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Improved Catalysts for the Iridium-Catalyzed Asymmetric Isomerization of Primary Allylic Alcohols Based on Charton Analysis

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Abstract: An improved generation of chiral cationic iridium catalysts for the asymmetric isomerization of primary allylic alcohols is disclosed. The design of these air-stable complexes relied on the preliminary mechanistic information available, and on Charton analyses using two preceding generations of iridium catalysts developed for this highly challenging transformation. Sterically unbiased chiral aldehydes that were not accessible previously have been obtained with high levels of enantioselectivity, thus validating the initial hypothesis regarding the selected ligand-design elements. A rationale for the high enantioselectivities achieved in most cases is also presented.

Keywords: asymmetric catalysis · Charton analysis · iridium · isomerization · ligand design

Introduction

The Rh-catalyzed asymmetric isomerization of primary allylic amines into the corresponding chiral enamines distinguishes itself as one of the very few transition-metal-catalyzed asymmetric reactions that have been successfully brought to the industrial scale. The high enantioselectivities, mild reaction conditions, wide substrate scope, high turnover-numbers (TON), accessibility and recyclability of the catalyst, and a detailed understanding of the reaction mechanism are parameters that have all favored the implementation of this reaction as the key step in the yearly production of high tonnages of enantiopure (−)-menthol by the Takasago Company in Japan.[1,2] In sharp contrast, and perhaps surprisingly as both reactions were initially investigated by the same research groups at the same time, the asymmetric isomerization of primary allylic alcohols into the corresponding chiral aldehydes has not reached the same level of achievement.[3] In 2008, when we initiated a research program in this challenging area, the best catalysts reported in the literature were incontestably the cationic planar chiral phosphaferrocene–rhodium complexes developed by Fu and coworkers (Figure 1).[2b,4,5] Whereas catalyst **A** performed well only for *Z*-configured primary allylic alcohols, catalyst **B**, with bulkier *o*-tolyl phosphine substituents, appeared more general and displayed interesting catalytic activities for both *E* and *Z* isomers. Promising to satisfactory levels of enantioselectivity (50–80% *ee*) could be obtained for most substrates surveyed, and very good enantioselectivities (>90% *ee*) were obtained for the sterically more demanding derivatives. Thorough mechanistic studies showed that this rhodium-catalyzed asymmetric isomerization reaction proceeds through an intramolecular 1,3-hydrogen migration pathway. Despite unprecedented reactivity and selectivity patterns, these rhodium catalysts suffer from several important limitations, which have hampered their dissemination into the synthetic community: 1) practical quantities of enantiomerically pure ligands were only accessible after iterative preparative HPLC separations; 2) the rhodium complexes needed to be pre-activated by hydrogenating off the diolefin ancillary ligand, before the reaction was run at temperatures higher than the solvent boiling point (typically at 100–150 °C in THF); 3) despite these forcing conditions, the catalyst activity remained relatively low, and typical reaction times ranged from 24 to 48 h, with yields varying from 60–90%; 4) with one exception, the substrate scope was limited to primary allylic alcohols combining an aryl ring with an alkyl substituent.

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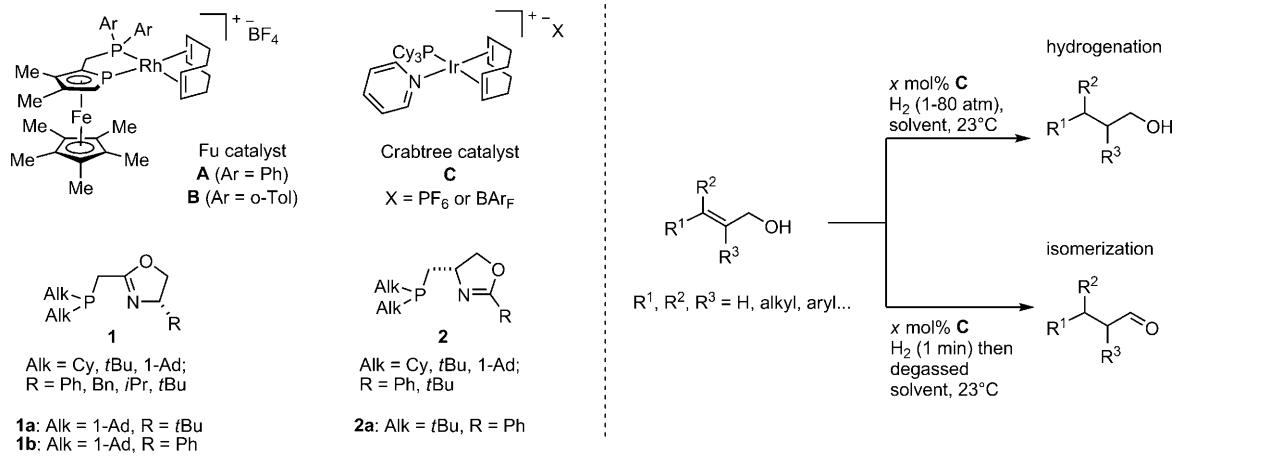

Figure 1. Successful catalysts and ligands for the (asymmetric) isomerization of primary allylic alcohols (left). Appropriate experimental conditions for either the exclusive hydrogenation or isomerization reaction using **C** (right).

