Organic LETTERS

Letter

pubs.acs.org/OrgLett

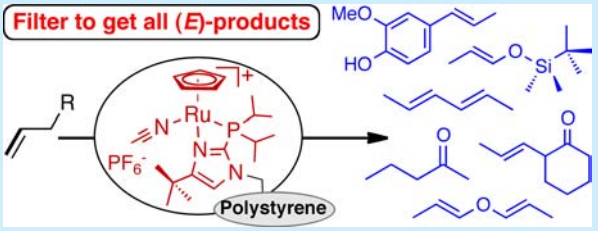
Supported Imidazolylphosphine Catalysts for Highly (*E*)-Selective Alkene Isomerization

Gulin Erdogan and Douglas B. Grotjahn*

Department of Chemistry and Biochemistry, 5500 Campanile Drive, San Diego State University, San Diego, California 92182-1030, United States

Supporting Information

ABSTRACT: For fine chemical synthesis, immobilized catalysts offer little advantage if they produce a product mixture that must be separated. Selective isomerization of terminal olefins is achieved by heterogenized bifunctional catalysts. Outstanding and consistent (*E*)-selectivity (>99%) even in cases where (*E*) and (*Z*) isomers are of comparable stability, combined with modest catalyst loadings (1 to 2 mol %), set these catalysts apart from previously reported systems. Ease of catalyst removal and high geometric selectivity avoid tedious purifications.

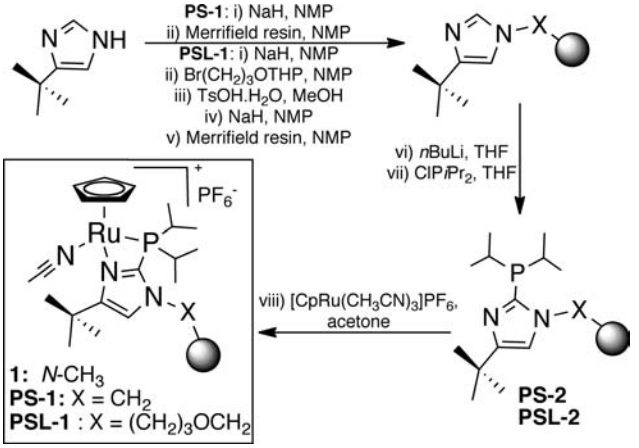


The advantages of using supported reagents or catalysts in synthesis and discovery methodologies have been summarized.[1] Our search of the literature on heterogeneous[2] or heterogenized[3] alkene isomerization catalysts revealed a lack of highly selective systems. Some heterogeneous alkene isomerization systems use strong acid[2b,e,f] or base[2g,h] catalytic sites while others use metal centers for transformations. The literature systems either suffer from forming mixtures of positional isomers[3b,f] (in thermodynamic ratios) and/or mixtures of geometric isomers.[2,3] Among these, perhaps the best system is reported by Ley et al. in the concise and elegant synthesis of the natural product carpanone, where a polymer-supported form of Felkin's iridium catalyst gave (*E*)-olefin selectivity up to >98%. However, several other cases gave only 50% (*E*)-selectivity and required an ~40 mol % catalytic loading and 24 h reaction time at room temperature. Moreover, prior activation of the catalyst with hydrogen was required and small amounts of an alkane from hydrogenation of an alkene appeared.[3h] It is important to note that when a direct comparison was made in one case, this promising polymer-supported system was reported to be less (*E*)-selective than the related homogeneous catalyst.[3h] In contrast, here we report a catalyst which is universally (*E*)-selective even with challenging substrates, which works at reasonable (1−2 mol %) loadings and even with neat substrates.

Previously reported homogeneous catalyst **1** (Scheme 1) isomerizes many alkenes to (*E*)-internal alkene products with low loading and temperatures (2−5 mol %, 25−70 °C).[4] The pendant base is proposed to activate allylic protons during isomerization. Moreover, in the presence of deuterium oxide, **1** can achieve H/D exchange at the allylic positions accessible during isomerization.[5]

Here we report two related immobilized forms of catalyst **1**, using a polystyrene polymer (Merrifield resin[6]) that has been adopted for numerous organic reactions to facilitate product purification and catalyst recovery. Catalysts can be immobilized

Scheme 1. Synthesis of Immobilized Catalysts



on other insoluble materials such as activated carbon,[7] zeolites,[8a,b] metal oxides,[8a,c] mesoporous silica nanoparticles,[8a,d] and insoluble polymer resins;[6b,9] here Merrifield resin offered a straightforward approach to our catalyst design (Scheme 1). The point of attachment to the resin was chosen as N1 on the pendant base, which is proposed on the basis of X-ray diffraction studies[10] to be away from the catalyst active site. Compared to their homogeneous counterparts, in general, heterogeneous catalysts are harder to characterize and suffer from slower diffusion rates and lower activity.[9] In order to explore the effects of having the active site further away from the resin matrix with possibly improved substrate and product transport rates,[11] in addition to **PS-1** a second version of the

Received: March 23, 2014
Published: May 8, 2014

   dx.doi.org/10.1021/ol500327k | *Org. Lett.* 2014, 16, 2818−2821

catalyst (**PSL-1**) featuring a tether of five atoms was also envisioned.

