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Steric Parameters in the Ir-Catalyzed Regio- and Diastereoselective Isomerization of Primary Allylic Alcohols

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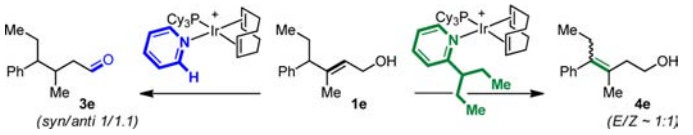
ABSTRACT



The iridium-catalyzed diastereo- and regioselective isomerization of primary allylic alcohols using Crabtree's catalyst or sterically modified analogs is reported. The importance of the size of the substituents on either the substrates or the catalysts has been rationalized by linear free energy relationships.

The systematic evaluation of the influence of electronic and steric parameters in the outcome of selective catalytic transformations is of prime importance, as it permits rationales and predictive models to be elaborated. Since the emergence of asymmetric catalysis in the late 1960s, such exercises have been regularly practiced.[1] Interestingly the main focus has been placed on enantioselective catalysis rather than diastereoselective catalysis.[2] Similarly, the quantification of electronic rather than steric parameters has often been favored. Recently, Sigman and co-workers have demonstrated that Charton and Sterimol parameters could be appropriately used in the context of enantioselective catalysis.[3,4] They convincingly established that the log of the enantiomeric ratio (*er*) of various asymmetric transformations can be correlated with descriptors of the size of the substituents of either the chiral ligands or the substrates. Noticeably, examples of such analysis for diastereoselective transformations are less common.[5]

As part of our program on the iridium-catalyzed enantioselective isomerization of primary allylic alcohols,[6−8] we have shown that excellent Linear Free Energy

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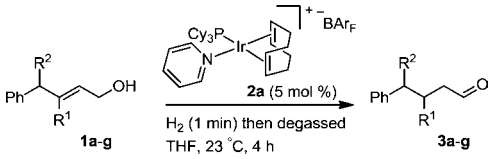
Relationships (LFER) could be obtained by correlating log(*er*) to the Charton values of the substrate substituent. This eventually led to the design of an improved generation of catalysts.[7d] As a direct continuation of this work we questioned whether LFER could also be elaborated for the diastereoselective isomerization of primary allylic alcohols with a vicinal stereocenter using achiral iridium catalysts. We anticipated that, if successful, such a correlation might certainly serve as a predictive tool in the design of complex molecules synthesis.

At the outset, because alkyl/alkyl and aryl/alkyl primary allylic alcohols behave differently in the enantioselective isomerization,[6] racemic substrates belonging to these two classes were synthesized. Starting from the appropriate α-substituted ketones, the geometrically pure (*E*) primary allylic alcohols **1a**–**c** (R^1 = Ph, R^2 = alkyl) and **1d**–**g** (R^1 = Me, R^2 = alkyl) were prepared in practical yields following a Horner–Wadsworth–Emmons olefination/selective reduction sequence (see Supporting Information (SI) for details). The seven substrates were then subjected to the standard isomerization protocol developed in our group using 5 mol % of the Crabtree catalyst **2a** (BAr_F as anion, activation by H_2 (1 min) followed by degassing). The products were systematically isolated in excellent yield, and the *dr*'s were measured by ^{1}H NMR spectroscopy. For the aryl/alkyl substrates **1a**–**c**, the LFER between log(*dr*) and the Charton steric parameter was satisfactory, though the *syn*/*anti* ratios were moderate across the series, with the *anti* isomer being always slightly favored (Table 1, entries 1–3 and Figure 1 (top)). For **1d**–**g**, from a modest 1/2.4 *syn*/*anti* ratio for **1d**, the selectivity increased to 30/1 in favor of the *syn* isomer for **1g** (Table 1, entries 4–7). Remarkably, an excellent linear correlation between log(*dr*) and the corresponding Charton values *ν* was obtained (Figure 1 (bottom)).[9,10]

To evaluate the potential influence of the ligand structure on the diastereoselectivity of the isomerization reaction, we prepared a series of Crabtree catalyst analogs using *ortho* substituted pyridyl derivatives (R = Me, *i*Pr, and $CHEt_2$) according to the one-pot protocol recently developed in our laboratory.[7f,11] Complexes **2b**–**d** were isolated as air-stable orange solids in excellent yields (72–97%). When 8-methyl-quinoline was employed, an unexpected monohydride complex **2e** was isolated in 89% yield after chromatography (Scheme 1). Its molecular

