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# Mild Iridium-Catalysed Isomerization of Epoxides. Computational Insights and Application to the Synthesis of β-Alkyl Amines

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**Abstract.** The isomerization of epoxides to aldehydes using the readily available Crabtree's reagent is described. The aldehydes were transformed into synthetically useful amines by a one-pot reductive amination using pyrrolidine as imine-formation catalyst. The reactions worked with low catalyst loadings in very mild conditions. The procedure is operationally simple and tolerates a wide range of functional groups. A DFT study of its mechanism is presented showing that the isomerization takes place via an iridium hydride mechanism with a low energy barrier, in agreement with the mild reaction conditions.

**Keywords:** iridium; epoxides; isomerization; Crabtree's catalyst; β-alkyl amines.

Epoxides can be interconverted into a variety of functional groups and are thus valuable synthetic intermediates.[1] The high reactivity of the strained 3-membered ring of epoxides commonly enables a wide range of stereospecific nucleophilic ring opening reactions.[2] The isomerization into the corresponding carbonyl analogs is usually referred to as the Meinwald rearrangement.[3] Due to its excellent efficiency and atom economy, this reaction has gained relevance for the synthesis of carbonyl compounds,[4a] ring expansion reactions,[4b,c] and tandem processes.[4d,e] The Lewis acid-promoted Meinwald rearrangement has found application in fine chemistry and industrial processes.[4] However, the regiochemical outcome is a common issue since it depends on the promoter and the migratory capacity of the substituents.[5] The use of stoichiometric amounts of Lewis acids such as $BF_3{\cdot}Et_2O$,[6] lithium salts[7] and magnesium bromide[8] are the most widely used conditions. The catalytic version using copper salts,[9] indium chloride[10] or iridium chloride[11] has also been described. However, a number of limitations, namely moderate product selectivity, high temperature and catalyst loading, and toxicity of the catalysts, remain to be addressed when employing catalytic conditions.

In recent years, other alternative procedures have been reported such as the use of metal-free self-assembled organic supramolecular capsules[12] or heterogeneous mesoporous aluminosilicate materials.[13] In the organometallic field, Mazet and co-workers reported the most relevant breakthrough using novel palladium[14] and iridium[15] catalysts. However, high temperatures (85-140°C and 100°C respectively) were needed in both cases.

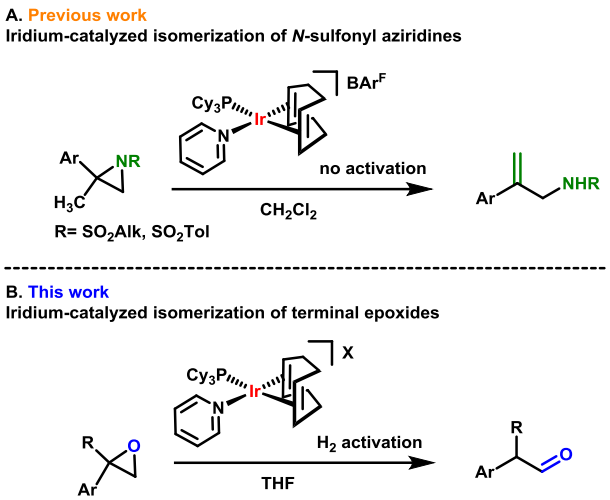
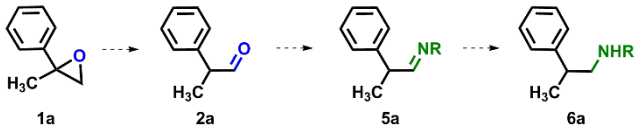



**Figure 1.** Crabtree's catalyst in isomerization reactions.

We recently reported that the readily available Crabtree's reagent[16] is an efficient catalyst for the isomerization of *N*-sulfonyl aziridines into allyl amines (Fig. 1A).[17] Encouraged by this result we envisioned that this catalyst could also be used in the isomerization of epoxides. We found that, after activation,[18] Crabtree's catalyst isomerized terminal epoxides into aldehydes (Figure 1B). One of the drawbacks of this transformation was the handling of the resulting aldehydes. Therefore, we set up a one-pot reductive amination procedure using primary amines to isolate stable, easy to handle amines.

