Asymmetric Catalysis

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Iridium-Catalyzed Asymmetric Isomerization of Primary Allylic Alcohols**

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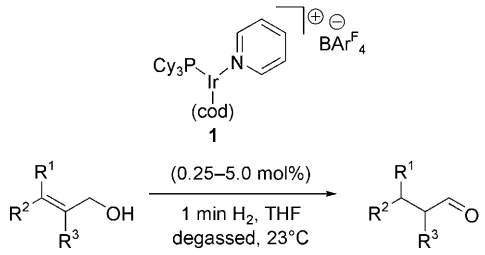
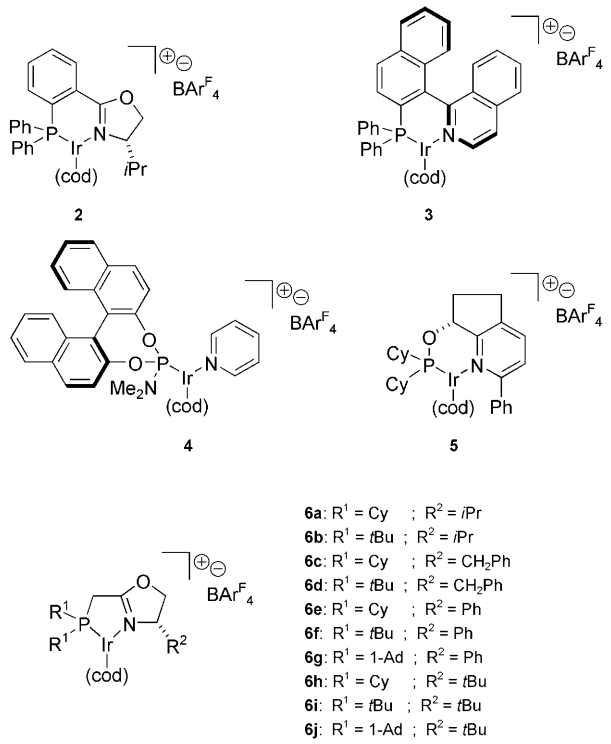
Undoubtedly, the catalytic asymmetric isomerization of allylic amines into enamines stands out as one of the most accomplished and well-studied reaction in asymmetric catalysis as illustrated by its industrial application.[1,2] In contrast, the related asymmetric isomerization of primary allylic alcohols to the corresponding aldehydes still constitutes a significant challenge in organic synthesis.[2] Successful examples of highly active and selective catalysts for this transformation remain rare and rely almost solely on the use of chiral rhodium complexes.[3] Furthermore, high catalyst loadings, elevated temperatures, long reaction times, poor catalyst accessibility, and limited substrate scope have prevented widespread use of this method. We have recently shown that the hydrogenation catalyst $[Ir(PCy_3)(pyridine)(cod)]BAr^F{}_4$ **1** (Cy = cyclohexyl, cod = 1,5-cyclooctadiene, $BAr^F{}_4$ = tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate) promoted exclusively the isomerization of primary allylic alcohols under appropriate experimental conditions (Scheme 1).[4]

Very low loadings of this analogue of Crabtree's catalyst were used to quantitatively isomerize a wide range of substrates at room temperature with appreciable reaction rates. On one hand, the mild reaction conditions appeared well-suited for studying the asymmetric version of the reaction. On the other hand, any variation of the electronic and steric requirements of **1** induced a complete loss of catalytic activity, suggesting this might impose severe constraints on the design of related chiral complexes. Herein, we report the identification of a highly active and selective iridium catalyst for the asymmetric isomerization of primary allylic alcohols into the corresponding chiral aldehydes.