With these clear limitations for the rhodium-catalyzed asymmetric isomerization of primary allylic alcohols, we sought to develop readily accessible catalysts that would follow a fundamentally different mechanistic path, and which would allow us to work under experimental conditions more suitable for the development of an asymmetric variant of the isomerization reaction. The basis of our reasoning originated from the general observation that olefin isomerization is the most common side-reaction in (asymmetric) hydrogenation processes, the undesired competing isomerization being usually suppressed by increasing the molecular hydrogen pressure.[6] Inspired by precedents in the literature, we initially hypothesized that, under appropriate experimental conditions, selected chiral hydrogenation catalysts may be detracted from their initial task, and could exclusively perform the asymmetric isomerization reactions instead. In 1978, Baudry and Ephritikhine showed that the cationic bis-phosphine–iridium hydrogenation catalyst $[(Me(Ph)_2P)_2Ir(cod)]PF_6$ was promoting exclusively the isomerization of some primary allylic alcohols to aldehydes (cod = 1,5-cyclooctadiene).[7] In their experimental procedure, the iridium precatalyst had to be activated by molecular hydrogen, and the solution was subsequently degassed to avoid competing hydrogenation. The catalyst displayed interesting TON for substrates having a mono- or disubstituted double bond, but was ineffective for allylic alcohols with higher substitution patterns (i.e., potential prochiral substrates). More recently, Fehr and Farris observed that Crabtree's hydrogenation catalyst **C** (Figure 1) promoted an exclusive isomerization/lactolization sequence rather than the initially expected hydrogenation, even though a hydrogen atmosphere was maintained.[8,9] The observation by Baudry and Ephritikhine that **C** was also competent at promoting the isomerization of allylic alcohols, albeit with reproducibility issues, suggested the isomerization/lactolization sequence discovered by Fehr and Farris may be very substrate specific. Crabtree's catalyst **C** was initially discovered in the late 1970s for the hydrogenation of unfunctionalized olefins (i.e., olefins lacking a proximal functional group to steer the hydrogenation reaction upon chelation to the metal center), outperforming the most potent rhodium and ruthenium catalysts for this particular class of substrates.[10] A few years later, Stork and Kahne[11] and Crabtree and Davis[12] independently demonstrated that the same iridium catalyst was highly efficient in the directed hydrogenation of primary allylic and homoallylic alcohols. A high degree of stereocontrol in the hydrogenation of various cyclohexenol derivatives served to establish the two-point binding mode adopted by the substrate during catalysis. Only low loadings of **C** were usually necessary to reduce quantitatively a variety of diversely substituted allylic alcohols at room temperature. Owing to the very high catalytic activity, and, moreover, to the virtual insensitivity of the catalyst to the degree of substitution of the double bond of the allylic alcohols, this useful methodology has become a standard tool for the synthetic chemist, as emphasized by its numerous utilizations in the elaboration of complex molecules since its discovery.[13]

Building on these precedents, we recently established that Crabtree's catalyst is indeed a very general catalyst for the isomerization of primary allylic alcohols, given that an experimental protocol analogous to that developed by Baudry and Ephritikhine is employed.[14] Much like in the directed hydrogenation reaction, the scope of the related isomerization reaction turned out to be extremely broad, and allylic alcohols having a di-, tri-, or tetrasubstituted double bond were isomerized quantitatively under very mild conditions using low loadings of **C**. While optimizing the experimental protocol to promote exclusively the isomerization pathway, we identified crucial electronic features responsible for the catalytic activity. Any variation from the original structure of Crabtree's catalyst, which combines a trialkylphosphine with an sp^2-hybridized N-donor ligand, led to a complete loss of catalytic activity. The use of the less coordinating, bulky, and lipophilic BAr_F anion provided enhanced catalyst activity compared to the original PF_6 analogue (BAr_F = tetrakis-[3,5-bis-(trifluoromethyl)-phenyl]borate). The high

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degree of reproducibility and the substrate scope generality contrasted strongly with earlier observations, and were attributed to the increased chemical stability of the catalyst also provided by the counteranion.[15,16] These electronic prerequisites were instrumental in identifying two generations of isomeric chiral (dialkyl)phosphinoalkyloxazoline iridium complexes for the asymmetric version of the isomerization reaction.[17,18] Ligand scaffolds **1** and **2** introduced by Helmchen[19] and Burgess,[20] respectively, in the context of Pd-catalyzed asymmetric allylic alkylations, were tuned according to the design elements identified with the achiral catalyst **C** (Figure 1). Under similarly mild reaction conditions, using the same activation protocol, the best candidates of each generation (**1a** and **2a**) displayed catalytic activities approaching that of **C** for 3,3-disubstituted primary allylic alcohols. This was accompanied by unprecedented levels of enantioselectivity in the case of *E*-configured substrates combining a large alkyl substituent with an aryl group. When a smaller alkyl substituent was combined with the aryl group, lower enantioselectivity along with competing *E*/*Z* isomerization of the starting material were observed. Allylic alcohols with a *Z* configuration were much less reactive, and delivered the chiral aldehyde of opposite absolute configuration with substantially lower enantioselectivities. Concomitant isomerization of the allylic alcohol double bond was also observed for this substrate class. Catalyst **2a** was found to outperform catalyst **1a** in the isomerization of the more challenging 3,3-dialkyl primary allylic alcohols. Tetrasubstituted or 2,3-disubstituted primary allylic alcohols, homoallylic alcohols, and secondary allylic alcohols were not isomerized with these iridium catalysts.

Mechanism: Preliminary mechanistic investigations have shed light on the mechanism at play in the asymmetric isomerization of primary allylic alcohols using chiral (dialkyl)-phosphinoalkyloxazoline iridium complexes.[17] On the basis of NMR analyses, labeling and cross-over experiments, an unprecedented intermolecular dihydride mechanism was proposed to be operative (Figure 2). The conformational binding of the allylic alcohol to the active dihydride iridium(III) intermediate characterized by ^{1}H and ^{31}P NMR spectroscopy is crucial in the general outcome of the reaction. In the productive isomerization pathway, the migratory insertion at C2 is believed to be both the rate- and the enantiodetermining step. Competing migratory insertion at C3 is postulated to be responsible for the *E*/*Z* isomerization observed for *E*-configured 3,3-disubstituted allylic alcohols with a small alkyl substituent and for *Z*-configured substrates. The lower enantioselectivities measured in these cases were attributed to the difference in rate between the multiple competing isomerization pathways ($E \rightarrow Z \rightarrow E$; $E \rightarrow$ chiral aldehyde; $Z \rightarrow$*ent*-chiral aldehyde). Similar observations were made during isomerization of the model substrate when ligands of type **1** or **2** with small alkyl groups on the P atom were employed, which emphasize the strong dependency of the isomerization reaction with respect to steric factors arising from the ligand structure and/or the substrate structure.[21]

Despite these significant advances in the asymmetric isomerization of primary allylic alcohols, in particular regarding the accessibility of the catalyst and the mild reaction conditions, expanding the scope to substrates that are not biased with a large alkyl group remains particularly challenging. In this article, we describe in detail the rationale we followed for the development of a new generation of iridium catalysts for the highly enantioselective isomerization of primary allylic alcohols that were not successfully isomerized using the first generations of catalysts.