Here, we describe the isomerization of terminal epoxides into aldehydes using Crabtree's catalyst (Figure 1B), followed by the reductive amination of the *in situ* formed aldimines to afford synthetically useful amines (Scheme 1). Our one-pot procedure gave excellent selectivity. The resulting amines, containing an alkyl group in the β position, are important motifs in numerous drugs and biologically active compounds.[19]



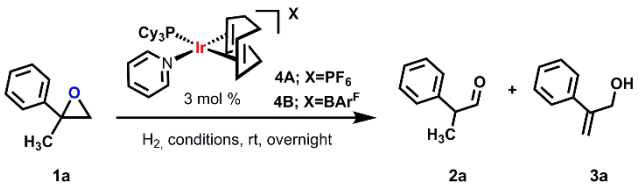

**Scheme 1.** One-pot procedure of the Meinwald rearrangement and reductive amination.

2-Methyl-2-phenyloxirane **1a**, easily synthesized by the Corey-Chaykosvky reaction,[20] was selected as model substrate. Isomerization of **1a** can, *a priori*, afford aldehyde **2a** or allylic alcohol **3a** (Table 1). We first tested Crabtree's catalyst (**4A**) in 1 mol %, without activation in dichloromethane. After 17 h, only 35% of conversion was detected by $^1$H NMR (Table 1, entry 1). Aldehyde was selectively formed as the major product. We then activated the catalyst with $H_2$, to form a putative dihydride species.[21] Overnight stirring at room temperature increased the conversion up to 68% (Table 1, entry 2). Gratifyingly, the aldehyde was not affected by the presence of $H_2$. Therefore, we increased the catalyst loading up to 3 mol %. The reaction went to completion after 17 h, and an aldehyde/alcohol ratio of 80:20 was achieved (Table 1, entry 3). We then performed a solvent screening. Diethyl ether or toluene did not improve the results (Table 1, entries 4 and 5). This result could be explained by the low solubility of Crabtree's catalyst in these organic solvents. Therefore, we replaced $PF_6$ by $BAr^F$ as counter ion. Using the Pfaltz's version of Crabtree's catalyst (**4B**)[22] in toluene we were pleased to see that full conversion was achieved after 17 h and with a slight improvement in selectivity (Table 1, entry 6). Finally, using either activated catalyst **4A** or **4B** in THF the reaction was complete after overnight stirring at room temperature reaching a selectivity of 93:7. Of note the selectivity in THF was similar in both cases (Table 1, entries 7 and 8). Since the hydrogen is only necessary to activate the catalyst the pressure is not important. We used 3 bars as standard procedure but the reaction can be done using hydrogen at atmospheric pressure (balloon). Purging the vessel to degas $H_2$ once the catalytic active species was formed did not affect neither the reactivity nor the selectivity (Table 1, entry 9).

Once the optimal conditions for the isomerization reaction had been determined, we proceeded to study the reductive amination. Otte and co-workers pioneered a tandem Meinwald rearrangement-reductive amination using $B(C_6F_5)_3$[23] However, the scope of the amine was limited to anilines.

We reasoned that benzhydrylamine would be a convenient amine since it can be considered a synthetic equivalent of ammonia due to its easy hydrogenolysis. Therefore, we devised a two-step procedure that could be done *in situ*. To avoid the use of reagents such as $TiCl_4$ or $Ti(iPrO)_4$, which are usually required for imine formation and could interfere with our catalyst of choice we selected the aminocatalytic procedure developed by Cid and co-workers.[24] The addition of 10 mol % of pyrrolidine led to the formation of the aldimine of benzhydrylamine **5a** with total conversion after 2 h. With the optimal conditions for the imine formation in hand, we sought a reducing agent. Since the reduction could not be performed by hydrogen due to deactivation of iridium catalyst by the amine, we tested sodium cyanoborohydride (Table 2, entry 1). Conversion after 2 h was low, so we then tested a stronger reductant, $NaBH_4$, and added MeOH to the mixture. Under these conditions the reaction went to completion and amine **6a** was afforded in an isolated yield of 67 % (Table 2, entry 2). The optimized protocol was scaled up to 1g of epoxide using only 1 mol % of iridium catalyst **4B**, yielding a remarkable 51% overall yield for the three steps.

