Expanded scope for the iridium-catalyzed asymmetric isomerization of primary allylic alcohols using readily accessible second-generation catalysts†

Luca Mantilli and Clément Mazet*

Received (in College Park, MD, USA) 29th September 2009, Accepted 19th November 2009
First published as an Advance Article on the web 3rd December 2009
DOI: 10.1039/b920342g

A second generation of chiral (P,N)-iridium catalysts—readily accessible from inexpensive L-serine—displays expanded scope for the asymmetric isomerization of primary allylic alcohols.

In modern asymmetric catalysis, at the first stage of their development, chiral catalysts are primarily evaluated based on their intrinsic ability to deliver the targeted products in high yields and enantioselectivities. Optimization of the reaction conditions (catalyst loading, solvent choice, optimal temperature *etc.*) and investigation of the substrate scope are considered next.[1] Catalyst accessibility—which ultimately relies on an efficient, short and modular synthetic route using inexpensive starting material from the chiral pool—is often underappreciated. In homogeneous transition-metal-based asymmetric catalysis, this has sometimes led to paradoxal situations where the organic chiral ligands are more expensive by a few order of magnitude than the precious metal salts. We have recently disclosed that chiral (dialkyl)phosphanyl-alkyloxazoline-iridium catalysts promote the asymmetric isomerization of primary allylic alcohols to the corresponding aldehydes under mild reaction conditions.[2–4] The most selective and general candidate **1a** was unfortunately derived from expensive, non-natural, L-*tert*-leucine. Although they exclusively varied the oxazoline substituent R^2 while keeping the diphenylphosphine moiety unchanged, Burgess and co-workers have convincingly demonstrated the highly modular nature of ligand **L-2** in the context of Pd-catalyzed asymmetric allylic substitution (Fig. 1).[5]

Inspired by this work, we report herein a second generation of iridium catalysts for the asymmetric isomerization of primary allylic alcohols. This second generation of catalysts is readily available from dialkylphosphine precursors and inexpensive L- or D-serine.[6] They display similar reactivity and selectivity to catalyst **1a** for most substrates and *improved performance for the more challenging 3,3-dialkyl primary allylic alcohols.*

The synthetic routes leading to the protected ligands **L-1** and **L-2** have been described in the literature and compare relatively well in terms of efficiency (number of steps, overall yield). Both are equally modular since in each case a final S_N2 reaction allows one to combine the oxazoline building block with commercially available protected dialkylphosphines (see ESI† for details). *Nonetheless, when comparing the limited number of natural amino acids with the virtually infinite catalogue of carboxylic acids, ligand scaffold* **L-2** *offers a potentially higher structural diversity at* R^2. In order to access a small but structurally relevant library of six iridium pre-catalysts, we limited ourselves to two sets of complexes having a trialkylphosphine moiety on the left-hand-side (R^1 = Cy, *t*-Bu, 1-Ad) and either an sp^2 or sp^3 hybridized carbon at R^2 (R^2 = Ph for **2a–c** and *t*-Bu for **2d–f**, respectively).

Ligand deprotection, iridium complexation and subsequent chloride abstraction with $NaBAr^F$ were performed in a one-pot process combining standard literature procedures affording **2a–f** in good yields (Scheme 1).[7] Each of the air-stable iridium complexes **2a–c** (R^2 = Ph) are systematically obtained as a mixture of two non-interconverting isomers as evidenced by ^1H and $^{31}P\{^1H\}$ variable-temperature NMR measurements performed between −50 °C and +60 °C. Interestingly, the ratio decreases as the size of the phosphorus substituents R^1 and/or the phenyl group at R^2 with the cyclooctadiene moiety. Complexes **2d–f** (R^2 = *t*-Bu) are virtually obtained as a single isomer.

In order to evaluate the potential of catalysts **2a–f** in the asymmetric isomerization of primary allylic alcohols, a comparative study using model substrate (*E*)-4-methyl-3-phenylpent-2-enol **3a** was carried out (Table 1). The reactions were performed in THF at room temperature using 5 mol% catalyst loading. The solution was degassed after activation by molecular hydrogen to prevent competing hydrogenation. Whereas catalysts **2d–f** performed poorly, delivering the

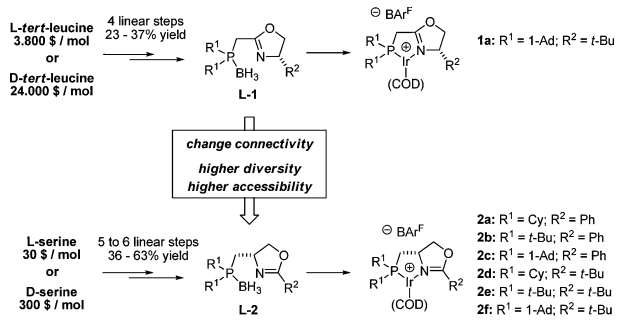
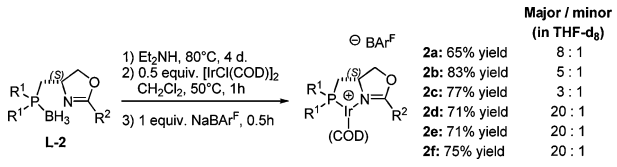


Fig. 1 Comparative synthetic routes leading to ligands **L-1** and **L-2** (Cy = cyclohexyl; *t*-Bu = *tert*-butyl; 1-Ad = 1-adamantyl, BAr^F = tetrakis-[3,5-bis-(trifluoromethyl)phenyl]borate; COD = 1,5-cyclooctadiene).