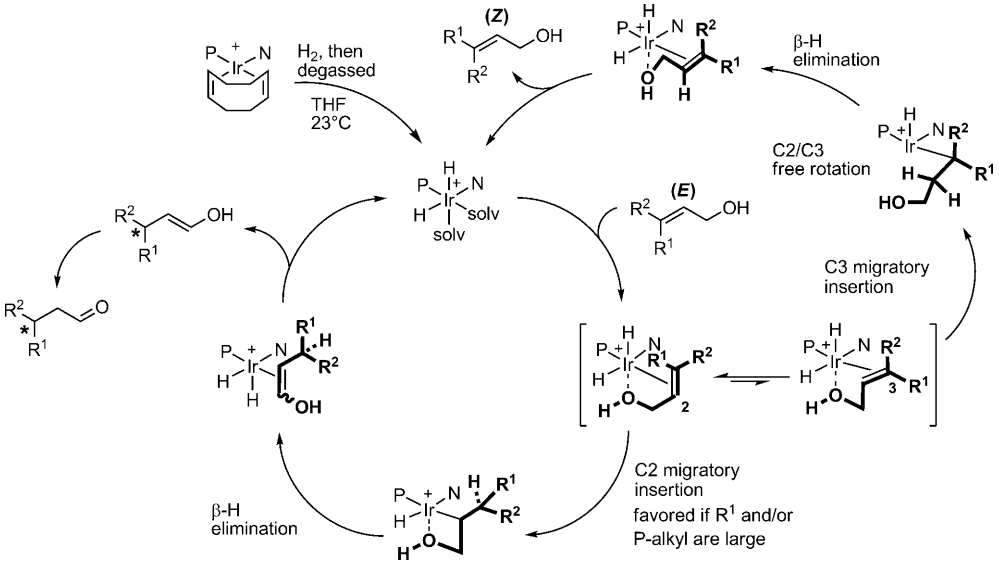

Figure 2. Mechanism for the isomerization of primary allylic alcohols using iridium catalysts with ligands of type **1** or **2**.

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Results and Discussion

Ligand and catalyst design: Miller and Sigman have recently described the possibility to elaborate the linear free energy relationship (LFER) between steric parameters (Charton value) and enantiomeric ratios (e.r.) for a variety of well-established catalytic asymmetric reactions, thus demonstrating that the substituent effects on the catalyst and/or the substrate can be correlated.[22,23] These Charton analyses provide insight into the transition state with respect to steric factors and offer an attractive complement to Hammet plots, which only give a measurement of the electronic effects. More importantly, Miller and Sigman anticipated these correlations may ultimately serve as a new platform for catalyst structure optimization. Indeed, despite important advances in computational methods, ligand design in asymmetric catalysis remains a challenging task that relies mostly on screening and intuition, in particular in the absence of any mechanistic information. Figure 3 shows Charton analyses for the isomerization of two different classes of *E*-configured 3,3-disubstituted primary allylic alcohols obtained using our first two generations of iridium catalysts **1** and **2**.[17,18] The excellent correlation in the first plot indicates that *E*-configured 3,3-disubstituted primary allylic alcohols, combining a phenyl substituent with alkyl groups of various volumes, are isomerized via a similar transition state using the most selective catalyst of the first generation **1a**. The value of the sensitivity factor (i.e., slope; $\Psi = 2.32$) reveals that variation in e.r. as a function of the steric demand is strongly marked for this substrate class. Consequently, for alkyl groups smaller than isopropyl, the enantiomeric ratio is sharply reduced ($ee = 90\% \rightarrow \log(95/5) = 1.278$). The second plot shows that a good correlation is also obtained for 3,3-dialkyl substituted primary allylic alcohols using the optimal structure of second generation **2a**, suggesting that again the reaction follows a similar mechanism for all substrates investigated. Importantly, 3,3-dialkyl-substituted primary allylic alcohols are notoriously more challenging substrates for isomerization. They barely reacted using the first generation of catalysts (type **1**). Although the enantioselectivity values are lower in this case, the lower sensitivity value ($\Psi = 0.90$) indicates a less pronounced dependence of this substrate class on steric variations using catalyst **2a**.

On the basis of these Charton analyses, and the observation that an increased steric demand on the substrate and/or the ligand steers the isomerization reaction towards the productive pathway, we sought to design new catalysts that would perform equally well for sterically biased and unbiased allylic alcohols by transferring the steric demand exclusively on the ligand structure. Nevertheless, we anticipated that a potential risk in following such an approach would be the complete hampering of substrate coordination to the metal. Starting from the more general scaffold **2**, we reasoned that bringing the P-alkyl groups and the oxazoline substituent closer to the coordination sites where the reaction takes place (by a formal homologation of the ligand bridge) would have a beneficial impact on the enantioselectivity of the isomerization reaction, while maintaining enough flexibility in the ligand backbone to ensure substrate coordination (Scheme 1).

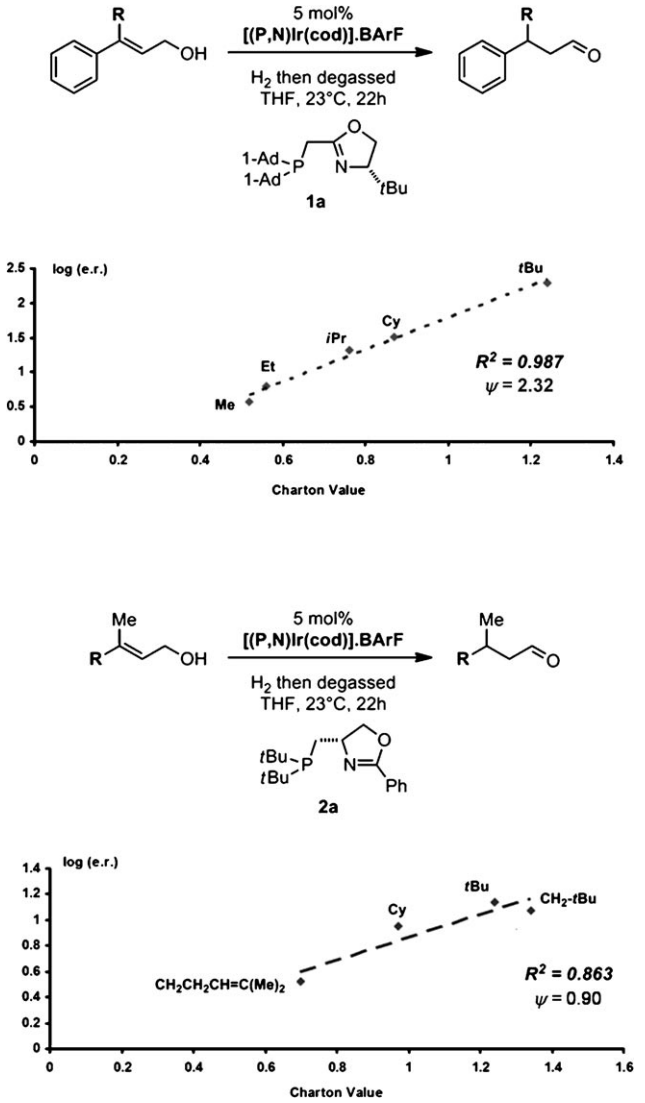
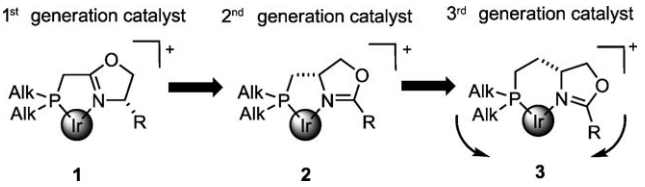