**Table 1.** Optimization of the isomerization reaction.

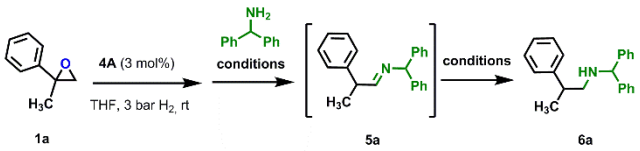



| Entry | Cat. | Solvent | Conv. | Yield 2a (%)[a] (ratio 2a:3a) |
|---|---|---|---|---|
| 1 [b] [c] | **A** | $CH_2Cl_2$ | 35% | - |
| 2 [b] | **A** | $CH_2Cl_2$ | 68% | - |
| 3 | **A** | $CH_2Cl_2$ | >99 | 75 (80:20) |
| 4 | **A** | $Et_2O$ | 30% | - |
| 5 | **A** | Toluene | 33% | - |
| 6 | **B** | Toluene | >99 | 79 (86:14) |
| 7 | **A** | THF | >99 | 85 (94:6) |
| 8 | **B** | THF | >99 | 84 (93:7) |
| 9 [d] | **A** | THF | >99 | 84 (94:6) |

Reactions were performed in a pressure tube, at room temperature and stirring overnight. The catalyst (3 mol %) and substrate were weighted, brought to a dry box, dissolved in anhydrous solvent and charged with hydrogen. [a] NMR yield using 1,4-dimethoxybenzene as internal standard.

A small percentage of diol was observed in case of air moisture. [b] 1 mol % of catalyst was used. [c] Without external activation. [d] $H_2$ for 1 minute; then degas.

**Table 2.** Optimization of the reductive amination.




| entry | Conditions | Conversion[a] (3-step yield)[b] |
|---|---|---|
| 1 | 1) pyrrolidine (10 mol%) 2) $NaBH_3CN$ in THF, 2h | **6a**: 70% (54%) |
| 2 | 1) pyrrolidine (10 mol%) 2) $NaBH_4$ in MeOH, 2h | **6a**: 100% (67%;51%[c]) |

[a] Detected by $^1$H NMR. [b] Isolated yield. [c] Isolated yield in gram scale, using 1 mol% of catalyst **4B**.

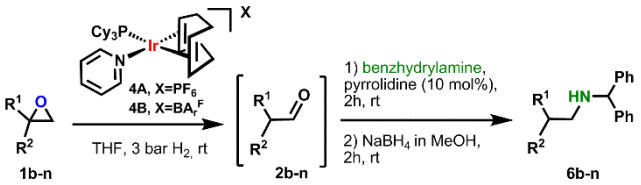
We then proceeded to study the scope of the reaction. To this end, a set of 13 2,2-disubstituted epoxides (**1b-n**) were tested (Table 3). The substituent pattern slightly altered the optimal conditions found for the isomerization reaction. We observed that the use of electron-withdrawing substituents was well tolerated.

Amine **6b** derived from 2-(4-fluorophenyl)-2-methyloxirane **1b** was obtained with an overall yield of 57 % (Table 3, entry 1). The isomerization reaction starting from the *p*-chlorophenyl oxirane **1b** (Table 3, entry 2), took place in only 2 h and the corresponding amine **6c** was obtained in 67 % isolated yield. In the case of *p*-Br and *p*-I derivatives **1d-e** the reaction lasted longer (48 h). However, this drawback could be solved by modifying the counter ion from $PF_6$ to $BAr^F$. In these cases, the reaction times were reduced to 12 h and the alcoholic species were minimized. After the reductive amination procedure, the resulting amines **6d-e** were obtained in synthetically useful yields (63-74 %)(Table 3, entries 3-4).