Catalysts were built on Merrifield resin stepwise[12] by displacement of the chloride by the sodium salt of 4-(*tert*-butyl)-1*H*-imidazole (for **PS-1**) or the alkoxide needed for **PSL-1**, followed by installation of phosphine functionality using BuLi, then $i\mathrm{Pr}_2\mathrm{PCl}$, and finally complexation employing $[\mathrm{CpRu}(\mathrm{CH}_3\mathrm{CN})_3]\mathrm{PF}_6$ as a precursor. The polymer was extensively washed at each step, and composition of the polymer was determined by elemental analysis via nitrogen percent weight.

Moreover, ^{31}P NMR data for PS-2 show a single peak at −18.7 ppm, which is in agreement with data for the solution-phase imidazolylphosphine (−18.5 ppm in acetone-d_6). After addition of $[\mathrm{CpRu}(\mathrm{CH}_3\mathrm{CN})_3]\mathrm{PF}_6$ and drying, the absence of the peak at −18.7 ppm confirmed that the complexation was complete, and the chemical shift of 41.5 ppm (along with a sharp septet at −142.9 ppm for PF_6^-) was consistent with the presence of **PS-1**. The ligands in **PSL-1** and **PS-1** appear to be the first polymer-supported imidazolylphosphines, and their synthesis on the resin is more straightforward than that for related pyridylphosphines,[13] which may pave the way to more widespread applications.

Isomerization of alkene substrates was achieved at low (usually 1−2 mol %) catalyst loadings in acetone as solvent, either at room temperature or at 70 °C. At room temperature, reactions were performed in vials with Teflon-lined caps that were placed on a nutator in order to produce mixing without mechanical degradation of the polymer beads. Reactions at elevated temperatures were conducted in resealable J. Young NMR tubes without mechanical mixing of any kind; further optimization of the mixing technique during heating could be expected to lead to even better results. The performance of heterogenized catalysts **PS-1** and **PSL-1** was compared with that of soluble catalyst **1** by subjecting substrates to similar conditions and observing the progress of isomerization by ^{1}H NMR spectroscopy.

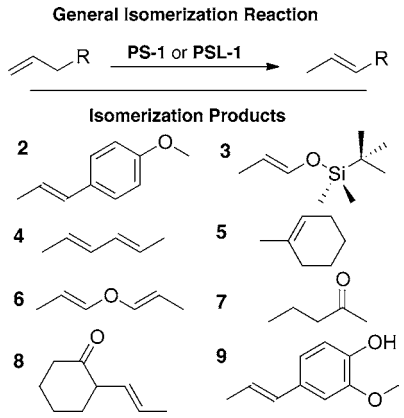
Isomerization of 4-allyl anisole, eugenol, and diallyl ether was achieved at room temperature (Table 1). In each case the performances of **PS-1** and **PSL-1** were comparable, where both catalysts retained the very high stereoselectivity of solution phase catalyst **1** to yield (*E*)-isomers. **PS-1** outperformed **PSL-1** with substrates that either require multiple bond movements or are sterically more challenging. Products **2**, **3**, **6**, **8**, and **9** (Scheme 2) are especially noteworthy, because within limits of NMR detection (estimated 0.5% to 2%[14]), none of the (*Z*)-isomers were seen, which should eliminate the need for tedious separation of closely related alkene isomers by chromatography. Products **3** and **6** show the ability to make single geometric isomers of enol ethers, which in many cases have comparable thermodynamic stability[15a−d] and could be sensitive to chromatographic separation techniques. Significantly, results with **PS-1** and **PSL-1** stand apart from previous work on enol ethers: with careful monitoring of reactions to prevent significant *E*−*Z* equilibration, solution-phase Felkin catalysts can in some cases give high (*E*)-selectivity,[15e] but the reported polymer-supported version generally gives approximately equal amounts of (*E*)- and (*Z*)-products.[3h] Finally, (*E*,*E*)-2,4-hexadiene (**4**) is a high value chemical that is challenging to produce in high yield and selectivity;[16] here **4** is formed in higher yield that with **1**, which generates unidentified products besides **4**.[4b]