Table 1. Diastereoselective Isomerization of Primary Allylic Alcohols **1a**–**g**



entry[a]	1	R^1	R^2 (Charton value, *ν*)	yield[b] (%)	*dr*[c,d] (*syn*/*anti*)
1	**1a**	Ph	Me (0.52)	78	1/2.6
2	**1b**	Ph	Et (0.56)	89	1/2.3
3	**1c**	Ph	*n*Pr (0.68)	81	1/2.1
4	**1d**	Me	Me (0.52)	94	1/2.4
5	**1e**	Me	Et (0.56)	96	1./1.1
6	**1f**	Me	*i*Pr (0.76)	92	22/1
7	**1g**	Me	Cy (0.87)	94	30/1

[a] Average of two runs (0.1 mmol of **1a**–**g**). [b] Isolated yield of the corresponding alcohol after reduction. [c] Determined by ^{1}H NMR. [d] Relative configuration assigned by chemical correlation or by analogy.

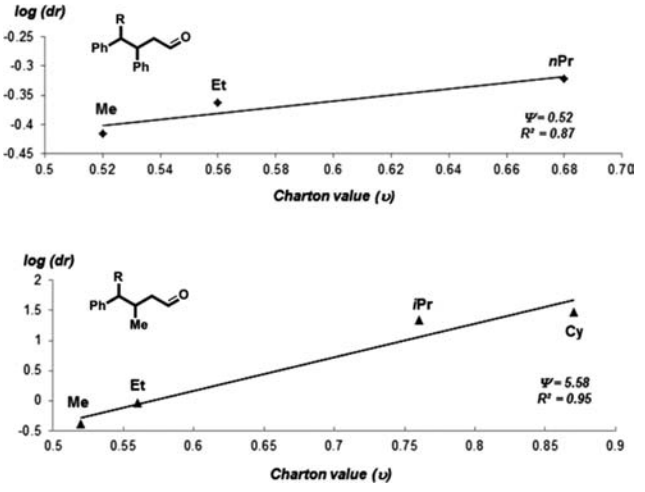


Figure 1. Charton plot for the diastereoselective isomerization of **1a**–**c** (top) and **1d**–**g** (bottom) with catalyst **2a**.

structure was unambiguously determined by ^{1}H, ^{31}P, ^{13}C, and 2D NMR spectroscopy (see SI). It is noteworthy that cyclometalation occurred by a C(sp^3)–H bond activation at room temperature.[12]

The diastereoselective isomerization of **1a** using these five precatalysts was investigated next. Whereas complex **2e** was found to be completely inactive using our activation protocol, **2b**–**d** all delivered quantitatively the desired aldehyde after 4 h at room temperature. Interestingly, the *syn*/*anti* ratio decreased gradually from 1/2.6 (**2a**) to 1/1.7 (**2d**) as the size of the *ortho* substituent of the pyridine ligand increased (Table 2).[13] This trend is particularly well visualized on the plot of log(*dr*) as a function of the Charton values as displayed in Figure 2 for which, again, an excellent correlation was obtained.[14]

(9) (a) Charton, M. *J. Am. Chem. Soc.* **1969**, *91*, 615. (b) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552. (c) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 3691. (d) Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 3694.

(10) Excellent correlations were also obtained using the Sterimol parameters. See Supporting Information.

(11) (a) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331. (b) Crabtree, R. H.; Gautier, A.; Giordano, G.; Kahn, T. *J. Organomet. Chem.* **1977**, *141*, 113. (c) Wüstenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174.

(12) Cyclometallated cationic iridium hydride complexes are not common and are usually the result of a C(sp^2)–H bond activation. For relevant examples, see: (a) Crabtree, R. H.; Lavin, M.; Bonneviot, L. *J. Am. Chem. Soc.* **1986**, *108*, 4032. (b) Patel, B. P.; Crabtree, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 13105. (c) Li, X.; Incarvito, C. D.; Crabtree, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 3698. (d) Esteruelas, M. A.; Fernandez-Alvarez, F. J.; Olivan, M.; Onate, E. *Organometallics* **2009**, *28*, 2276. (e) Song, G.; Su, Y.; Periana, R. A.; Crabtree, R. H.; Han, K.; Zhang, H.; Li, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 912.