We then studied the effect of electron-donating groups (methyl and methoxy) in *ortho* or *para*-position of the aromatic ring. Using the optimized conditions, all reactions were completed after 12 h (Table 3, entries 6-8) with the exception of the *ortho*-methyl compound **1f** which due to steric hindrance, lasted 48 h (Table 3, entry 5). The ratio of alcoholic species formed were minimal in all cases, thus demonstrating the high selectivity of this transformation. The 2-naphthy substituent **1j** afforded the corresponding amine **6j** in 62 % yield (Table 3, entry 9) using standard conditions. To prove the versatility of this reaction, the methyl group was also modified. When using an ethyl substituent, the amine **6k** was afforded in 70 % yield and no alcoholic species were detected after the isomerization reaction (Table 3, entry 10).

For the branched alkyl substituent, catalyst **4B** was necessary for completion of the reaction. The isomerization reaction showed excellent selectivity towards the aldehyde and **6l** and **6m** were afforded in 57 % and 75 % yield, respectively (Table 3, entries 11-12). Finally, as an example of dialkyl epoxide, the phenethyl oxirane **1n** was also studied. In this regard, when using 5 mol % of **4B**, the reaction went to completion after 12 h with only few traces of alcohol species and afforded the corresponding amine **6n** in 79% yield (Table 3, entry 13).

**Table 3.** Epoxide scope of the reaction. All reactions were performed in a pressure tube. Ratio **2:3** is the selectivity towards the aldehyde when the isomerization reaction is finished, measured by $^1$H NMR..



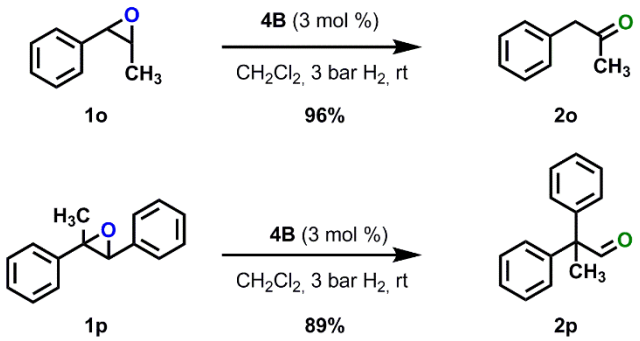

| entry | 1 | $R^1$ | $R^2$ | cat. Time[b] | ratio 2:3 | Yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **1b** | *p*-F-Ph | Me | **4A;** 17 h | 94:6 | 57 |
| 2 | **1c** | *p*-Cl-Ph | Me | **4A;** 2h | 95:5 | 67 |
| 3 | **1d** | *p*-Br-Ph | Me | **4B;** 12h | >99 | 74 |
| 4 | **1e** | *p*-I-Ph | Me | **4B;** 12h | 92:8 | 63 |
| 5 | **1f** | *o*-Me-Ph | Me | **4A:** 48h | 97:3 | 80 |
| 6 | **1g** | *p*-Me-Ph | Me | **4A;** 12h | 94:6 | 45 |
| 7 | **1h** | *o*-MeO-Ph | Me | **4A;** 12h | 98:2 | 71 |
| 8 | **1i** | *p*-MeO-Ph | Me | **4A;** 12h | >99 | 45 |
| 9 | **1j** | 2-Naphth | Me | **4A;** 12h | 91:9 | 62 |
| 10 | **1k** | Ph | Et | **4A;** 12h | >99 | 70 |
| 11 | **1l** | Ph | iPr | **4B;** 3h | >99 | 57 |
| 12 | **1m** | Ph | Cy | **4B;** 12h | >99 | 75 |
| 13[a] | **1n** | $PhCH_2CH_2$ | Me | **4B;** 12h | 98:2 | 79 |

[a] 5 mol % of catalyst **4B** was used. [b]Isomerization time. [c] Overall isolated yields.