Figure 3. Charton analysis for the isomerization of aromatic primary allylic alcohols using **1a** (top) and 3,3-dialkyl primary allylic alcohols using **2a** (bottom).

Both ligand scaffolds **2** and **3** were originally designed by Burgess and co-workers in the context of Pd-catalyzed asymmetric alkylation reactions.[19,24] Ligands **L3** (JM-phos ligands) were also used later in the Ir-catalyzed asymmetric



Scheme 1. Conceptual approach for catalyst optimization based on the reaction mechanism rationale and the Charton analyses.

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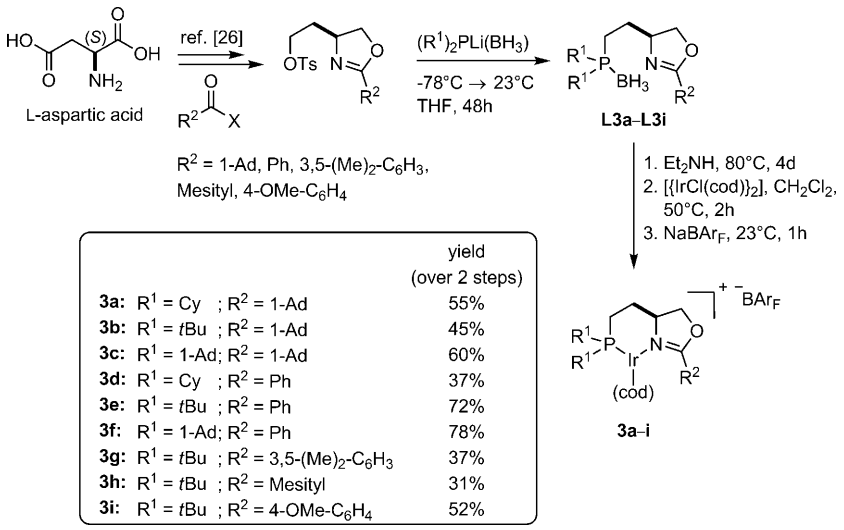
hydrogenation of unfunctionalized alkenes.[25] Exploiting the virtually infinite catalogue of carboxylic acid precursors, systematic variation of the exocyclic substituent of the oxazoline ring served to demonstrate the highly modular nature of these structures. Nevertheless, only diarylphosphine moieties were implemented on the left-hand side of the ligand. The presence of a formal trialkylphosphine along with an sp^2-hybridized N-donor being a necessary requirement to ensure catalytic activity in the isomerization of primary allylic alcohols,[14,17,18] we focused on the synthesis of a structurally relevant library of nine new iridium complexes, all possessing a formal trialkyl-P donor (R^1 = Cy, *t*Bu, 1-adamantyl (1-Ad)) combined with oxazoline rings having either C-sp^2 or C-sp^3 exocyclic substituents (R^2 = 1-Ad or aryl) (Scheme 2).

Protected ligand and iridium complex syntheses: Access to diversely substituted tosyl-oxazoline derivatives was achieved using the most recent four-step procedure reported by Burgess and co-workers, starting from inexpensive L-aspartic acid.[26] The modular combination of these five oxazoline electrophiles with three different borane-protected dialkylphosphines readily gave access to a library of six new (P,N) ligands (**L3a–f**). Ligands **L3g–i** were synthesized after initial evaluation of the catalysts in the asymmetric isomerization of our model substrate (vide infra). S_N2 displacement of the tosyl anion by reaction with in situ generated borane-protected lithium dialkylphosphanide precursors in THF at −78 °C yielded the protected ligands as air-stable white solids in moderate to good yields after 48 h. The one-pot deprotection/complexation sequence recently optimized in our laboratory was carried out next. Deprotection of the phosphine was secured by reacting the borane adducts with an excess of diethylamine at reflux in a sealed tube. After evaporation of the volatiles, half an equivalent of $[\{IrCl(cod)\}_2]$ was added in dichloromethane and heated at reflux for a further two hours. Halide abstraction was performed by addition of a slight excess of $NaBAr_F$ followed by vigorous stirring for one hour. All iridium complexes were purified by standard silica gel chromatography, and isolated in pure form in average to excellent yields depending on the R^1/R^2 combination. The red–orange solids were all bench-stable, but were kept in a −35 °C freezer under an inert atmosphere. No loss of catalytic activity was observed even after several months.

Catalyst structure optimization: In a preliminary survey, the six new iridium complexes **3a–f** were evaluated for their ability to catalyze the isomerization of (*E*)-4-methyl-3-phenylpent-2-enol, a model substrate that has proven relevant in previous studies. The reactions were performed using the standard protocol for the isomerization of primary allylic alcohols recently developed in our laboratory. The iridium complexes were activated by bubbling molecular hydrogen directly through a solution of the complexes in THF for five minutes. The substrate was added only after complete degassing of the excess of hydrogen to avoid undesired hydrogenation. The reactions were run for 4 to 14 h at room temperature using 5 mol% of iridium precatalyst **3a–f** (Table 1, entries 1–8).