Table 1. Products Formed and Reaction Conditions[a]

product formed	catalyst	mol %	temp (°C)	time	% yield
2	**PS-1**	2	25	20 min	96
	PSL-1	2	25	20 min	99
	1	2	25	10 min	99
3	**PS-1**	2	25	30 min	97
	PSL-1	2	25	30 min	96
	1	2	25	4 min	>99
4	**PS-1**	2	70	7 h	94
	PSL-1	2	70	7 h	98
	1[b]	5	70	1 h	77
5	**PS-1**	2	70	48 h	91
	PSL-1	2	70	72 h	84
	1	2	70	1 h	98
6	**PS-1**	2	25	5 h	97
	PSL-1	2	25	5 h	99
	1[b]	2	25	40 min	96
7	**PS-1**	2	70	2 h	91
	PSL-1	2	70	1 h	90
	1	2	70	1 h	97
8	**PS-1**	2 (1[c])	70	1 h (5 h[c])	78 (90[c])
	PSL-1	2 (1[c])	70	23 h (5 h[c])	82 (99[c])
	1	2	25	45 min	92
9	**PS-1**	1	25	45 min	98
	PSL-1	1	25	52 min	94
	1	1	25	4 min	99

[a]Unless otherwise specified all reactions were run in acetone-d_6. [b]Reaction conditions and yields from ref 4a. [c]Reaction run in neat substrate.

Scheme 2. General Isomerization Reaction and Products Formed in This Paper



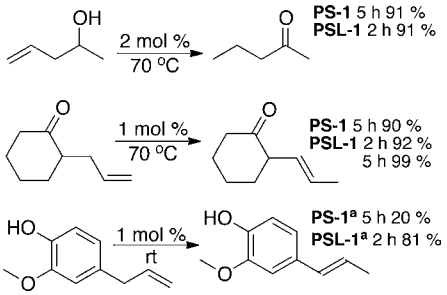
Significantly, our experience with **PS-1** and **PSL-1** is that reactions left up to >10 to 100 times longer than the time needed for complete positional isomerization did not show the appearance of a detectable (*Z*)-isomer, resulting in attractive operational simplicity because of the low risk of the separation problems resulting from overisomerization.

Solvent-free reactions can lead to new environmentally benign procedures that save resources and energy, reducing the burden of organic solvent disposal, and also handling costs by simplifying the experimental procedure and workup technique, saving costs during industrial production.[17] Our attempt to circumvent using organic solvents lead to the observation of reversal of the relative performances of **PS-1** and **PSL-1**, though both were effective (Scheme 3). Under neat conditions, **PSL-1**

dx.doi.org/10.1021/ol500327k | *Org. Lett.* 2014, 16, 2818−2821

isomerizes 4-penten-2-ol, eugenol, and 2-allylcyclohexanone in a shorter time than does **PS-1**.

Scheme 3. Isomerizations under Neat Conditions



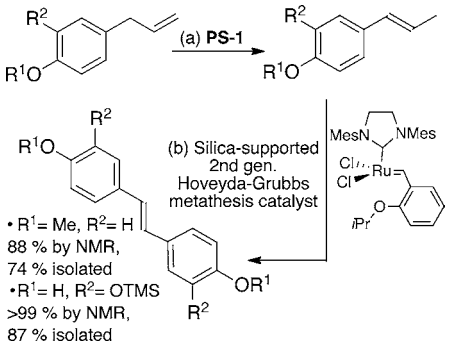
[a]Completion in 24 h (^{1}H NMR). Yields at earlier times reported so as to show relative rates of **PS-1** and **PSL-1**.

Alkenyl aromatics, such as 4-allylanisole, eugenol, and their isomers, are used in a wide range of flavoring, cosmetic, fragrance, and pharmaceutical applications. Isoeugenol is extracted from natural sources or traditionally generated from eugenol by isomerization using a stoichiometric excess of KOH in alcoholic solutions at high temperature (200 °C).[18] Recycling and recovery studies were carried out with **PS-1** isomerization of eugenol to (*E*)-isoeugenol because of commercial interest in obtaining the product free of the (*Z*)-isomer, as well as free of metal residues. The ruthenium content of combined filtrates and washes of each cycle was determined by inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis.[19] The conversion during each of the five cycles is near quantitative, and in total, only ~1.3% of the initial Ru loading is lost. The higher leaching at the first cycle (0.7%) suggests the presence of more loosely held ruthenium species, perhaps deposited in the pores of the polymer. In order to reduce metal contamination further, pretreatment of the polymer-supported catalysts was performed. On a 2-g scale isomerization of eugenol, prior to use **PS-1** was washed with acetone (2 mL × 3). ICP-OES analysis of the washes showed that ~0.3% Ru was leached whereas the product, isoeugenol, did not contain a detectable amount (estimated limit <0.5 ppm) of Ru in the isolated product (1.93 g, 96% yield after distillation).