The benzhydrylamine moiety can be easily removed by hydrogenolysis to afford free amines that can be further derivatized (See ESI†).

The isomerization reaction also took place in epoxides with different substitution patterns. Using 1 mol % of **4B** in dichloromethane, 2-methyl-3-phenyloxirane **1o** isomerized to methyl ketone **2o** in excellent yield

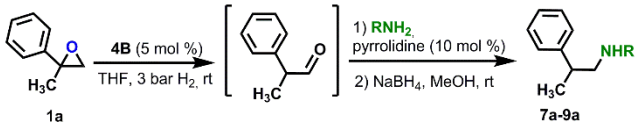
(Scheme 2). In the case of trisubstituted epoxide **1p**, instead of hydride migration we observed phenyl migration yielding aldehyde **2p** as a single product (89% isolated yield). Again, the hydrogen pressure did not affect the reaction. 2,2-Diaryloxiranes are extremely reactive. 2-(4-Chlorophenyl)-2-phenyloxirane (**1q**) gave 30% yield of the corresponding aldehyde (**2q**), along with 65% of demethylenation product in only 2 h of reaction and using 1 mol % of **4A** (See ESI†)




**Scheme 2.** Iridium-catalyzed isomerization of 1,2-di- and tri-substituted epoxides.

On the other hand, the amine scope could also be expanded. *p*-Methoxyaniline (Table 4, entry 1), benzylamine (Table 4, entry 2) and enantiomerically pure *(R)*-(+)-1-phenylethan-1-amine (Table 4, entry 3) were successfully tested with synthetically useful yields. In the latter example, the separation of the two diastereoisomers enabled the formation of enantioenriched amines after hydrogenolysis (See ESI†).

**Table 4.** Amine scope of the reaction. Reactions were performed in a pressure tube, using **4B** (5 mol %) as catalyst and 1.1 equiv. of amine.

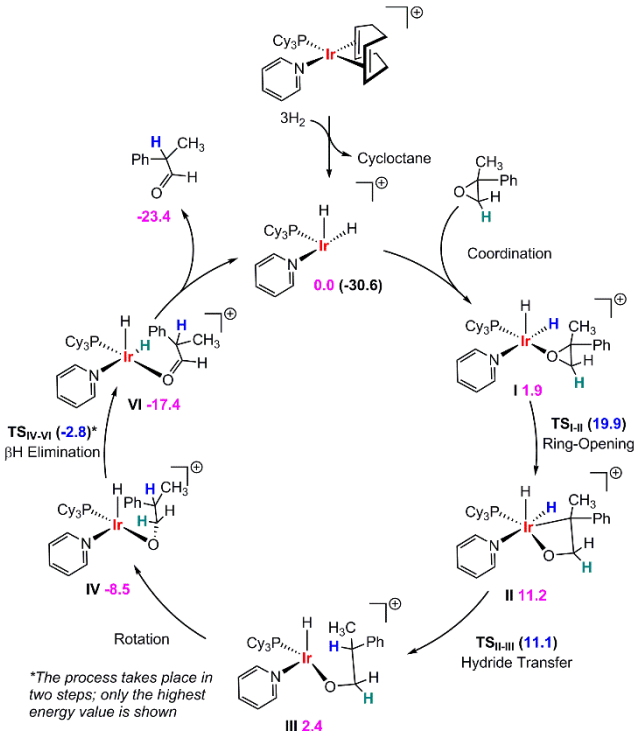



| entry | amine | Yield (%)[a] |
|---|---|---|
| 1 | *p*-OMe-aniline | **7a,** 64% |
| 2 | Benzylamine | **8a,** 55% |
| 3 | *(R)*-(+)-1-Phenylethylamine | **9a,** 56% (3:2 dr) |

[a] Isolated yields.