University of Geneva, Organic Chemistry Department, Quai Ernest Ansermet 30, 1211-Geneva, Switzerland. E-mail: clement.mazet@unige.ch; Fax: +41 (0) 22 3793215; Tel: +41 (0) 22 3796288

† Electronic supplementary information (ESI) available: Full experimental data and characterization for all new compounds. See DOI: 10.1039/b920342g



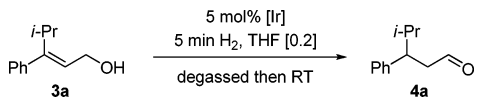
Scheme 1 Synthesis of cationic iridium complexes using ligands **L-2**.

desired aldehyde with modest yields and low enantioselectivities (entry 5–7), catalysts **2a–c** afforded **4a** in acceptable to high yields and good to excellent levels of enantioselectivity (entry 2–4). In this series, the activity decreases as the size of the substituents on the phosphorus atom increases. The enantioselectivity reaches 96% when the P-atom bears tertiary alkyl substituents (R^1 = *t*-Bu or 1-Ad). Overall, catalyst **2b** offers the best balance in terms of activity and enantioselectivity and compares well with the first-generation catalyst **1a** on both fronts (compare entry 1 and 3).

Next, a survey of prototypical allylic alcohols (**3b–g**) and some more challenging 3,3-dialkyl primary allylic alcohols (**3h–k**) was performed with catalysts **1a** and **2b** using the standard experimental conditions for the isomerization reaction (Fig. 2). Derivatives with either electron-donating (**3b–c**) or electron-withdrawing (**3d**) substituents on the *para* position of the aryl moiety were isomerized with similar efficiency. Catalyst **2b** displayed a slightly reduced activity for substrates **3e** and **3f** having bulkier alkyl groups. Nevertheless, **4e** and **4f** were still obtained with high enantioselectivities (94% ee and >99% ee, respectively). Similarly, **4g** was obtained with 40% yield and 97% ee with **2b** whereas catalyst **1a** afforded this aldehyde with 65% yield and 93% ee.[8]

Catalyst **2b** clearly outperforms catalyst **1a** for the asymmetric isomerization of 3,3-dialkyl primary allylic alcohols **3h–k**. The bulky, weakly coordinating, allylic alcohol **3h** was isomerized in 79% yield and 90% ee with **2b**. In contrast, with catalyst **1a**, the same substrate undergoes complete conversion into an almost racemic product (8% ee). This striking discrepancy suggests the two catalysts may follow completely unrelated mechanistic pathways. Aldehyde **4i** is obtained both with

Table 1 Iridium-catalyzed asymmetric isomerization of (*E*)-4-methyl-3-phenylpent-2-enol **3a**



Entry[a]	Catalyst	*t*/h	**4a** (%)[b]	ee (%)[c]
1[d]	**1a**	22	75	97
2	**2a**	4	83	84
3	**2b**	4	73	96
4	**2c**	4	54	96
5	**2d**	4	33	6
6	**2e**	4	35	21
7	**2f**	4	23	17

[a] Average of two independent runs. Reaction conditions: 0.1 mmol, 0.2 M in dry and degassed THF. H_2 was bubbled for 5 min and **3a** added dropwise after degassing the solution and stirred at room temperature for the indicated time. [b] Determined by ^{1}H NMR and/or GC using an internal standard. Isolated yields after purification by chromatography closely match conversions. [c] Determined by GC. [d] See ref. 2.

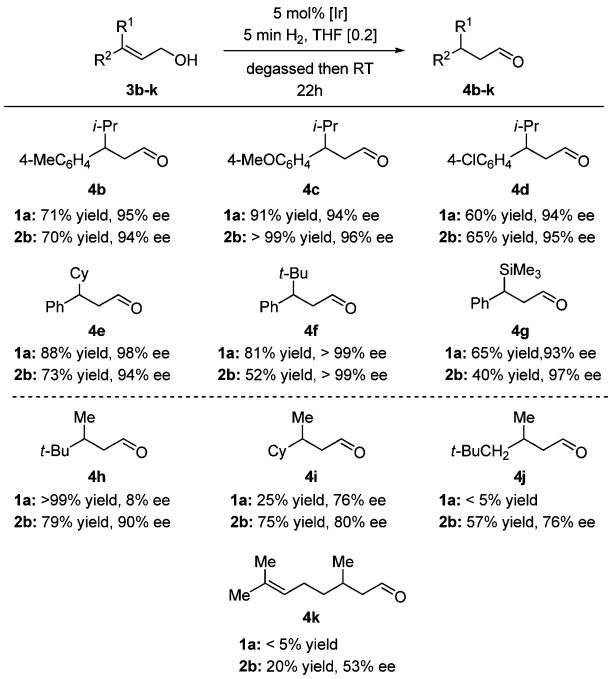


Fig. 2 Comparative study between **1a** and **2b** for the isomerization of various allylic alcohols. For reaction conditions see Table 1. Yields were determined by ^{1}H NMR and/or GC using an internal standard. Isolated yields after purification by chromatography closely match conversions.

