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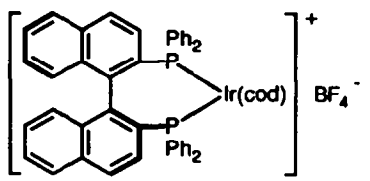
Enantioselective Hydrogenation of Acyclic Aromatic Ketones Catalyzed by BINAP—Ir(I)—Aminophosphine Systems

Xiaoyong Zhang, Hidenori Kumobayashi,† and Hidemasa Takaya*

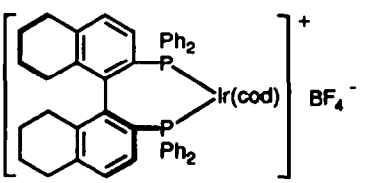
Division of Material Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan
†Central Research Laboratory, Takasago International Corporation, Nishiyawata, Hiratsuka, Kanagawa 254, Japan

Abstract: Enantioselective hydrogenation of acyclic aromatic ketones PhCOR (R = alkyl or cycloalkyl group) has been accomplished by using the catalytic systems derived from [Ir((*S*)-binap)(cod)]BF_4 or [Ir((*S*)-H_8-binap)(cod)]BF_4 [H_8-BINAP = 2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl] and bis(*o*-dimethylaminophenyl)phenylphosphine. The enantiomeric excesses as well as the absolute configurations of the corresponding alcohols depend markedly on the steric size of the alkyl or cycloalkyl groups, and the highest *ee*'s are obtained when the alkyl groups R are *i*-Pr (84%, *R*) and *c*-C_6H_{11} (80%, *R*), respectively.

Asymmetric reduction of prochiral ketones to optically active secondary alcohols is one of the most active research areas of asymmetric synthesis. Although excellent asymmetric induction is now attainable for various ketones by means of chiral reducing agents[1,2] and microbial transformations,[3] the intensive and ever-increasing efforts to develop efficient chiral transition metal catalysts for this purpose have so far led to only limited successes, as represented by the asymmetric catalytic hydrosilylation[4] and transfer hydrogenation[5] of certain aromatic ketones as well as hydrogenation of heterofunctionalized ketones.[6] With an exception in which up to 82% *ee* was obtained for the enantioselective hydrogenation of acetophenone catalyzed by an (*S,S*)-BDPP—Rh(I) complex [BDPP = 2,4-bis(diphenylphosphino)pentane],[7] asymmetric catalytic hydrogenation of prochiral ketones without a second ligating group usually gave poor enantioselectivities. Recently we have explored the new catalytic systems consisting of [Ir(binap)(cod)]BF_4 (**1**)[8] or [Ir(H_8-binap)(cod)]BF_4 (**2**)[8,9] and a mixed *P,N*-donor ligand, bis(*o*-dimethylaminophenyl)phenylphosphine (**3**), which showed outstanding



(*S*)-1



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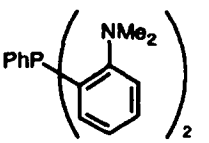

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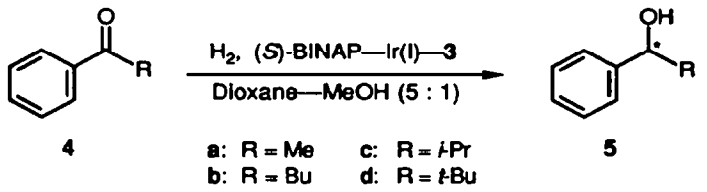
enantioselectivities in the asymmetric hydrogenation of a series of relatively simple prochiral ketones such as 1,2-benzocycloalkanones and β-thiacycloalkanones.[10] This paper describes the subsequent developments in application of these new catalytic systems to the enantioselective hydrogenation of acyclic aromatic ketones.



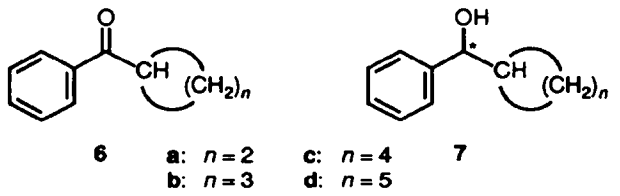


Table 1. Asymmetric Hydrogenation of Ketones **4** and **6** Catalyzed by (*S*)-**1**—**3** and (*S*)-**2**—**3** Systems[a]

			conditions				product			
				temp	time	conv[d]		yield[e]	ee[f]	
entry	substrate	catalyst[b]	S/C[c]	°C	h	%		%	%	config[g]
1	**4a**	(*S*)-**1**—**3**	100	60	126	70	**5a**	63	54	(*S*)-(-)
2	**4a**	(*S*)-**1**—**3**	201	90	22	51	**5a**	46	40	(*S*)-(-)
3	**4a**	(*S*)-**1**—**3**	200	120	37	99	**5a**	93	30	(*S*)-(-)
4	**4b**	(*S*)-**1**—**3**	200	90	106	81	**5b**	77	3	(*S*)-(-)
5	**4c**	(*S*)-**1**—**3**	200	90	160	85	**5c**	78	84[h]	(*R*)-(+)
6	**4c**	(*S*)-**1**—**3**	200	120	61	66	**5c**	64	80[h]	(*R*)-(+)
7	**4d**	(*S*)-**1**—**3**	200	120	141	68	**5d**	59	19	(*S*)-(-)
8	**6a**	(*S*)-**1**—**3**	202	90	115	54	**7a**	21[i]	33	(*S*)-(-)
9	**6b**	(*S*)-**1**—**3**	211	90	210	99	**7b**	92	39	(+)
10	**6c**	(*S*)-**1**—**3**	200	90	167	50	**7c**	49	73	(+)
11	**6d**	(*S*)-**1**—**3**	202	90	113	54	**7d**	51	79[h]	(*R*)-(+)
12	**6d**	(*S*)-**1**—**3**	199	120	74	83	**7d**	74	76[h]	(*R*)-(+)
13	**6d**	(*S*)-**2**—**3**	202	90	166	30	**7d**	27	80[h]	(*R*)-(+)