To gain a thorough understanding of the isomerization step, we performed a DFT study of its reaction mechanism using the B3LYP-D3[25] functional and a continuum model of the THF solvent[26] (see ESI† for details). We initially studied the activation of the Crabtree's catalyst, entailing hydrogenation of the COD ligand and cyclooctane release and formation of the unsaturated dihydride complex. This step is very exergonic ($\Delta G$= -30.6 kcal·mol$^{-1}$) and generates the catalytic active specie $[Ir^{III}(H)_2(py)(PCy_3)]^+$ in a octahedral arrangement with two vacancies. Several possible isomers were evaluated for this species, concluding that the most stable configurations are those with the H and $PCy_3$ ligands mutually *cis* and the second hydride in the axial position. An isomer with the hydride *trans* to the phosphine ligand was found *ca.* 17.0 kcal·mol$^{-1}$ above. The equatorial hydride can be coordinated *trans* a vacancy or *trans* pyridine with very similar energies ($\Delta G$ of 1.1 kcal·mol$^{-1}$) and easy interconversion (Gibbs energy barrier 9.0 kcal·mol$^{-1}$) highlighting a fast equilibrium between these two relative orientations (Scheme SI1 of the ESI†). Between them, the species with H *trans* pyridine can better accommodate the incoming substrate and has been taken as the catalytic configuration.

The O-coordination of **1a** at the empty equatorial position generates intermediate **I** at 1.9 kcal·mol$^{-1}$ and gives rise to the catalytic cycle depicted in Scheme 3.




**Scheme 3.** DFT computed mechanism (B3LYP-D3 in THF) for the Ir-catalysed isomerization of epoxide **1a** to aldehyde **2a**. Relative Gibbs energies (in purple) in kcal·mol$^{-1}$ are referred to the separated catalytically active species $[Ir^{III}(H)_2(py)(PCy_3)]^+$ and substrate **1a**; transition state energies are shown in parenthesis and blue.

The associated Gibbs energy profile can be found at ESI† (Figure SI1). Subsequent concerted ring-opening and C-coordination leads to the formation of a five-member ring metallacycle, **II**, with a relative energy of 11.2 kcal·mol$^{-1}$, overcoming an energy barrier of 19.9 kcal·mol$^{-1}$, $\mathbf{TS_{I\text{-}II}}$ (Figure 2a). This transition state is the highest point in the Gibbs energy profile, making the ring-opening step the rate-determining step. Intermediate **II** is a highly distorted octahedron with the oxygen in the axial position and the equatorial hydride close to the β-carbon of **1a** ($C_\beta \cdots$HIr 2.219 Å). From this intermediate an easy hydride insertion to the γ-carbon-Ir bond opens the metallacycle leading to

Intermediate **III**, falling at 2.4 kcal·mol$^{-1}$. This is practically a barrierless process with its transition sate (**TS$_{II-III}$**, Figure 2b) at the same energy (11.1 kcal·mol$^{-1}$) than intermediate **II.** According to this mechanism the reaction should proceed with retention of configuration. This was confirmed experimentally. Starting from enantiomerically pure **(*R*)-1a**, enantiomerically enriched **(*S*)-2a** was obtained, albeit with low ee (26% ee) due to substantial racemization of the aldehyde in the reaction conditions (See ESI†) [27]

To complete the isomerization, a hydrogen from the substrate must end up at the metal. Consequently, β-hydride elimination is the last step of the isomerization process. Previously, substrate reorientation in intermediate **III** is required to place the β H near to the vacant equatorial position at iridium. The rotation process occurs barrierless and leads to the more stable conformation of intermediate **IV** at -8.5 kcal·mol$^{-1}$ (βH···Ir 2.927 Å). β-hydride elimination from intermediate **IV** is a two-step process in which, first a strong βH-Ir agostic interaction takes place (βH···Ir 1.736 Å, **V,** -7.0 kcal·mol$^{-1}$), followed by the β-H-C elimination, with relative Gibbs energies of -2.8 and -6.3 kcal·mol$^{-1}$ for **TS$_{IV-V}$** and **TS$_{V-VI}$,** respectively (Figures 2c and 2d). Finally, from intermediate **VI** (-17.4 kcal·mol$^{-1}$) the replacement of the aldehyde by a reactant molecule closes the catalytic cycle.