improved yield and enantioselectivity when switching from **1a** to **2b** (25% yield, 76% ee and 75% yield, 80% ee, respectively). This marked reactivity difference is also well reflected for substrates **3j–k** having two primary alkyl substituents at C(3). Catalyst **1a** is virtually ineffective at promoting the isomerization of such allylic alcohols whereas **2b** gives 3,5,5-trimethylhexanal **4j** in 57% yield and a promising 76% ee, and isomerizes geraniol **3k** into citronellal **4k** in 20% yield and 53% ee.

In conclusion we have developed a second generation of chiral (P,N)-iridium catalysts readily available from inexpensive L-serine. These catalysts display a wider substrate scope in the asymmetric isomerization of primary allylic alcohols, in particular for the less reactive 3,3-dialkyl-substituted derivatives. Current studies in our laboratory are aiming at designing new catalysts to further broaden the scope of this isomerization reaction with emphasis on (*Z*)-configured allylic alcohols.[9]

Financial support from the Swiss National Foundation and the University of Geneva is acknowledged. Professor A. Alexakis is warmly thanked for access to his analytical facilities, D. Gérard and S. Torche for assistance in synthesis, and Johnson-Matthey for a generous loan of iridium precursors. R. Novikov is acknowledged for a gift of substrate **3f**.

Notes and references

1 *Asymmetric catalysis on industrial scale: challenges, approaches, and solutions*, ed. H. U. Blaser and E. Schmidt, Wiley-VCH, Weinheim, 2003.
2 L. Mantilli, D. Gérard, S. Torche, C. Besnard and C. Mazet, *Angew. Chem., Int. Ed.*, 2009, **48**, 5143.
3 For recent reviews, see: (*a*) R. C. Van der Drift, E. Bouwman and E. Drent, *J. Organomet. Chem.*, 2002, **650**, 1; (*b*) R. Uma, C. Crévisy

and R. Grée, *Chem. Rev.*, 2003, **103**, 27; (*c*) V. Cadierno, P. Crochet and J. Gimeno, *Synlett*, 2008, **8**, 1105.
4 For other examples of enantioselective isomerization of primary allylic alcohols, see: (*a*) C. Botteghi and G. Giacomelli, *Gazz. Chim. Ital.*, 1976, **106**, 1131; (*b*) K. Tanaka, S. Qiao, M. Tobisu, M. M.-C. Lo and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 9870; (*c*) K. Tanaka and G. C. Fu, *J. Org. Chem.*, 2001, **66**, 8177; (*d*) C. Chapuis, M. Barthe and J.-Y. de Saint Laumer, *Helv. Chim. Acta*, 2001, **84**, 230; (*e*) F. Boeda, P. Mosset and C. Crévisy, *Tetrahedron Lett.*, 2006, **47**, 5021; (*f*) A. Doppiu and A. Salzer, *Eur. J. Inorg. Chem.*, 2004, 2244; (*g*) S. Bovo, A. Scrivanti, M. Bertoldini, V. Beghetto and U. Matteoli, *Synthesis*, 2008, **16**, 2547. For isomerization of secondary allylic alcohols, see for instance; (*h*) M. Ito, S. Kitahara and T. Ikariya, *J. Am. Chem. Soc.*, 2005, **127**, 6172.
5 (*a*) A. M. Porte, J. Reibenspies and K. Burgess, *J. Am. Chem. Soc.*, 1998, **120**, 9180; (*b*) K. Burgess and A. M. Porte, *Tetrahedron: Asymmetry*, 1998, **9**, 2465.
6 Prices for each enantiomer of *tert*-leucine and serine in US $ per mol were calculated using the largest amount available from Bachem AG (September 2009).
7 (*a*) D. B. G. Williams, H. Lombard, M. van Niekerk, P. P. Coetzee and C. W. Holzapfel, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 2799; (*b*) A. Lightfoot, P. Schnider and A. Pfaltz, *Angew. Chem., Int. Ed.*, 1998, **37**, 2897.
8 For consistency, all reactions in Fig. 2 have been run for 22 h. Some isomerization reactions may require shorter reaction time to reach the indicated yields. Nevertheless, if the isomerizations are run for longer period of time, the yields are not improved. For allylic alcohols **3a–e**, reactions have been scaled up to a 2 mmol scale using **2b** without erosion of neither the yields nor the enantioselectivities.
9 Isomerization of (*Z*)-configured primary allylic alcohols is still problematic with these (P,N)-iridium catalysts. Low conversions and enantioselectivities along with substantial competing (*E*)/(*Z*) isomerization were obtained. See also ref. 2 and 4*a*.