Initial investigations began with a survey of known chiral (P,N) iridium complexes which have been shown to be highly active and selective catalysts in the asymmetric hydrogenation of olefins (**2**–**6a**, Figure 1).[5–6] Reactions were carried out on the model substrate **7** in THF at room temperature for 18 hours using 5 mol% of the precatalyst (Table 1, entries 1–5). The iridium complexes were activated by slowly bubbling hydrogen directly through the solution for 5 minutes. To favor isomerization and to avoid competing hydrogenation, the substrate was added only after complete extrusion of excess hydrogen by degassing the solution. Whereas complexes **2**–**4** did not display any catalytic activity, the pyridyl/phosphinite catalyst **5** afforded 19% of the aldehyde **8**, albeit in a nearly



Scheme 1. Iridium-catalyzed isomerization of primary allylic alcohols.



6a: R^1 = Cy ; R^2 = *i*Pr
6b: R^1 = *t*Bu ; R^2 = *i*Pr
6c: R^1 = Cy ; R^2 = CH_2Ph
6d: R^1 = *t*Bu ; R^2 = CH_2Ph
6e: R^1 = Cy ; R^2 = Ph
6f: R^1 = *t*Bu ; R^2 = Ph
6g: R^1 = 1-Ad ; R^2 = Ph
6h: R^1 = Cy ; R^2 = *t*Bu
6i: R^1 = *t*Bu ; R^2 = *t*Bu
6j: R^1 = 1-Ad ; R^2 = *t*Bu

Figure 1. Scope of iridium catalysts investigated. Cy = cyclohexyl, Ad = adamantyl.

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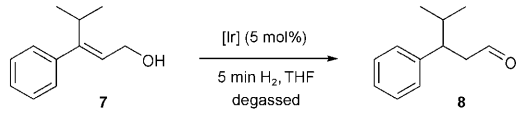
Table 1: Catalyst survey for the asymmetric isomerization of allylic alcohol **7**.



7 **8**

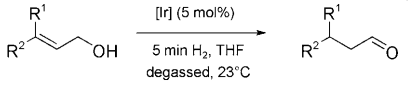
Entry[a]	Catalyst	*T* [°C]	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	(*S*)-**2**	23	18	<5	n.d.
2	(*R*)-**3**	23	18	<5	n.d.
3	(*S*)-**4**	23	18	<5	n.d.
4	(*R*)-**5**	23	18	19[d]	5 (*S*)
5	(*S*)-**6a**	23	18	98	11 (*R*)
6	(*S*)-**6b**	23	18	75	28 (*S*)
7	(*S*)-**6c**	23	2	>99	30 (*S*)
8	(*S*)-**6d**	23	2	>99	45 (*S*)
9	(*R*)-**6e**	23	2	>99	75 (*R*)
10	(*R*)-**6f**	23	2	>99	84 (*R*)
11	(*R*)-**6f**	−10	4	>99	90 (*R*)
12	(*R*)-**6f**	−30	14	>99	90 (*R*)
13	(*R*)-**6f**	−50	22	85	90 (*R*)
14	(*R*)-**6g**	23	4	95	91 (*R*)
15	(*R*)-**6g**	23	14	20	90 (*R*)[e]
16	(*R*)-**6g**	−10	22	6	93 (*R*)
17	(*S*)-**6h**	23	12	>99	89 (*S*)
18	(*S*)-**6i**	23	12	98	95 (*S*)
19	(*S*)-**6j**	23	22	75	97 (*S*)

[a] Reported results are the average of at least two runs. [b] Determined by GC or ^{1}H NMR methods. [c] Determined by GC or SFC methods using a chiral stationary phase. Absolute configuration (shown in parentheses) based on the sign of the optical rotation and by comparison with literature data. See Ref. [3b]. [d] The remaining 81% is a 2:1 mixture of *E*/*Z* isomers of **7**. [e] 2.5 mol% of the catalyst used. n.d. = not determined.