The reactions with catalysts **3a–c**, which displayed very low reactivities, were run for 14 h to obtain sufficient material to facilitate the subsequent analyses. In this series (R^1 = alkyl, R^2 = 1-Ad), both the yield and the enantiomeric excess decreased as the size of the substituents on the phosphorus atom increased. Indeed, whereas catalyst **3a** delivered the chiral aldehyde in 41% yield and 93% *ee*, catalysts **3b** and **3c** gave the isomerization product in substantially reduced yields (28 and 17%, respectively) and lower enantioselectivity values (84 and 26%, respectively). Catalysts **3d–f** (R^1 = alkyl, R^2 = Ph) were more reactive, and the reactions were run for only 4 h. Again, the yields were reduced as the steric demand of the P-alkyl substituents was increased, but the enantioselectivity followed an inverse trend. All three catalysts gave the desired product with excellent to almost perfect enantioselectivity levels (90, 97, and 98% *ee*, respectively); catalyst **3e** (R^1 = *t*Bu, R^2 = Ph) offered the best balance between reactivity and selectivity. Because the flexibility of the general synthetic route developed by Burgess and co-workers allows straightforward structural optimization, modification of the electronic and steric properties of the phenyl group (R^2) in **3e** was carried out next, while maintaining *tert*-butyl substituents on the P atom. Complexes **3g–i** were prepared in modest to moderate yields (Scheme 2)



	yield (over 2 steps)
3a: R^1 = Cy ; R^2 = 1-Ad	55%
3b: R^1 = *t*Bu ; R^2 = 1-Ad	45%
3c: R^1 = 1-Ad; R^2 = 1-Ad	60%
3d: R^1 = Cy ; R^2 = Ph	37%
3e: R^1 = *t*Bu ; R^2 = Ph	72%
3f: R^1 = 1-Ad; R^2 = Ph	78%
3g: R^1 = *t*Bu ; R^2 = 3,5-$(Me)_2$-C_6H_3	37%
3h: R^1 = *t*Bu ; R^2 = Mesityl	31%
3i: R^1 = *t*Bu ; R^2 = 4-OMe-C_6H_4	52%

Scheme 2. Synthetic route for the synthesis of the iridium precatalysts **3a–i**.

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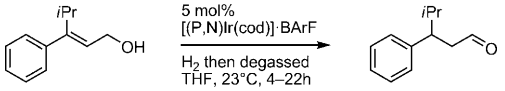
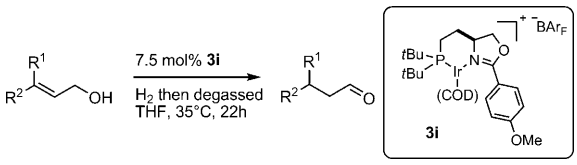
Table 1. Catalyst evaluation through asymmetric isomerization of (*E*)-4-methyl-3-phenylpent-2-enol.[a]



	Catalyst[b] [(P,N)Ir(cod)]BAr_F	*t* [h]	Yield [%][c]	*ee* [%][d]
1	(*S*)-**1a**	22	75	97 (*S*)[e]
2	(*S*)-**2a**	4	73	96 (*R*)[f]
3	(*S*)-**3a**	14	41	93 (*R*)
4	(*S*)-**3b**	14	28	84 (*R*)
5	(*S*)-**3c**	14	17	26 (*R*)
6	(*S*)-**3d**	4	60	90 (*R*)
7	(*S*)-**3e**	4	57	97 (*R*)
8	(*S*)-**3f**	4	30	98 (*R*)
9	(*S*)-**3g**	4	<5	nd[g]
10	(*S*)-**3h**	4	11	89 (*R*)
11	(*S*)-**3i**	4	43	>99 (*R*)
12	(*S*)-**3i**	4	65	>99 (*R*)[h]
13	(*S*)-**3i**	4	52	96 (*R*)[i]
14	(*S*)-**3i**	22	64	98 (*R*)[j]

[a] Average of at least two runs. [b] Reaction on a 0.2 mmol scale using 5 mol% of catalyst. [c] Determined by ^{1}H NMR spectroscopy using an internal standard and/or GC analysis. [d] Determined by chiral GC. [e] See reference [17]. [f] See reference [18]. [g] Not determined. [h] Using 10 mol% of catalyst. [i] At 50°C. [j] Using 7.5 mol% of catalyst at 35°C.

Table 2. Asymmetric isomerization of *E* and *Z*-configured aromatic primary allylic alcohols.[a,b]



	R^1	R^2	Olefin config	Yield [%][c]	*ee* [%][d]
1	*t*Bu	Ph	*E*	55	99 (*R*)
2	*i*Bu	Ph	*E*	50	96 (*R*)
3	Cy	Ph	*E*	85	98 (*R*)
4	*i*Pr	Ph	*E*	64	98 (*R*)
5	Et	Ph	*E*	24	90 (*S*)
6	Me	Ph	*E*	26	80 (*S*)
7	*i*Pr	4-OMe−C_6H_4	*E*	87	99 (*R*)
8	*i*Pr	4-Me−C_6H_5	*E*	77	98 (*R*)
9	*i*Pr	4-Cl−C_6H_4	*E*	50	97 (*R*)
10	Me	2-Me−C_6H_4	*E*	12	92 (*S*)[e]
11	$SiMe_3$	Ph	*Z*	60	97 (*S*)
12	Ph	Me	*Z*	<5	nd[f]
13	Ph	*i*Pr	*Z*	19	61 (*S*)

[a] Average of at least two runs. [b] Reaction on a 0.1 mmol scale using 7.5 mol% of catalyst. [c] Determined by ^{1}H NMR spectroscopy using an internal standard and/or GC analysis. [d] Determined by chiral GC or SFC. [e] Catalyst **3f** was used. [f] Not determined.

and subsequently evaluated in the asymmetric isomerization of our test substrate, giving rise to contrasting results (Table 1, entries 9–13). Catalysts **3g** and **3h** proved much less reactive than their parent structure **3e**, suggesting that the introduction of substituents on either the *ortho* or *meta* position may interfere with substrate coordination (Table 1, entries 9 and 10). Catalyst **3i** (R^2=*p*-anisyl) turned out to be slightly less reactive than **3e** but more enantioselective, delivering the aldehyde with virtually perfect enantioselectivity. Further optimization showed that the yield can be improved if either the catalyst loading or the temperature is increased, albeit at the expense of the enantioselectivity in the latter case (Table 1, entries 11–13). Running the reaction in a thermostated bath at 35°C using 7.5 mol% of catalyst offered a convenient compromise, and these conditions were uniformly used for the isomerization of other primary allylic alcohols.[27] Under these conditions, **3i** reached performances similar to those displayed by the best catalysts of the first and second generation, that is, **1a** and **2a**, respectively.

