hydrogenation



Entry	Aldehyde **1**	Alcohol **2**	er (ee)
1[b]	 **1a**	 **2a**	95 : 5 (90%)
2[b]	 **1b**	 **2b**	97 : 3 (94%)
3	 **1c**	 **2c**	99 : 1 (98%)
4[b]	 **1d**	 **2d**	97 : 3 (94%)
5	 **1e**	 **2e**	97 : 3 (94%)
6[c]	 **1f**	 **2f**	96 : 4 (92%)
7	 **1g**	 **2g**	95 : 5 (90%)

[a] Determined by GC. [b] With [$RuCl_2$(**3c**)(**8**)] in ^{i}PrOH. [c] With [**1f**] = 0.5 M and 0.02 mol% catalyst loading, the er of alcohol **2f** was 95 : 5 (quant. conversion after 18 h).

substrate. Thus 2-phenylbutyraldehyde (**1b**) gave the corresponding alcohol in 97 : 3 er (entry 2) and 2-phenylisovaleraldehyde (**1c**) provided alcohol **2c** in 99 : 1 er (entry 3). Cyclopentyl-substituted aldehyde **1d** furnished alcohol **2d** in 97 : 3 er (entry 4). Substituents at the aryl ring are also tolerated and 2-arylpropionaldehydes **1e**–**1g** gave the desired products **2e**–**2g** in $\geqslant$ 95 : 5 er (entries 5–7). Ibuprofen precursor **1f**, which can be easily obtained *via* hydroformylation of the corresponding styrene,[8] gave known alcohol **2f** in 96 : 4 er. In this case the catalyst loading could be reduced to 0.02 mol% without significantly affecting the enantioselectivity. Product **2f** was obtained in quantitative yield and was converted into the biologically active (*S*)-enantiomer of the non-steroidal anti-inflammatory drug ibuprofen *via* an established and racemisation-free oxidation with potassium permanganate [Eq. 3].[9]



(3)

In summary, we have developed a remarkably efficient and highly enantioselective hydrogenation of racemic α-branched aldehydes to the corresponding primary alcohols *via* dynamic kinetic resolution. As the best catalyst we have identified a Noyori-type [Ru(diphosphine)(diamine)]-complex. Under our reaction conditions the important class of *α-methyl* substituted aldehydes including precursors to non-steroidal anti-inflammatory drugs such as ibuprofen can be effectively processed with enantioselectivities of up to 97 : 3 er. We propose that the sequence hydroformylation–asymmetric hydrogenation–oxidation could be of potential use for the industrial synthesis of α-aryl propionic acids and similar pharmaceutically highly relevant compounds.

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Notes and references

† **General procedure for the asymmetric hydrogenation of α-arylaldehydes**
A 6-mL glass vial was charged with the ruthenium catalyst derived from (*R*)-xylyl-BINAP and (*R*,*R*)-DPEN (1.1 mg, 1 μmol) in the open air. After purging with argon three times, *n*-hexanol (4.8 mL) was introduced and the mixture was stirred for 5 minutes. Then a solution of KO^{t}Bu in 2-methyl-2-propanol (0.12 mL, 1.0 M, 0.12 mmol) was added followed by addition of the α-arylaldehyde (1 mmol). The vial was transferred to a high pressure autoclave. After purging with 10 bar H_2 three times, the autoclave was pressurized with H_2 to 20 bar and the reactions were magnetically stirred at room temperature for 16–18 h. After carefully releasing H_2, a sample was taken and passed through a small amount of silica gel prior to GC analysis to determine the conversion and HPLC analysis for enantiomeric ratio determination.

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