racemic form. In any case the saturated alcohol resulting from competitive hydrogenation was detected. Despite a very low but measurable enantiomeric excess, catalyst **6a** furnished the isomerization product almost quantitatively. At this point, we reasoned that a bulky trialkylphosphine moiety might be crucial to restore a catalytic activity similar to that of **1**, whereas switching from a pyridine to a less basic oxazoline ring has little impact on the outcome of the reaction. The high modularity of the readily available chiral (P,N) ligands **6** prompted us to synthesize a series of 10 different dialkylphosphanylmethyl oxazoline–iridium complexes **6a–j** using literature procedures.[7] The model substrate **7** was used to evaluate the potential of these catalysts in promoting the asymmetric isomerization (Table 1). The identity of the substituent on both the phosphorus atom and the oxazoline ring has an impact on the rate and the selectivity of the reaction. For a given substituent, R^2, at the stereogenic center of the oxazoline ring, increasing the steric demand of the substituents (*i*Pr, *t*Bu, 1-Ad) on the phosphorus atom systematically improved the enantiomeric excess of the aldehyde **8**. Catalysts having an aryl-substituted oxazoline moiety (**6c–f**; $R^1 = CH_2Ph$ or Ph) displayed a markedly faster rate than the alkyl-substituted analogues **6a**,**b** ($R^1 = i$Pr) and **6h–j** ($R^1 = t$Bu) (compare entries 5, 6 and 17–19 with 7–10 and 14, respectively, in Table 1). Higher enantioselectivities were achieved by carrying out the reaction at lower temperatures, the best results being obtained at −10 °C wherein the rates are still acceptable (Table 1, entries 11–13 and 16).

A series of other (*E*)-3,3-disubstituted allylic alcohols were examined to assess the scope and limitations of our methodology (Table 2).[8] The catalysts **6f**,**g**, which displayed high levels of enantioinduction and impressive reaction rates in the isomerization of **7**, and catalyst **6j**, which gave the highest enantioselectivity, were systematically investigated. High enantioselectivities were still achieved when either electron-donating or electron-withdrawing substituents were introduced in the *para* position of the aryl group R^2 (Table 2, entries 1–7). Reducing the size of the alkyl substituent affects both the yield and the enantioselectivity of the isomerization reaction (Table 2, entries 8–12). In contrast, it is apparent that a bulky alkyl substituent R^1 favors excellent to virtually perfect enantioselectivities (Table 2, entries 13–17). Interestingly, when both the steric hindrance on the phosphorus atom of the ligand and on the substrate is reduced, *E*/*Z* isomerization of the olefin is exclusively observed (Table 2, entry 10). Promising levels of enantioselectivity were measured for a 3,3-dialkyl allylic alcohol (Table 2, entries 18–20). The isomerization of *Z*-configured primary allylic alcohols did not provide satisfactory results (Table 2, entries 21 and 22).

Table 2: Asymmetric isomerization of 3,3-disubstituted allylic alcohols.



Entry[a]	Catalyst	R^1	R^2	*t* [h]	Conv. [%][b]	*ee* [%][c]
1	(*R*)-**6f**	*i*Pr	4-Me-C_6H_4	22	50	56 (*R*)
2	(*R*)-**6g**	*i*Pr	4-Me-C_6H_4	22	84	86 (*R*)
3	(*S*)-**6j**	*i*Pr	4-Me-C_6H_4	22	71	95 (*S*)
4	(*R*)-**6g**	*i*Pr	4-MeO-C_6H_4	22	>99	90 (*R*)
5	(*S*)-**6j**	*i*Pr	4-MeO-C_6H_4	22	91	94 (*S*)
6	(*R*)-**6g**	*i*Pr	4-Cl-C_6H_4	22	88	82 (*R*)
7	(*S*)-**6j**	*i*Pr	4-Cl-C_6H_4	22	60	94 (*S*)
8	(*R*)-**6f**	Me	C_6H_5	22	30	34 (*S*)
9	(*R*)-**6g**	Me	C_6H_5	22	10	57 (*S*)
10	(*S*)-**6h**	Me	C_6H_5	22	<5[d]	n.d.
11	(*R*)-**6f**	Et	C_6H_5	8	35	60 (*S*)
12	(*R*)-**6g**	Et	C_6H_5	22	30	73 (*S*)
13	(*R*)-**6f**	Cy	C_6H_5	6	78	87 (*R*)
14	(*R*)-**6g**	Cy	C_6H_5	6	85	94 (*R*)
15	(*S*)-**6j**	Cy	C_6H_5	22	88	98 (*S*)
16	(*R*)-**6g**	*t*Bu	C_6H_5	22	80	99 (*R*)
17	(*S*)-**6j**	*t*Bu	C_6H_5	22	81	>99 (*S*)
18	(*R*)-**6f**	Me	Cy	22	70	60 (*S*)
19	(*R*)-**6g**	Me	Cy	22	90	68 (*S*)
20	(*S*)-**6j**	Me	Cy	18	25	76 (*R*)
21	(*R*)-**6g**	Ph	*i*Pr	22	26[e]	46 (S)
22	(*R*)-**6g**	Ph	Me	22	18	25 (R)