Asymmetric isomerization of *E*- and *Z*-configured aromatic primary allylic alcohols: To explore the effect of the ligand bridge homologation, a series of aromatic primary allylic alcohols with alkyl groups of various sizes at C3 were subjected to the optimized conditions developed for the asymmetric isomerization using **3i** (Table 2). Substrates with large alkyl substituents (R^1=*t*Bu, *i*Bu, Cy, *i*Pr) delivered the corresponding aldehydes in moderate to good yields, with extremely high levels of enantioselectivity (96–99% *ee*; Table 2, entries 1–4). Remarkably, aromatic primary allylic alcohols with small alkyl groups (R^1=Me, Et; Table 2, entries 5 and 6) were isomerized in modest yields but with a significant improvement of the enantioselectivity value compared to the first and second generations of catalysts. Importantly, no competing *E*/*Z* isomerization was detected when monitoring the reaction by ^{1}H NMR spectroscopy and GC. These results validate the structural modification of the phosphinoalkyloxazoline ligands (**2**→**3**) based on our mechanistic proposal and Charton analyses. They further suggest that the increased steric demand in the vicinity of the reactive sites funnels the reactions exclusively through the productive isomerization pathway. The improved catalytic performances of **3i** over **1a** are better visualized on the comparative Charton analysis plotted on Figure 4. The reduced value of the sensitivity factor Ψ (1.75 vs. 2.32) clearly indicates that a change in the enantiomeric ratio as a factor of steric demand is less pronounced with **3i** than with **1a**.

We also observed that a gradual increase of the electronic density of the aromatic ring of the model substrate had a beneficial impact both on the activity and the enantioselectivity, whereas a decrease led to a slightly reduced yield and *ee* value (compare entries 4 and 7–9 in Table 2). Substitution at the *ortho* position was barely tolerated in terms of catalytic activity, but the aldehyde was still obtained with excellent enantioselectivity (Table 2, entry 10). This observation may be paralleled with the detrimental effect on the catalytic activity of *ortho* and *meta* substitution of the aryl group of the oxazoline in the ligand structure (Table 1, entries 9 and 10). The aromatic primary allylic alcohol with R^1=$SiMe_3$, which has a formal *Z*-configured double bond, was isomerized with good yield and enantioselectivity (60% yield, 97% *ee*), whereas other *Z*-configured allylic alcohols, in

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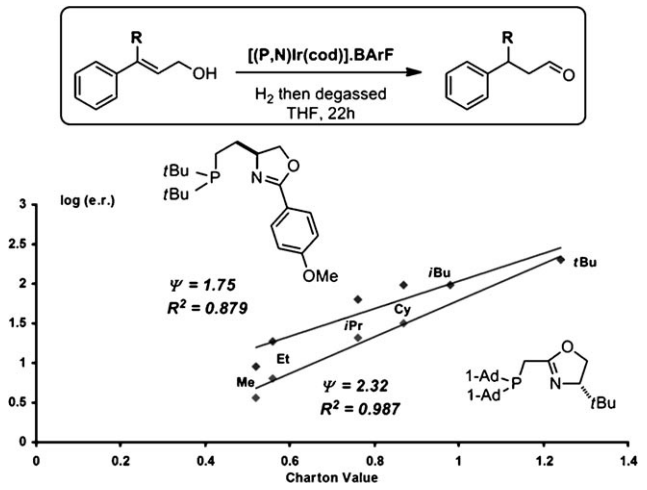


Figure 4. Comparative Charton analysis for aromatic primary allylic alcohols using **1a** and **3i** (corresponding to entries 1–6 in Table 2).

which the positions of the phenyl and alkyl groups are reversed, remain challenging targets (Table 2, entries 11–13). Interestingly, in these reactions, again no competing *E*/*Z* isomerization was observed.

Asymmetric isomerization of 3,3-dialkyl primary allylic alcohols: Catalyst **3i** was further evaluated in the asymmetric isomerization of the more challenging 3,3-dialkyl primary allylic alcohols using the optimized reaction conditions (Table 3).

All substrates investigated were efficiently isomerized, delivering the chiral aldehydes in average to good yields with promising enantioselectivity levels. In any case, parasite *E*/*Z* isomerization was detected. Remarkably, geraniol was isomerized into citronellal with an unprecedented enantioselectivity value, which, coincidentally, matches the value of natural citronellal (82% *ee*; Table 3, entry 4). Isomerization of nerol turned out to be more challenging, and citronellal was obtained in much lower yield and enantioselectivity (26% yield, 31% *ee*; Table 3, entry 5). A Charton analysis corresponding to the isomerization of the *E*-configured 3,3-dialkyl allylic alcohols is plotted in Figure 5. A linear, free-energy relationship can be traced for the substrates, for

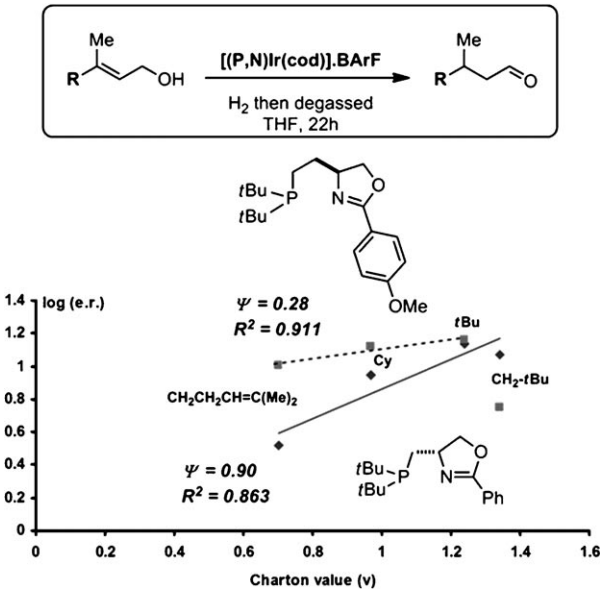
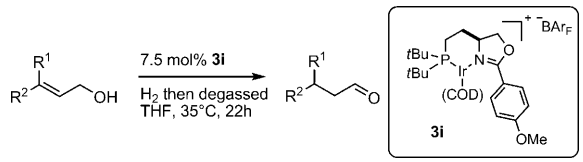


Figure 5. Comparative Charton analysis for 3,3-dialkyl primary allylic alcohols using **2a** and **3i** (corresponding to entries 1–4 in Table 3).

which **3i** clearly outperforms **2a** ($R^1 = CH_2CH_2CH{=}C(Me)_2$, Cy, *t*Bu; Ψ 0.28, $R^2 = 0.911$) provided that the derivative with a neopentyl substituent is excluded from the analysis. According to Miller and Sigman's hypothesis, the apparent kink in the correlation could be tentatively attributed to a change in the conformation of the substrate and/or the ligand. Alternatively the reaction may follow a different mechanistic pathway. In the present case, we believe the increased flexibility provided by the methylene homologation in ligands of type **3** may account for the observed result.