[a] Hydrogenation was carried out in an autoclave under an initial hydrogen pressure of 54—61 atm in dioxane—MeOH (5:1). Solvent/substrate ratio was 5 mL/g. [b] **3**/[Ir] ratio was 2. [c] Substrate/[Ir] ratio (mol/mol). [d] As given by GLC analysis. [e] Isolation yield obtained on column chromatography. [f] Determined by HPLC analysis with a DAICEL CHIRALCEL OD or OJ column unless otherwise indicated. [g] Determined by the signs of optical rotation, which are given in parentheses, where possible. [h] Determined by ^{19}F NMR analysis of the (*R*)-MTPA esters. [i] GLC and ^{1}H NMR analyses showed that a mixture of **7a** (40%) and cyclopropylmethoxyphenylmethane[11] (60%) was formed.

Some preliminary results obtained in the asymmetric hydrogenation of two representative types of aromatic ketones, alkyl phenyl ketones **4** and cycloalkyl phenyl ketones **6**, by use of the catalytic system derived from (*S*)-**1** and **3** [1:2, hereafter abbreviated (*S*)-**1**—**3** system] are shown in Table 1. Except for acetophenone (**4a**) (entries 1—3), the reaction rates are generally slower than those observed for hydrogenation of 1,2-benzocycloalkanones and β-thiacycloalkanones under similar conditions,[10] presumably due to the bulkiness of the present substrates. Reactions at elevated temperatures caused notable decreases in the *ee*'s in hydrogenation of **4a**. Such effects, however, are much smaller for ketones bearing a bulky alkyl group, such as isobutyrophenone (**4c**) (entries 5 and 6) and cyclohexyl phenyl ketone (**6d**) (entries 11 and 12).

The most noteworthy aspect of the present catalysis is that both the *ee*'s and absolute configurations of the alcoholic products are largely dependent on the steric size of the alkyl/cycloalkyl group. As were the cases of 1,2-benzocycloalkanones and β-thiacycloalkanones,[10] hydrogenation of acetophenone (**4a**) using the (*S*)-**1**—**3** catalytic system afforded (*S*)-1-phenylethanol [(*S*)-**5a**] in 40% *ee* at 90 °C (entry 2). When the methyl group of **4a** was replaced by a bulkier alkyl group, the hydrogenation proceeded in much lower enantioselectivity or even produced an alcohol with the opposite absolute configuration. Thus, hydrogenation of valerophenone (**4b**) catalyzed by the same (*S*)-**1**—**3** system at the same temperature gave almost racemic **5b** [3% *ee* (*S*), entry 4], while that of isobutyrophenone (**4c**) yielded (*R*)-**5c** in as high as 84% *ee* (entry 5). In other words, the [*R*]/[*S*] ratio increases as the alkyl group of ketones **4** get bulkier in the order Me < Bu < *i*-Pr.[12] A similar tendency is observed in the hydrogenation of cycloalkyl phenyl ketones **6**, where the sense of enantioselectivity is also reversed as the ring size of cycloalkyl group increases, from 33% (*S*) for **6a** to 79% (*R*) for **6d** (entries 8—11). Interestingly, use of complex (*S*)-**2** containing the bulkier diphosphine ligand H_8-BINAP[9] instead of (*S*)-**1** led to a slight increase in enantioselectivity in the hydrogenation of the bulky ketone **6d** at the expense of reaction rate (entry 13 vs entry 11).

However, when the steric size of the alkyl group is further increased, the hydrogenation again gives the *S*-enantiomer as the major product, as was found in the hydrogenation of 2,2-dimethylpropiophenone (**4d**) [19% *ee* (*S*) at 120 °C, entry 7].

Inversion in the sense of chiral induction due to steric bulkiness of the alkyl group(s) of ketonic substrates has previously been observed in, for example, the stoichiometric reduction of alkyl phenyl ketones by a chiral borane, Ipc_2BCl (diisopinocampheylchloroborane).[13] To our knowledge, however, no previous examples of such inversion have been reported either for transition metal-catalyzed asymmetric hydrosilylation[4a,c] and transfer hydrogenation[5] of aromatic ketones or for hydrogenation of heterofunctionalized ketones.[6] The results described above indicate that the enantioselectivity in the present catalytic hydrogenation is mainly the result of a balance between the steric effects of the phenyl ring and the alkyl/cycloalkyl group. This is in consistent with our earlier proposition that in the catalytic cycle of BINAP—Ir(I)—aminophosphine-catalyzed hydrogenation an aromatic ketone acts as a monodentate substrate and does not form a chelate complex through coordition of the carbonyl group and the aromatic ring.[10] We are currently exploring further applications of these novel asymmetric catalytic systems.

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