[a] Reported results are the average of at least two runs. [b] Determined by GC or ^{1}H NMR methods. [c] Determined by GC or SFC methods using a chiral stationary phase. Absolute configuration (shown in parentheses) based on the sign of the optical rotation and by comparison with literature data. See Ref. [3b]. [d] A 3:1 mixture of *E*/*Z* isomers was recovered. [e] The remaining 74% is a 3.5:1 mixture of *E*/*Z* isomers.

Crystals of suitable quality for X-ray crystal analysis were obtained by slow diffusion of hexanes in a concentrated dichloromethane solution of the PF_6 analogue of complex (*R*)-**6g** (Figure 2).[9] The iridium complex adopts a distorted square-planar coordination geometry (P-Ir-N = 82.43(17)°) where the metallacyclopentene chelate lies in a rigid and almost flat conformation. Consequently, the two bulky 1-adamantyl groups on the phosphorus atom do not display axial/equatorial orientations but instead occupy nearly

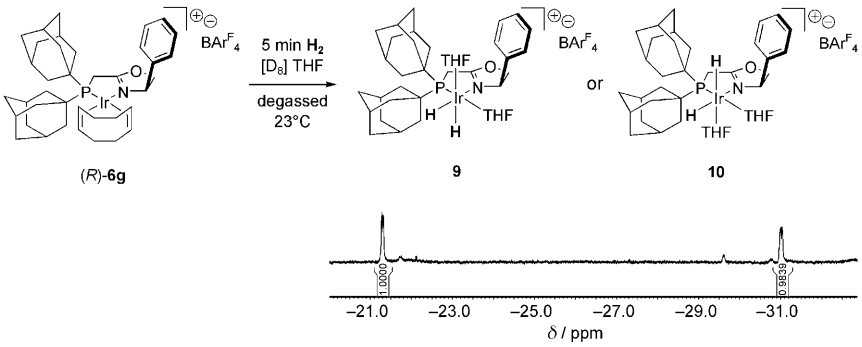


Figure 3. Activation of (*R*)-**6g** by H_2 at room temperature in [D_8]THF. The hydride region of the ^{1}H NMR spectrum (recorded at 223 K) is shown.