Attempts to promote the asymmetric isomerization of tetrasubstituted or 2,3-disubstituted primary allylic alcohols with catalysts **3** were met with failure. Homoallylic alcohols and secondary allylic alcohols were not isomerized either with these iridium catalysts.

Table 3. Asymmetric isomerization of (*E*)-and (*Z*)-3,3-dialkyl primary allylic alcohols.[a,b]



	R^1	R^2	Olefin config	Yield [%][c]	*ee* [%][d]
1	Me	$tBuCH_2$	*E*	60	70 (*R*)
2	Me	*t*Bu	*E*	43	87 (*S*)
3	Me	Cy	*E*	96	86 (*S*)
4	Me	$(CH_3)_2C{=}CHCH_2CH_2$[e]	*E*	49	82 (*R*)
5	$(CH_3)_2C{=}CHCH_2CH_2$[e]	Me	*Z*	26	31 (*S*)

[a] Average of at least two runs. [b] Reaction on a 0.1 mmol scale using 7.5 mol% of catalyst. [c] Determined by ^1H NMR spectroscopy using an internal standard and/or GC analysis. [d] Determined by chiral GC. [e] A Charton value of 0.70 was used.

X-ray analysis and mechanistic model: Crystals of suitable quality for an X-ray crystallographic analysis of **3i** were obtained by indirect diffusion of hexanes into a saturated solution of the iridium complex in toluene.[28] Figure 6 contains a comparison of the crystallographic structures of iridium complexes (*R*)-**1b**[17] (R^1 = 1-

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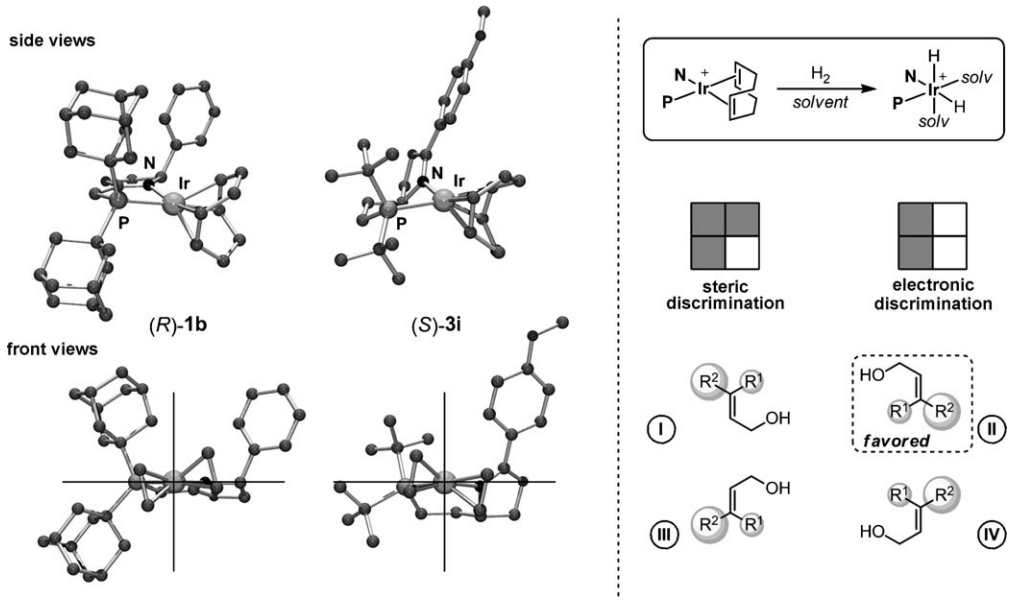
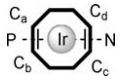


Figure 6. Side and front views of the molecular structures of complexes (*R*)-**1b** and (*S*)-**3i**. The counteranion in both views and the $CH_{2\,cod}$ in the front views have been omitted for clarity (left). Sense of the oxidative addition of H_2 to C_1-symmetric $[(P,N)Ir(cod)]^+$ (top right); quadrant diagrams to explain the preferred binding of *E*-configured substrates to the catalysts (bottom right).

Ad, R^2 = Ph) and (*S*)-**3i**, along with quadrant diagrams and a rationale for the preferred two-point binding of the primary allylic alcohols to the catalysts. Both d^8 complexes adopt a distorted square planar arrangement around the metal center, with a wider bite angle for the six-membered chelate of **3i** than for the five-membered chelate of **1b** (87.88(11)° versus 80.43(17)°, respectively). In both structures the cyclooctadiene ligand is severely twisted out of the coordination plane, counterclockwise for **1b** and clockwise for **3i**. Consequently, one carbon of each double bond is nearly in plane with the N, Ir, and P atoms. The strong *trans* influence of the phosphorus atom of the C_1-symmetric ligands is well reflected by the noticeably longer Ir–C_{cod} bonds, in particular for the C_{cod} in plane with the other donor atoms. (see Table 4). The different connectivity of the oxazoline (Csp^2 in **1b** versus Csp^3 in **3i**) and the ligand bridge homologation impose a fundamentally different orientation of the oxazoline ring. Whereas the oxazoline is in plane with the chelate in the more rigid structure of **1b**, the increased flexibility in **3i** places the heterocycle almost perpendicular to the coordination plane, thus projecting the anisyl substituent above this plane. Although these structures give only insight into the thermodynamics of precatalysts for the asymmetric isomerization of primary allylic alcohols, they can be exploited to develop a rationale for the preferred two-point binding of the substrate to the metal center. The quadrant diagrams established on the basis of the molecular structures of (*R*)-**1b** and (*S*)-**3i** clearly indicate that only the south-eastern quadrant is spatially accessible. Furthermore, it is now well accepted that the oxidative addition of molecular hydrogen to (P,N)–iridium complexes is steered by the C_1-symmetric nature of the ligand.[29] Hence, after complete hydrogenation of the ancillary diolefinic ligand, highly reactive iridium(III) intermediates in which the two hydrides are located *cis* to the phosphorus are generated (Figure 6, top right). If chiral (P,N) ligands are used, up to two isomeric complexes may be generated, leaving in any case the two eastern quadrants *trans* to the phosphorus electronically open.[17,30] The conjunction of the electronic and steric discriminations suggest that binding mode **II** will better accommodate the substituents of the *E*-configured primary allylic alcohol on the open quadrant (Figure 6, bottom right).