Scheme 1. Synthesis of Crabtree Catalyst Analogs

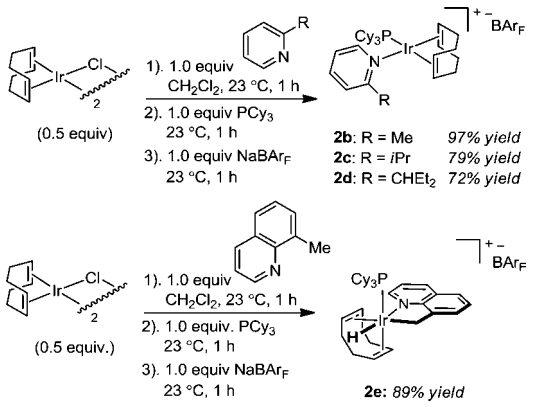
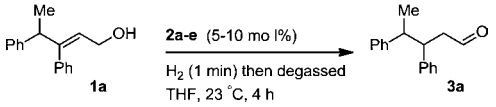


Table 2. Diastereoselective Isomerization of **1a** with Catalysts **2a**–**e**



entry[a]	**2**	loading (mol %)	R (Charton value, ν)	yield[b] (%)	*dr*[b] (*syn*/*anti*)
1	**2a**	5.0	H (0.52)	>99	1/2.6
2	**2b**	7.5	Me (0.56)	>99	1/2.3
3	**2c**	7.5	*i*Pr (0.76)	>99	1/1.9
4	**2d**	10.0	$CHEt_2$ (1.51)	>99	1/1.7
5	**2e**	7.5	–	*nr*[c]	*nd*[d]

[a] Average of two runs (0.1 mmol of **1a**). [b] Determined by ^{1}H NMR. [c] No reaction. [d] Not determined.

A strikingly different outcome was observed when the same study was performed using an alkyl/alkyl substrate such as **1e**. Whereas Crabtree catalyst **2a** delivered **3e** quantitatively after 4 h at room temperature (*syn*/*anti* = 1/1.1) (Table 3, entry 1), a mixture of aldehyde **3e** and of homoallylic alcohols **4e** (*E*/*Z* = 1:1) was obtained with the sterically more demanding catalysts **2b**–**d** (Table 3, entries 2–4). The homoallylic alcohols were always measured as the major products, the best regioselectivity being obtained with catalyst **2c** (**3e**/**4e** = 15/85; Table 3, entry 3).

To account for this observation, we propose that the *ortho* substituent of the pyridine ligand in **2b**–**d** might project toward the first coordination sphere of the metal center and prevent 2-point binding of the allylic alcohol, a necessary requirement for productive isomerization of the aldehyde (Figure 3).[6,7] In line with this hypothesis, when isomerization of **1e** by Crabtree catalyst **2a** was performed in the presence of controlled amounts of water (5–100 mol %, Table 3, entries 5–6), a *ca.* 80:20 mixture of aldehyde **3e** and homoallylic alcohol **4e** was measured.[15] Similar results were obtained when CH_3CN was used as additive (5 mol %, Table 3, entry 7), further suggesting that 2-point binding of the allylic alcohol might also be perturbed by competitive coordination of polar solvents.[16,17] Furthermore, the electronically disfavored insertion of iridium hydride in α styrenyl positions might account for the distinct regioselectivity observed for aryl/alkyl and alkyl/alkyl allylic alcohols.[18]

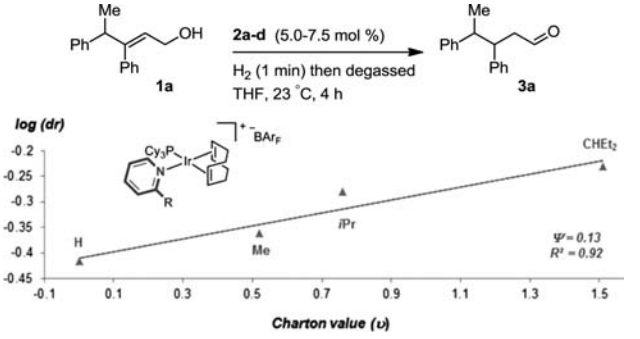
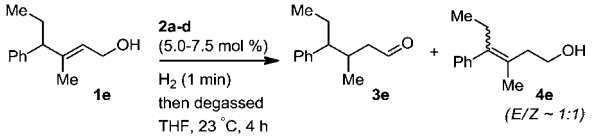


Figure 2. Charton plot for the diastereoselective isomerization of **1a** with catalysts **2a**–**d**.

