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Enantioselective Synthesis of β-Methyl Amines *via* Iridium-Catalyzed Asymmetric Hydrogenation of *N*-Sulfonyl Allyl Amines

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Abstract. The iridium-catalyzed asymmetric hydrogenation of several *N*-sulfonyl allyl amines is reported. All substrates can be easily obtained by the Ir-catalyzed isomerization of *N*-tosylaziridines reported previously. The commercially available threonine-derived phosphinite (UbaPHOX) iridium complex has been found to be the best catalyst for this catalytic application, affording β-methyl amines with good to excellent ee values (up to 94%). The synthetic potential of this novel methodology was demonstrated by the formal synthesis of Lorcaserin and LY-404187.

Keywords: iridium complexes; asymmetric catalysis; hydrogenation; β-alkyl amines; Drug synthesis; Chiral P,N-ligands

Chiral amines are key structural features in natural products and fine chemicals.[1,2] Amines bearing a β-methyl stereogenic center are present in numerous bioactive compounds and pharmaceuticals.[3-5] Several examples of this type of drugs are shown in Figure 1. For example, Lorcaserin is a marketed anorectic for which a synthesis based on asymmetric hydrogenation have not been described to date.[3] Biarylpropylsulfonamides such as LY-404187 are potent positive allosteric modulators of 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)-propanoic acid (AMPA) receptors.[4] NPS-1392 is a potent stereoselective antagonist of the NMDA receptor.[5]

The asymmetric hydrogenation is one of the most important catalytic reactions in the preparation of pharmaceuticals due to its atom economy, low environmental impact and operational simplicity.[6] Ru or Rh catalysts, which usually bear chiral phosphines, can induce high enantioselectivity on substrates functionalized with a coordinating group.[7] However, when facing minimally functionalized olefins, these catalysts commonly show low reactivity and asymmetric induction. Conversely, Ir complexes bearing chiral P,N-ligands[8] can be used in the hydrogenation of poorly coordinative alkenes. Although several minimally functionalized olefins have been enantioselectively hydrogenated with Ir complexes,[9] the range of substrates available is still limited. In this context, reports of the asymmetric synthesis of β-methyl amines from 2-aryl allylamines are scarce. Zhang and co-workers developed a highly enantioselective method for the synthesis of β-methyl phthalimides based on the asymmetric hydrogenation of 2-alkyl allylphthalimides using a Ru-C_3-tunephos catalyst.[10] However, hydrogenation of the only example of 2-aryl allylphthalimide described in the paper took place with low enantiomeric excess (55% ee). The hydrogenation of *N*-acetamido 2-phenyl allylamine using a cationic Ru complex bearing the axially chiral ligand (-)-TMBTP gave an ee of 80%.[11] However, in this case, the hydrogenation occurred after partial isomerization to the enamide. Therefore, to the best of our knowledge, there are no precedents of Ir-catalyzed asymmetric hydrogenation of *N*-sulfonyl 2-aryl allylamines.

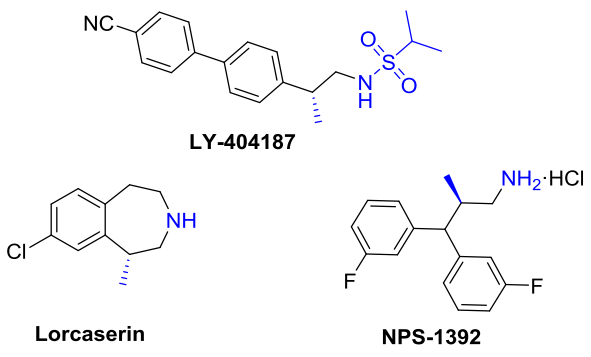
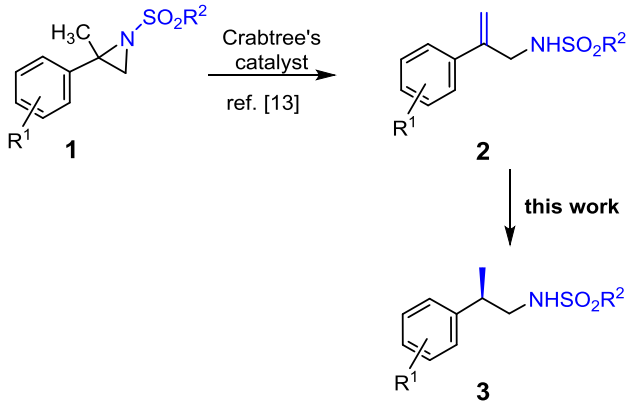


Figure 1. Examples of pharmaceutically active chiral β-methyl amines.