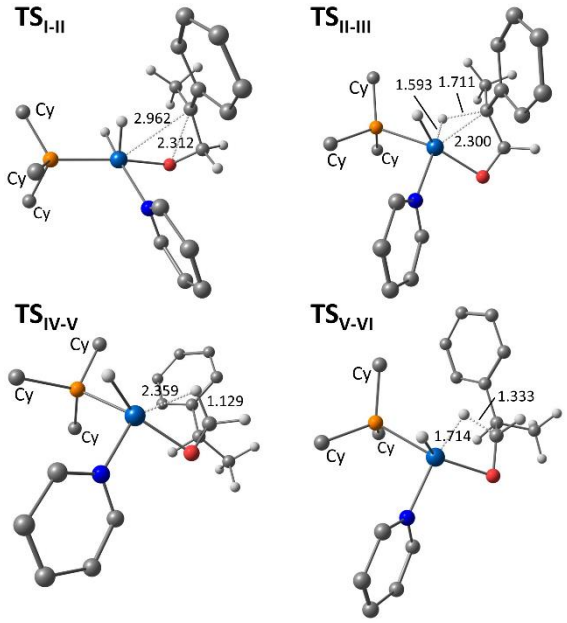



**Figure 2**. Transition state optimised geometries for: ring opening, **TS$_{I-II}$**; hydride transfer, **TS$_{II-III}$**; (C$_β$-H)-Ir agostic formation, **TS$_{IV-V}$**; β-H elimination, **TS$_{V-VI}$**. The most important distances are also reported in Å. Hydrogen atoms and cyclohexyl (Cy) groups have been omitted for clarity.

The general reaction sequence we have computed is equivalent to the mechanism proposed by Mazet and co-workers for the Pd-hydride catalyzed isomerization of epoxides to aldehydes.[14] Initially the metal breaks the epoxide ring and then successive hydride migration to the γ-carbon and β hydride elimination yields the aldehyde. Despite this general mechanistic similarity, some differences arise between the palladium and iridium hydride-catalysed epoxide isomerization. First, ring-opening of the epoxide is notably easier in presence of the iridium catalyst (Gibbs energy barriers in THF of 24.0 and 19.9 kcal mol$^{-1}$ for the Pd and Ir complexes, [14,15] respectively). This behaviour can be related to the highly unsaturated nature of the Ir-catalyst, which has two vacant sites. This feature also allows the stabilization of a metallocycle intermediate (**II**) absent in the palladium system. Correspondingly, the overall barrier for the isomerization is lower for the Ir-catalyst than for Pd (19.9 *vs.* 26.4 kcal mol$^{-1}$) in agreement with the milder conditions at which the reaction takes place (room temperature, see Tables 1 and 3).

In conclusion, the selective isomerization of terminal epoxides to aldehydes has been accomplished using low catalyst loadings (up to 1 mol%) of the readily available Crabtree's reagent. The pre-catalyst requires activation with hydrogen but there is no need to degas the vessel afterwards. The reaction occurs under milder conditions than in previous reports were high temperatures were required. DFT calculations reveal that the isomerization takes place via a hydride mechanism similar to that described for a palladium hydride complex,[14] but with a considerably lower barrier, in agreement with the milder reaction conditions (room temperature). The reductive amination of the resulting aldehydes can be performed *in situ*. We have optimised a one-pot protocol based on the imine formation catalysed by pyrrolidine followed by reduction with $NaBH_4$. Using benzhydrylamine, up to 14 amines have been synthesized in good to excellent yields. The reaction can be easily scaled up. Other aryl or alkyl amines –including chiral ones- have been successfully used.

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# Mild Iridium-Catalysed Isomerization of Epoxides. Computational Insights and Application to the Synthesis of β-Alkyl Amines

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