Table 4. Comparison of selected structural features for (*R*)-**1b** and (*S*)-**3i**. Selected NMR data for (*S*)-**3i** (500 and 126 MHz in $CDCl_3$).



Selected bond lengths [Å] and angles [°]			Selected NMR data for (*S*)-**3i** (500 MHz or 126 MHz; $CDCl_3$)	
	(*R*)-**1b**	(*S*)-**3i**		δ [ppm]
N–Ir	2.110(6)	2.071(3)	H_a	5.19
P–Ir	2.345(5)	2.373(1)	H_b	4.06
Ir–C_a	2.138(7)	2.143(4)	H_c	4.60
Ir–C_b	2.125(8)	2.165(4)	H_d	3.15
Ir–C_c	2.202(8)	2.163(4)	C_a	70.5
Ir–C_d	2.178(8)	2.205(4)	C_b	63.0
C_a–C_b	1.40(1)	1.400(7)	C_c	90.6 ($^2J_{CP}$ = 16.0 Hz)
C_c–C_d	1.40(1)	1.399(7)	C_d	82.4 ($^2J_{CP}$ = 8.3 Hz)
N-Ir-P	80.43(17)	87.88(11)		

For aromatic primary allylic alcohols the phenyl ring will occupy the free quadrant, whereas the alkyl group will interact with the P substituent lying in the south-western quadrant. As the size of the alkyl increases this interaction may become more pronounced.[31] For 3,3-dialkyl primary allylic alcohols, the larger alkyl substituent may also be better ac-

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commodated in the sterically open quadrant. This model is in agreement with the stereochemical outcome of the reaction, because both catalysts deliver preferentially the same enantiomer of the aldehyde, although they have an opposite absolute configuration. Interestingly, the south-eastern quadrant for **3i** appears only semi-hindered if compared to that of **1b**. This observation, the increased flexibility of the ligand, and the wider bite angle in **3i** are likely to be determinant parameters coming into play to explain the improved reactivity and selectivity observed for substrates with smaller substituents in the asymmetric isomerization reaction. Using this model it is understandable that repulsive steric interactions may account for the absence of catalytic activity in the isomerization of tetrasubstituted and 2,3-disubstituted primary allylic alcohols, as well as in the isomerization of secondary allylic alcohols. The lower enantioselectivities observed for *Z*-configured allylic alcohols can be attributed to the orientation of either the phenyl substituent or the larger alkyl group in the south-western quadrant for aromatic primary allylic alcohols and 3,3-dialkyl primary allylic alcohols, respectively. Multinuclear mono- and bidimensional NMR analyses indicated that the structure of **3i** observed in the solid state remained nearly identical in solution. Both the cyclooctadiene twist and the manifestation of the *trans* influence are particularly visible in the ^{1}H and ^{13}C chemical shifts and the J_{CP} coupling constants (Table 4). The signals of the two carbon atoms in the coordination plane (C_a, C_c) and the signal of the two corresponding protons (H_a, H_c) are significantly deshielded with respect to the nuclei out of plane (C_b, C_d, H_b, H_d), thus reflecting the better electronic communication with the heteroatom located in the *trans* position. The average chemical shift differences are 1.13 and 1.29 ppm in the ^{1}H NMR spectrum, and 7.5 and 8.2 ppm in the $^{13}C\{^{1}H\}$ NMR spectrum. The better electronic communication is also emphasized by the greater $^{2}J_{CP}$ value for C_c (C_c: $^{2}J_{CP}=16.0$ Hz; C_d: $^{2}J_{CP}=8.2$ Hz). The *ortho* and *meta* protons of the anisyl substituent are equivalent, indicating rotation around the Csp^2–Csp^2 aryl–oxazoline bond on the timescale of the NMR experiment. The intense NOE contacts between H_d and the anisyl *ortho* protons, and between H_c and the proton at the stereogenic center, indicate the maximized stereochemical communication between the chiral oxazoline unit and the coordination site where the double bond of the primary allylic alcohol is expected to bind.

Conclusion

A new generation of well-defined chiral (P,N)-iridium catalysts for the asymmetric isomerization of primary allylic alcohols to aldehydes has been elaborated, based on the linear free energy relationship between steric parameters and enantiomeric ratios. Using a preceding ligand generation, the steric demand has been brought closer to the coordination sites where the reaction takes place by a formal homologation of the bridge linking the P and N donors. In terms of enantioselectivity, these new catalysts perform well for sterically biased and unbiased allylic alcohols, thus not only significantly expanding the substrate scope, but also validating the initial hypotheses. In addition, the detrimental competing *E*/*Z* isomerization of the substrate, a reaction that was assigned to weak steric interactions between the substrate and the catalyst, has been suppressed. In terms of reactivity, a parameter that could not be predicted using the Charton correlation, substrates having a small alkyl substituent are still obtained with unsatisfactory yields in some cases. A model in which steric and electronic effects are responsible for the high enantio-inductions measured in the asymmetric isomerization of primary allylic alcohols using these iridium catalysts has been proposed. Current investigations are underway to gain additional mechanistic insights into the isomerization reaction, and to develop more reactive catalysts, which further expand the scope of this transformation, in particular for *Z*-configured primary allylic alcohols.

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[27] If the conditions used for catalysts **1a** and **2a** are employed (5 mol%, 23 °C), the *ee* values reported in Tables 2 and 3 are virtually identical, but the yields are much lower. Therefore, it is still reasonable to compare the three generations of catalysts as represented in Figures 4 and 5.
[28] Crystals of suitable quality for X-ray analyses were grown using the PF_6 analogues of complexes (*R*)-**1b** and (*S*)-**3i**. CCDC-774476 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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[30] In agreement with our previous labeling experiments (see refs. [14] and [17]) and on the basis of the mechanism we propose, we believe these hydrides are exchanging rapidly in such species and hence the two isomers are interconverting at a faster rate than the rate-limiting migratory insertion.
[31] A phenyl substituent has two distinct Charton values (0.57 and 1.66). Consistent with our rationale, the phenyl group has a larger value than an Me (0.52) or an Et (0.56) substituent in any case. Nevertheless, the largest value is preferred for phenyl groups lying out of plane, as is presumably the case for the isomerization reaction studied herein.

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