Table 3. Regioselective Isomerization of **1e** into Aldehyde **3e** and Homoallylic Alcohol **4e**



entry[a]	**2**	loading (mol %)	additive	yield (%)[b]	**3e**/**4e**[b]
1	**2a**	5.0	–	>99	**100/0**
2	**2b**	7.5	–	>99	38/62
3	**2c**	7.5	–	>99	**15/85**(58)[c]
4	**2d**	7.5	–	>99	21/79
5	**2a**	5.0	H_2O (5 mol %)	>99	81/19
6	**2a**	5.0	H_2O (100 mol %)	>99	78/22
7	**2a**	5.0	CH_3CN (5 mol %)	97	69/31

[a] Average of two runs (0.1 mmol of **1e**). [b] Determined by ^{1}H NMR. [c] Isolated yield of **4e**.

(13) The catalyst loading was adjusted to achieve complete conversion of the starting material. The reduced catalytic activity for sterically demanding iridium complexes is in line with our previous results using chiral catalysts. See ref 7 for details.

(14) The $CHEt_2$ substituent has two Charton values: 1.28 and 1.51. The latter was used in this study, but correlation with the second value was equally good. See Supporting Information.

(15) Similar results were obtained if H_2O or CH_3CN were added prior or after activation of the iridium catalyst by molecular hydrogen.

(16) The effect of added water clearly indicates that the aged catalyst may result not only in lower performances but also in varying selectivity (if any). We indeed found that the iridium catalysts with the BAr_F anion are quite hygroscopic. Their performances are not altered with time if kept in a desiccator or a glovebox.

(17) Preliminary investigations showed that **1d** and **1f**–**g** behave similarly.

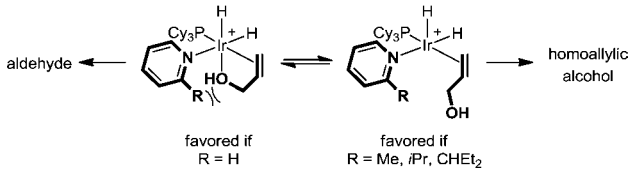
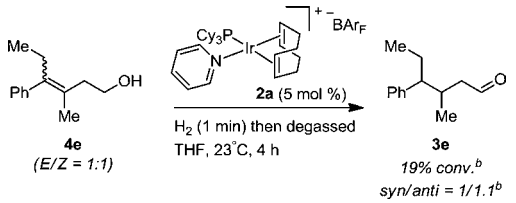


Figure 3. Plausible explanation for the switch in regioselectivity using bulkier analogs of Crabtree catalyst with alkyl/alkyl primary allylic alcohols.

Scheme 2. Isomerization of Homoallylic Alcohols **4e**[a]



[a] Average of two runs (0.1 mmol of **4e**). [b] Determined by ^{1}H NMR.

Finally, homoallylic alcohol **4e** was isolated as a 1/1 *E*/*Z* mixture and resubmitted to the standard isomerization conditions using Crabtree catalyst **2a** (Scheme 2). After 4 h at room temperature, aldehyde **3e** was obtained in only 19% yield (*syn*/*anti* = 1/1.1), clearly indicating that **4e** is not an intermediate in the isomerization of **1e** to **3e** but is rather produced by an independent catalytic manifold. Despite the low yield, this result is remarkable because the double bond in **4e** is tetrasubstituted and previous attempts to isomerize homoallylic alcohols with Crabtree catalyst were met with failure.[6−8]

In conclusion, we have shown that the diastereoselective isomerization of primary allylic alcohols can be quantified using steric descriptors for both the substrate substituents and the catalyst substituents. We also found that by using sterically demanding iridium catalysts with an alkyl/alkyl allylic alcohol the regioselectivity of the reaction can be switched toward the formation of homoallylic alcohols preferentially over the formation of aldehydes. Generalization of these observations and extension of this study to enantiopure substrates are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.