In theory, all compounds shown in Figure 1 can be prepared by asymmetric hydrogenation of a suitable allyl amine. However, the absence of appropriate methodologies might be explained by the lack of easy preparation procedures for 2-aryl allylamines. Our group recently uncovered a new isomerization reaction that provides *N*-sulfonyl 2-aryl allylamines **2** from *N*-sulfonyl aziridines **1** (Scheme 1).[12] The isomerization is catalyzed by the readily available Crabtree catalyst and takes place with low catalyst loading, high selectivity and mild reaction conditions.

Herein, we report the Ir-catalyzed asymmetric hydrogenation of *N*-sulfonyl allylic amines **2** to chiral β-methyl amines **3** (Scheme 1; 16 examples). The commercial iridium-UbaPhox catalyst[13] developed by Pfaltz gave complete conversions and good to excellent enantioselectivities. The high functional group tolerance and the mild conditions employed in this novel catalytic process are remarkable. To showcase the applicability of this new enantioselective methodology, the asymmetric synthesis of several biologically active compounds is also described.

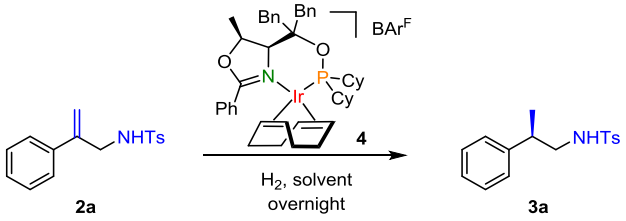


Scheme. 1. Synthetic approach to chiral β-methylamines

Our studies first began with the asymmetric hydrogenation of **2a**, which was chosen as model substrate (Table 1). This compound was easily obtained by isomerization of the corresponding *N*-tosyl aziridine which, in turn was prepared from 1-methylstyrene. With **2a** in hand, several Rh- and Ir-catalysts were tested for their asymmetric hydrogenation. However, the best results were obtained using [((4*S*,5*S*)-Cy2-Ubaphox)Ir(COD)] BAr^F (**4**), the threonine-based Ir-P,N catalysts developed by Pfaltz.[13] The optimization of the reaction conditions is shown in Table 1. Methanol gave low conversion (Table 1, entry 1). Ethers such as THF, dioxane and diethyl ether gave complete conversions but moderate ee values (Table 1, entries 2-4). Ethyl acetate and dichloromethane gave better results, but dichloroethane (DCE) (Table 1, entry 7,) emerged as the best solvent for the reaction, with full conversion and 93% ee. A decrease in the temperature of the reaction (Table 1, entry 8) or an increase of hydrogen pressure (Table 1, entry 9) had a small effect in the asymmetric induction. Finally, the reaction was achieved with 1 mol % of catalyst loading and 1 bar of hydrogen (Table 1, entry 10). Under these conditions the reaction reached completion in only 3 h.

We also tested the one pot procedure treating aziridine **1a** with hydrogen (1-50 bar) in the presence of catalyst **4** (see SI). Although the *N*-tosyl 2-phenylpropanamine **3a** was obtained cleanly, the maximum enantiomeric excess that we could obtain was 83% ee. We believe that this was due to the uncomplete selectivity of the isomerization reaction. The presence of 3-7% of racemic imine drops the enantioselectivity of the overall reaction.

Table 1. Solvent screening and optimization of the asymmetric hydrogenation of *N*-tosyl 2-phenyl allylamine **2a**.[a]



Entry	Catalyst (mol %)	Solvent	P, T	Conv. (%)[b]	ee (%)[c]
1	5	MeOH	1 bar, rt	30	75 (*R*)
2	5	THF	1 bar, rt	>99	82 (*R*)
3	5	dioxane	1 bar, rt	>99	76 (*R*)
4	5	Et_2O	1 bar, rt	>99	74 (*R*)
5	5	EtOAc	1 bar, rt	>99	83 (*R*)
6	5	CH_2Cl_2	1 bar, rt	>99	88 (*R*)
7	5	DCE	1 bar, rt	>99	93 (*R*)
8	5	DCE	1 bar, 0ºC	>99	93 (*R*)
9	5	DCE	50 bar, rt	>99	91 (*R*)
10[d]	1	DCE	1 bar, rt	>99	93 (*R*)

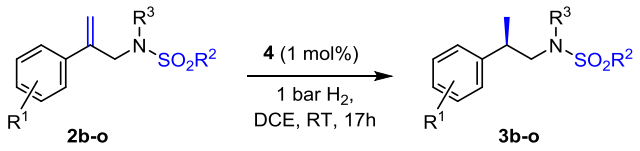
[a] See Supporting Information for experimental details. Reactions were run in a pressure reactor at 1 bar of H_2 pressure. [b] Conversion was measured by ^1H NMR. [c] Enantiomeric excess was determined by chiral HPLC. [d] The reaction was completed after 3 h.