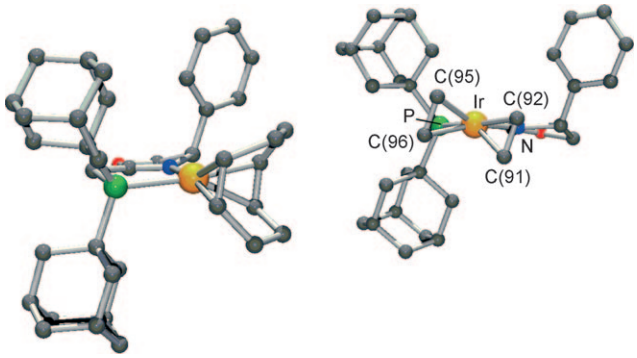


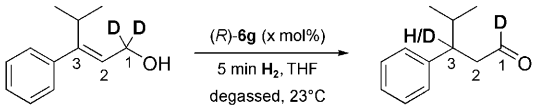
Figure 2. Crystal structure of complex (*R*)-**6g**; side view (left) and front view (right). H atoms and PF_6 counter anions have been omitted for clarity. The methylene fragments of the cod moiety have been removed in the front view. Selected bond distances [Å] and angles [°]: Ir–C(91) 2.202(8), Ir–C(92) 2.178(8), Ir–C(95) 2.138(7), Ir–C(96) 2.125(8), Ir–N 2.110(6), Ir–P 2.345(5); N-Ir-P 82.43(17).

equivalent positions. The cyclooctadiene ligand exhibit a strong clockwise twist bringing C(92) and C(96) almost in plane with the P-Ir-N chelate. The characteristically stronger *trans* influence of the phosphorus atom is manifested by longer Ir–C_{cod} bond distances. Two-dimensional NMR analyses recorded in [D_8]THF indicate that the solid-state structure of (*R*)-**6g** essentially remains in solution. Interestingly, a NOE contact was observed between the methylene protons of the "lower" adamantyl cage and the olefinic cod proton on C(91). This indicates that voluminous substituents on the phosphorus may exert a steric influence on both the *cis*- and *trans*-coordination sites, sites where the isomerization reaction is expected to take place.

To get a better understanding of the important features of the active species responsible for high activity and enantioselectivity in the asymmetric isomerization of primary allylic alcohols, the reactivity of (*R*)-**6g** with molecular hydrogen was investigated (Figure 3). Activation of the precatalyst in [D_8]THF was performed at room temperature as for standard catalytic experiments (see above). After degassing, the NMR tube was sealed and transferred to a 500 MHz spectrometer, which was precooled to 223 K to avoid decomposition into catalytically inactive iridium clusters.[10] The ^{1}H NMR spectrum displays a major *cis*-dihydride species, formally resulting from the oxidative addition of molecular hydrogen to the putative solvate complex [Ir(P,N)(C_4D_8O)$_2$]BAr$^F_4$.[11] Other hydride intermediates present in minor quantity can also be seen in the ^{1}H NMR spectrum depicted on Figure 3.[12,13]

The small $^2J_{HP}$ coupling constants (19 and 23 Hz) imply that both hydrides are *cis* to the phosphorus donor. Since the position of the hydride perpendicular to the plane of the metallacycle could not be ascertained by two-dimensional NMR spectroscopy, the identity of the major isomer (**9** or **10**) remains unclear.

Labeling experiments employing dideuterated test substrate [D_2]-**7** were conducted using the standard procedure for the isomerization reaction (Scheme 2).[14] At the end of the