To determine the scope of the reaction, we next applied these optimal conditions to a range of *N*-sulfonyl allylic amines. Up to 15 *N*-sulfonyl allylic amines were tested showing excellent reactivity and affording the chiral amines in high conversions and with good to excellent ee values (Table 2). We assumed that all products had *R* configuration by analogy with **3a**. The absolute configuration of **3a** had been stablished by derivatization of ethyl (*R*)-2-phenylpropanoate.[14] In all cases, except **2d-e,** the sign of the rotation matched with **3a**. We believe that in all cases the sense of the induction is the same. Substrates

presenting substituents in *ortho* position (Table 2, entries 3 and 6) and naphthalene (Table 2, entry 5) required an increase in catalyst loading (2 mol %) to assure full conversion. This novel catalytic transformation demonstrated high functional group tolerance when modifying the electronic character (electron-donor and electron-withdrawing substituents) in the aryl group. The sulfonyl group was also modified and we were pleased to see that when replacing the tosyl group by a methyl or isopropyl group, full conversion and excellent ee's were also achieved (Table 2, entries 10, 11, 12 and 13). Finally, *N*-methyl, *N*-sulfonyl allylic amines **2o** and **2p** were also hydrogenated affording the corresponding chiral amines with 94% of enantiomeric excess in both cases (Table 2, entries 14 and 15).

To check if the hydrogenation takes place after isomerization to the corresponding enamide, labeling studies were conducted. Allyl amine **2a** was hydrogenated with 1 bar of D_2 and 1 mol % of **4** in DCE. NMR analysis showed that the deuterium atoms were exclusively found at the methyl and benzylic positions. Therefore, the possible isomerization previous to hydrogenation was ruled out (see SI).

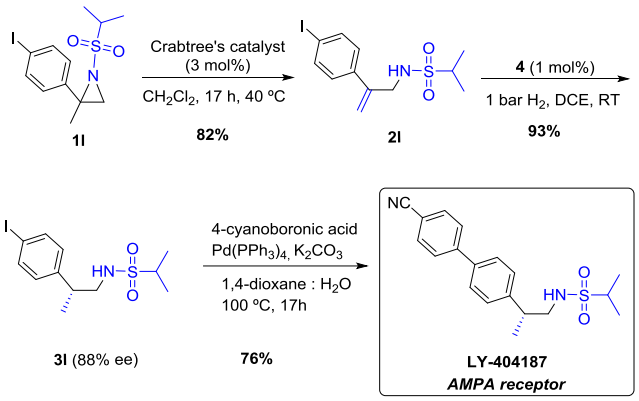
Table 2. Scope of Asymmetric Hydrogenation of *N*-Sulfonyl Allyl Amines



Entry		R^1	R^2	R^2	Conv. (%)[b]	ee (%)[c]
1	**2b**	*p*-Cl	*p*-tolyl	H	>99	85
2	**2c**	*m*-Cl	*p*-tolyl	H	>99	89
3[d]	**2d**	*o*-Cl	*p*-tolyl	H	>99	82
4	**2e**	*p*-Me	*p*-tolyl	H	>99	92
5[d]	**2f**	2-naphthyl	*p*-tolyl	H	>99	88
6[d]	**2g**	*o*-OMe	*p*-tolyl	H	>99	92
7	**2h**	p-F	*p*-tolyl	H	>99	91
8	**2i**	m-F	*p*-tolyl	H	>99	92
9	**2j**	*p*-CF_3	*p*-tolyl	H	>99	82
10	**2k**	*p*-Br	*i*Pr	H	>99	87
11	**2l**	*p*-I	*i*Pr	H	>99	88
12	**2m**	H	Me	H	>99	92
13	**2n**	*p*-*i*Bu	Me	H	>99	91
14	**2o**	H	Me	Me	>99	94
15	**2p**	H	*p*-tolyl	Me	>99	94

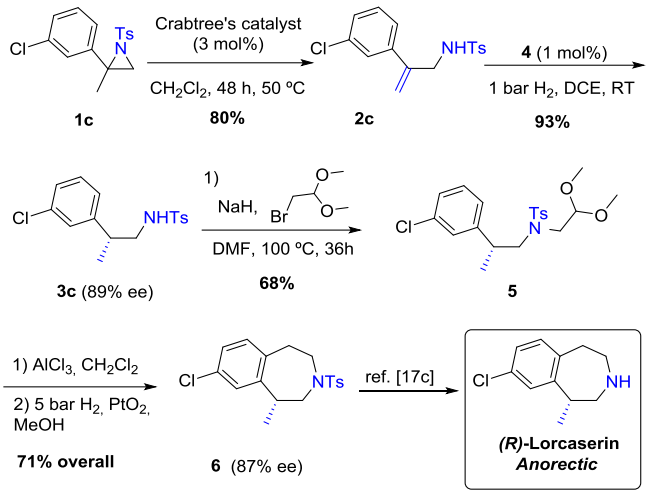
[a] All reactions were run in a pressure reactor at 1 bar of H_2 pressure. [b] Conversion was measured by ^{1}H NMR. [c] Enantiomeric ratio was determined by chiral HPLC. [d] 2 mol% of catalyst was used.

Many biologically active compounds have amines with a chiral methyl group in β-position. Compound **2a** is already a direct precursor of potassium channel inhibitors after simple tosyl deprotection and acylation [15,16] (see SI). The mesyl amine **2m** is also a key intermediate for the preparation of allosteric modulators of AMPA receptor.[16,17] However, to further showcase the applicability of our methodology, and encouraged by the relevance of these chiral β-methyl amines as fragments of biologically active compounds we envisioned easy access to LY-404187 and *(R)*-Lorcaserin. To obtain the biarylpropylsulfonamide LY-404187,[4] we designed a 3-step synthetic procedure starting from *N*-sulfonyl aziridine **1l**. The isomerization[12] of **1l** to **2l** and the subsequent asymmetric hydrogenation to **3l** took place in excellent yields. Finally, the chiral amine **3l** was converted to the final product by a Suzuki-Miyaura coupling. LY-404187, the potent potentiator of the AMPA receptor, was obtained as the only product with good yield and almost no loss of optical purity (Scheme 2).



Scheme 2. Synthesis of LY-404187

The anorectic drug Lorcaserin has a tetrahydro-3-benzazepine skeleton, a common structural feature in many natural and pharmaceutical products. Lorcaserin has serotonergic properties and is currently used as a weight-loss drug. Several racemic syntheses of this compound have been reported. Only a few strategies for the enantioenriched form of this drug can be found in the literature, and most of them use kinetic resolution or stoichiometric reagents.[18] We envisioned to apply our novel catalytic asymmetric methodology (Scheme 3). *N*-sulfonyl aziridine **1c** was isomerized[12] and the corresponding allyl amine was hydrogenated to afford **3c** in good yield and 89% ee. Subsequent *N*-alkylation gave **5** in 68% yield. Regioselective Lewis acid-promoted intramolecular Friedel-Craft alkylation[3b] afforded the unsaturated 7-membered ring. Finally, enamine hydrogenation gave desired compound **6**, which is a direct precursor of Lorcaserin.[18c]



Scheme 3. Formal synthesis of (*R*)-Lorcaserin.

In summary, we have shown that commercially available complex Ir(UbaPHOX) (**4**) is an excellent catalyst for the challenging asymmetric hydrogenation of 2-aryl *N*-sulfonyl allylamines. The hydrogenation takes place at low hydrogen pressure (1 bar) and with only 1 mol % of catalyst in DCE at room temperature. Since the starting amines can be easily obtained by Ir-catalyzed isomerization of *N*-tosylaziridines, which in turn can be prepared from the corresponding styrenes, the overall sequence provides a straightforward and practical route to chiral amines bearing a methyl group in β position. These compounds are useful synthetic intermediates since they are, or can be transformed into, precursors of several biologically active compounds. As a synthetic application of this methodology, we have described the formal synthesis of enantioenriched (*R*)-Lorcaserin and LY-404187.

Acknowledgements

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References

1 a) G.-Q. Lin, J.-G. Zhang, J.-F. Cheng, Overview of chirality and chiral drugs. In *Chiral Drugs*, John Wiley & Sons, Inc., 2011; pp 3-28. b) Macrolide Antibiotics (Ed: S. Omura), Academic Press, Orlando, FL, **1984**.