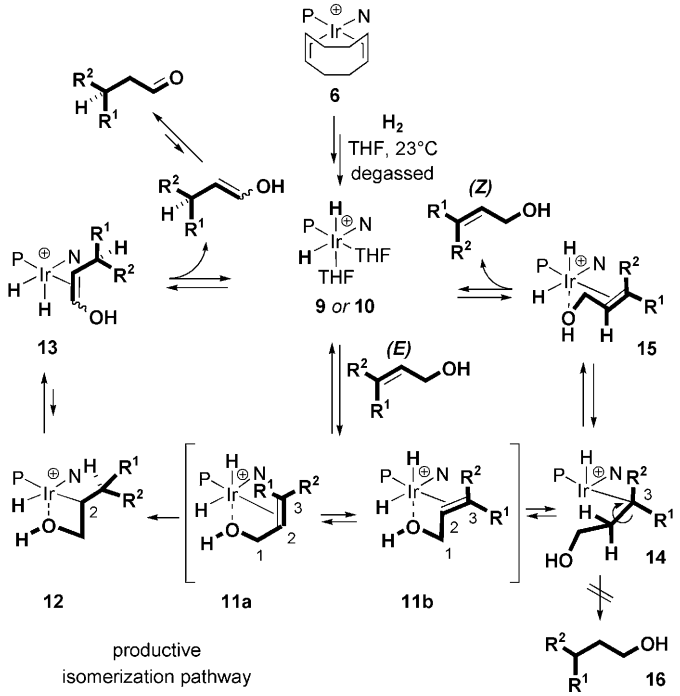


mol% [Ir]	H incorporation
5	10%
10	20%
20	40%

Scheme 2. Labeling experiments using dideuterated model substrate [D_2]-**7** and (*R*)-**6g**.

reaction, along with the dideuterated product [D_2]-**8**, the monodeuterated aldehyde [D_1]-**8** was detected by HRMS, revealing that an intermolecular process is at play. After completion of the reaction, ^{1}H NMR analysis showed exclusive incorporation of hydrogen at C3. The level of incorporation of hydrogen was found to be essentially twice proportional to the initial loading in (*R*)-**6g**, indicating that all the exogenous hydrogen had been transferred from the catalyst to the substrate during the course of the isomerization reaction.

A mechanistic rationale consistent with our experimental observations is depicted in Scheme 3. Initial chelation of the substrate on the *cis*-dihydride intermediate **9** or **10** is supported by the Stork[15] and Crabtree[16] studies of the directed hydrogenation of allylic alcohols catalyzed by [Ir(PCy$_3$)(pyridine)(cod)]PF$_6$.[17] The productive isomerization pathway starts with migratory insertion at C2 to produce a



Scheme 3. Proposed mechanisms for the isomerization of allylic alcohols (left) and the competing *E*/*Z* isomerization pathway (right).

secondary alkyl hydride intermediate (**11a**→**12**). Reversible binding of the alcohol functionality allows subsequent β-hydride elimination from C1 to generate the enol dihydride intermediate **13**. Rapid tautomerization, presumably outside the catalytic cycle, leads to the desired aldehyde.[18]

Interestingly, the *cis* dihydride regenerated at the end of the first cycle has a different coordination geometry than that of the initial active catalyst, and therefore offers a different stereochemical environment to the next molecule of substrate (i.e. if **9** was initially involved, **10** is generated after one turnover, and vice versa). A rapid isomerization between **9** and **10** is therefore likely to occur.[19] This hypothesis is in line with the results of the labeling experiments. In the key intermediate **11a** only one hydride is stereoelectronically aligned with the $\sigma^*_{C=C}$ to undergo migratory insertion. The transfer of all the hydrides from the catalyst to the product therefore implicates the existence of a fast *cis*-hydride exchange mechanism at some stage in the catalytic cycle.[20] Migratory insertion is likely to be the rate-determining step regarding the significant effect of olefin substituents and olefin geometry on the reaction rate. Decreasing the size of the R^1 substituent leads to migratory insertion at C3 and competitive *E*/*Z* isomerization (**11b**→**14**→**15**) (Table 2, entries 10 and 21). Reversible binding of the hydroxy group in **14** allows free rotation around the C3–C2 bond and β-hydride elimination of the diastereotopic proton on C2 to form **15**, wherein the olefin has the opposite conformation. In the absence of hydrogen pressure, the typical reductive elimination (**14**→**16**) in the hydrogenation pathway is not observed.

In conclusion, we have identified highly active and selective iridium catalysts for the asymmetric isomerization of primary allylic alcohols. Deviating hydrogenation catalysts from their initial goal towards productive isomerization by adequately tuning the experimental setup allows this most challenging transformation to take place under mild reaction conditions. Preliminary investigations have helped our understanding and rationalization of crucial features of the reaction mechanism. Additional work to completely elucidate the mechanism and the development of new catalysts to circumvent the current limitations of the present system is ongoing in our laboratory.

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[8] Geometrically pure *E* and *Z* substrates were synthesized according to literature procedures. See the Supporting Information for details.