2 Chiral amines with β-stereogenic centres: a) H. M. L. Davies, A. Ni, *Chem. Commun.* **2006**, 3110-3112; b) R. N. Harris, R. S. Stabler, D. B. Repke, J. M. Kress, K. A. Walker, R. S. Martin, J. M. Brothers, M. Ilnicka, S. W. Lee, T. Mirzadegan, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3436–3440. c) P. Ramesh, D. Suman, K. Reddy, *Synthesis* **2018**, *50*, 211–226. d) G. M. Nicholas, T. F. Molinski, *Tetrahedron* **2000**, *56*, 2921.

3 a) B. M. Smith, J. M. Smith, J. H. Tsai, J. A. Schultz, C. A. Gilson, S. A. Estrada, R. R. Chen, D. M. Park, E. B. Prieto, C. S. Gallardo, D. Sengupta, P. I. Dosa, J. A. Covel, A. Ren, R. R. Webb, N. R. A. Beeley, M. Martin, M. Morgan, S. Espitia, H. R. Saldana, C. Bjenning, K. T. Whelan, A. J. Grottick, F. Menzaghi, W. J. Thomsen, *J. Med. Chem.* **2008**, *51*, 305-313. b) D. Nikolic, P. P. Toth, A. Ferlita, V. Di Bartolo, G. Montalto, M. Banach, M. Rizzo, *Clin. Lipidol.* **2014**, *9*, 179–187. c) I. G. Smilovic, J. Cluzeau, F. Richter, S. Nerdinger, E. Schreiner, G. Laus, H. Schottenberger, *Bioorg. Med. Chem.* **2018**, *26*, 2686–2690. d)

4 a) P. L. Ornstein, D. M. Zimmerman, M. B. Arnold, T. J. Bleisch, B. Cantrell, R. Simon, H. Zarrinmayeh, S. R. Baker, M. Gates, J. P. Tizzano, D. Bleakman, A. Mandelzys, K. R. Jarvie, K. Ho, M. Deverill, R. K. Kamboj, *J. Med. Chem.* **2000**, *43*, 4354-4358. b)M. Gates, A. Ogden, D. Bleakman, *Neuropharmacology* **2001**, *40*, 984–991. c) N. Jones, M. J. O'Neill, M. Tricklebank, V. Libri, S. C. R. Williams, *Psychopharmacology* **2005**, *180*, 743–751.

5 S. T. Moe, S. M. Shimizu, D. L. Smith, B. C. Van Wagenen, E. G. DelMar, M. F. Balandrin, Y. Chien, J. L. Raszkiewicz, L. D. Artman, A. L. Mueller, E. Lobkovsky, J. Clardy, *Bioorganic & Medicinal Chemistry Letters* **1999**, *9*, 1915-1920.

6 a) *Catalytic Asymmetric Synthesis*. (Ed.I. Ojima), Wiley-VCH: Weinheim, **2000**; b) *Applied Homogeneous Catalysis with Organometallic Compounds*, (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH: Weinheim, **2002**; c) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*. (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH: Weinheim, **2004**. d) J. M. Brown. in *Comprehensive Asymmetric Catalysis Vol. I*; (Eds: Jacobsen, E. N., Pfaltz, A., Yamamoto, Y.); Springer: Berlin, 1999. e) H.-U. Blaser, B. Pugin, F. Spindler, *Top. Organomet. Chem.* **2012**, *42*, 65-102. f) P. Etayo, A. Vidal-Ferran, *Chem. Soc. Rev.* **2013**, *42*, 728-754. g) Z. Zhang, N. A. Butt, W. Zhang, *Chem. Rev.* **2016**, *116*, 14769-14827. h) C. Margarita, P. G. Andersson, *J. Am. Chem. Soc.* **2017**, *139*, 1346-1356.

7 E. Cristobal-Lecina, P. Etayo, S. Doran, M. Reves, P. Martin-Gago, A. Grabulosa, A. R. Costantino, A. Vidal-Ferran, A. Riera, X. Verdaguer, *Adv. Synth. Catal.* **2014**, *356*, 795-804.