[9] CCDC 724940 for complex [(*R*)-**6g**]·PF_6 contains 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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[12] The ^{31}P NMR spectrum shows complete consumption of (*R*)-**6g**, a major signal that corresponds to **9** (or **10**), and the presence of a non-hydride species according to $^{31}P/^{1}H$ HMQC. Monitoring of the stoichiometric or catalytic reactions by NMR spectroscopy, even at low temperature, did not allow detection of other intermediates. See the Supporting Information.

[13] Up to four different *cis*-dihydride species may be formed upon addition of molecular hydrogen. For similar studies using iridium complexes: a) R. H. Crabtree, H. Felkin, T. Fillbeen-Kahn, G. E. Morris, *J. Organomet. Chem.* **1979**, *168*, 183 – 195; b) R. H. Crabtree, P. C. Demou, D. Eden, J. M. Mihelic, C. A. Parnell, J. M. Quirk, G. E. Morris, *J. Am. Chem. Soc.* **1982**, *104*, 6994 – 7001; c) R. H. Crabtree, R. Uriarte, *Inorg. Chem.* **1983**, *22*, 4152 – 4154; d) R. H. Crabtree, G. G. Hlatky, C. A. Parnell, B. E. Segmueller, R. J. Uriarte, *Inorg. Chem.* **1984**, *23*, 354 – 358; e) B. F. M. Kimmich, E. Soomsook, C. R. Landi, *J. Am. Chem. Soc.* **1998**, *120*, 10115 – 10125; f) C. Mazet, S. P. Smidt, M. Meuwly, A. Pfaltz, *J. Am. Chem. Soc.* **2004**, *126*, 14176 – 14181.

[14] The reverse experiment using D_2 and **7** would not necessarily produce the same results since scrambling between iridium deuterides and cyclooctadiene protons during the activation step has been observed previously. See: a) J. M. Brown, A. E. Derome, G. D. Hughes, K. P. Monaghan, *Aust. J. Chem.* **1992**, *45*, 143 – 153; b) B. F. M. Kimmich, E. Somsook, C. R. Landis, *J. Am. Chem. Soc.* **1998**, *120*, 10115 – 10125.

[15] G. Stork, D. Kahne, *J. Am. Chem. Soc.* **1983**, *105*, 1072 – 1073.

[16] a) R. H. Crabtree, M. W. Davis, *Organometallics* **1983**, *2*, 681 – 682; b) R. H. Crabtree, M. W. Davis, *J. Org. Chem.* **1986**, *51*, 2655 – 2661.

[17] In agreement with theory, the ligands with stronger *trans* influence (H^-, PR_3) are coordinated *trans* to those with weaker *trans* influence (N, C=C, OH) in intermediates **11**. See: a) T. G. Appleton, H. C. Clark, L. E. Manzer, *Coord. Chem. Rev.* **1973**, *10*, 335 – 422. For a discussion on substrate directed reactions, see: b) A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307 – 1370.

[18] We assume that the tautomerization is taking place outside the catalytic cycle, since attempts to isomerize 2,3-disubstituted allylic alcohols gave the corresponding α-substituted aldehydes in racemic form. For 2,3-disubstituted allylic alcohols, the tautomerization is the enantiodetermining step. If the metal is not involved or if background tautomerization is too fast, racemic product is expected. For a relevant discussion, see: S. Bergens, B. Bosnich, *J. Am. Chem. Soc.* **1991**, *113*, 958 – 967.

[19] Labilization of a weakly bound molecule of solvent in **9** (or **10**) generates a pentacoordinated intermediate. Subsequent Berry pseudo-rotation may be invoked for the isomerization between **9** and **10**.

[20] For related interexchange on Group 9 metal *cis*-dihydride complexes, see for example: I. D. Gridnev, N. Higashi, K. Asakura, T. Imamoto, *J. Am. Chem. Soc.* **2000**, *122*, 7183 – 7194.