8 a) A. Pfaltz, J. Blankenstein, R. Hilgraf, E. Hörmann, S. McIntyre, F. Menges, M. Schönleber, S. P. Smidt, B. Wüstenberg, N. Zimmermann, *Adv. Synth. Catal.* **2003**, *345*, 33–43. b) J. J. Verendel, O. Pàmies, M. Diéguez, P. G. Andersson, *Chem. Rev.* **2014**, *114*, 2130–2169. c) M. A. Müller, S. Gruber, A. Pfaltz, *Adv. Synth. Catal.* **2018**, *360*, 1340–1345. d) W. J. Lu, Y. W. Chen, X. L. Hou, *Adv. Synth. Catal.* **2010**, *352*, 103–107. e) A. Trifonova, J. S. Diesen, C. J. Chapman, P. G. Andersson, *Org. Lett.* **2004**, *6*, 3825–3827. f) J. Q. Li, J. Liu, S. Krajangsri, N. Chumnanvej, T. Singh, P. G. Andersson, *ACS Catal.* **2016**, *6*, 8342–8349. g) E. Salomo, S. Orgue, A. Riera, X. Verdaguer, *Angew. Chem., Int. Ed.* **2016**,

55, 7988-7992. h) E. Salomo, A. Gallen, G. Sciortino, G. Ujaque, A. Grabulosa, A. Lledos, A. Riera, X. Verdaguer, *J. Am. Chem. Soc.* **2018**, *140*, 16967-16970.

9 a) S. J. Roseblade, A. Pfaltz, *Acc. Chem. Res.* **2007**, *40*, 1402–1411. b) S. McIntyre, E. Hörmann, F. Menges, S. P. Smidt, A. Pfaltz, *Adv. Synth. Catal.* **2005**, *347*, 282–288. c) J. Mazuela, J. J. Verendel, M. Coll, B. Schäffner, A. Börner, P. G. Andersson, O. Pàmies, M. Diéguez, *J. Am. Chem. Soc.* **2009**, *131*, 12344–12353. d) O. Pàmies, P. G. Andersson, M. Diéguez, *Chem. - A Eur. J.* **2010**, *16*, 14232–14240. e) D. H. Woodmansee, A. Pfaltz, *Chem. Commun.* **2011**, *47*, 7912–7916. f) J. Mazuela, O. Pàmies, M. Diéguez, *ChemCatChem* **2013**, *5*, 2410–2417. g) M. Biosca, E. Salomo, P. de la Cruz-Sanchez, A. Riera, X. Verdaguer, O. Pamies, M. Dieguez, *Org. Lett.* **2019**, *21*, 807-811.

10 C. J. Wang, X. Sun, X. Zhang, *Angew. Chem., Int. Ed.* **2005**, *44*, 4933–4935.

11 D. P. Steinhuebel, S. W. Krska, A. Alorati, J. M. Baxter, K. Belyk, B. Bishop, M. Palucki, Y. Sun, I. W. Davies, *Org. Lett.* **2010**, *12*, 4201–4203.

12 A. Cabre, G. Sciortino, G. Ujaque, X. Verdaguer, A. Lledos, A. Riera, *Org. Lett.* **2018**, *20*, 5747-5751.

13 a) J. Blankenstein, A. Pfaltz, *Angew. Chem. Int. Ed.* **2001**, *40*, 4445–4447. b) F. Menges, A. Pfaltz, *Adv. Synth. Catal.* **2002**, *344*, 40–41.

14 T. Nishikata, H. Nagashima, *Angew. Chem., Int. Ed.* **2012**, *51*, 5363–5366.

15 B. H. Kaae, K. Harpsøe, J. S. Kastrup, A. C. Sanz, D. S. Pickering, B. Metzler, R. P. Clausen, M. Gajhede, P. Sauerberg, T. Liljefors, et al., *Chem. Biol.* **2007**, *14*, 1294–1303.

16 J. Zhang, C. Liu, X. Wang, J. Chen, Z. Zhang, W. Zhang, *Chem. Commun.* **2018**, *54*, 6024–6027.

17 T. Drapier, P. Geubelle, C. Bouckaert, L. Nielsen, S. Laulumaa, E. Goffin, S. Dilly, P. Francotte, J. Hanson, L. Pochet, J. S. Kastrup, B. Pirotte, *J. Med. Chem.* **2018**, *61*, 5279-5291.

18 a) B. Xu, J. Su, J. Wang, G.-C. Zhou, *Aust. J. Chem.* **2016**, *69*, 770. b) A. Gini, J. Bamberger, J. Luis-Barrera, M. Zurro, R. Mas-Ballesté, J. Alemán, O. G. Mancheño, *Adv. Synth. Catal.* **2016**, *358*, 4049–4056. c) Q. Zhu, J. Wang, X. Bian, L. Zhang, P. Wei, Y. Xu, *Org. Process Res. Dev.* **2015**, *19*, 1263–1267.

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

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