To further highlight the advantages of an immobilized alkene isomerization catalyst, isomerization and metathesis have been performed sequentially (Scheme 4). Stilbenoids, especially resveratrol, have received attention due to their potential value in cancer prevention and therapy,[20] and they are accessible by metathesis.[20c] 4-Allylanisole and *tert*-butyldimethylsilyl-protected eugenol were isomerized with **PS-1**. After filtration, isomerized alkenes were subjected to metathesis with a silica-supported second generation Hoveyda–Grubbs catalyst which was prepared according to literature.[21] Metathesis products were isolated in 73.5% and 87% yield, respectively.

In summary, one unique feature of this work is that *the very high selectivity for formation of only (E)-isomers is completely retained on heterogenization.* In general, for many substrates both **PS-1** and **PSL-1** show a lower but still very useful *rate* of isomerization compared to that of **1**, which is a fast catalyst, particularly for linear or unhindered alkenes. Increased selectivity and hence product yield was observed for hexadiene using **PS-1** or **PSL-1**. **PSL-1** outperforms **PS-1** under neat conditions. The difference in activity may be attributed to easier

Scheme 4. Sequential Isomerization and Metathesis[a]



[a](a) 2 mol % **PS-1**, acetone-d_6, 2 h, rt. (b) 1.0–3.1 mol % SiO_2-supported Hoveyda–Grubbs catalyst, hexanes, 2–14 h, 60–70 °C.

access to the **PSL-1** active site provided by the longer tethering, or to its ability to swell faster with substrates containing functionalities with oxygen. The rate or selectivity of catalysts can be improved[22] or more commonly[1c,9] degraded upon immobilization; the outstanding feature of this work is that high *E*-selectivity is retained, which is important for avoiding subsequent tedious product purifications and retaining the utility of a supported catalyst. Overall, **1** is successfully heterogenized as **PS-1** and **PSL-1**; the selectivity of the catalyst is fully retained with very low metal leaching from the insoluble support. Ongoing work seeks to create faster heterogeneous bifunctional catalysts for a variety of applications, using novel heterogenized imidazolylphosphines.

■ ASSOCIATED CONTENT

Supporting Information

Details of reactions and results. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dbgrotjahn@mail.sdsu.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. LeRoy Lafferty (SDSU Chemistry and Biochemistry) for NMR assistance and Lisa Thurn (SDSU Biology) for assistance with ICP-OES. We thank the NSF (CHE 0719575, 1059107) for supporting this and related work.

■ REFERENCES

(1) (a) Lange, H.; Carpenter, M. J.; Jones, A. X.; Smith, C. J.; Nikbin, N.; Baxendale, I. R.; Ley, S. V. *Synlett* **2011**, *6*, 869–873. (b) Smith, M. D.; Stepan, A. F.; Ramarao, C.; Brennan, P. E.; Ley, S. V. *Chem. Commun.* **2003**, 2652–2653. (c) Hartley, F. R. *Supported Metal Complexes*; Reidel, D. Publishing: Dordrecht, Holland, 1985. (d) Yermakov, Y. I.; Kuznetsov, B. N.; Zakharov, V. A. *Catalysis by Supported Complexes*; Elsevier Scientific Publishing Company: Amsterdam, Holland, 1981. (e) Buchmeiser, M. R. *Polymeric Materials in Organic Synthesis and Catalysis*; Wiley-VCH, Weinheim, 2003. (f) Verkade, J. G. Converting Homogeneous to Heterogeneous Catalysts, U.S. Patent 4276195, June 30, 1981. (g) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17–57.

(2) (a) Tooley, P. A.; Arndt, L. W.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **1985**, *107*, 2422–2427. (b) Gee, J. C. Linear Olefin Isomerization

Using Molecular Sieve Catalysts, U.S. Patent 200916375, June 25, 2009. (c) Cano, M. L.; Doll, M. J.; Garza, H.; Springer, R. B.; Worstell, J. H. Process for Manufacture of Internal Olefins, W.O. Patent 2008124375, September 16, 2008. (d) Coleto, I.; Roldan, R.; Jimenez-Sanchidrian, C.; Gomez, J. P.; Romero-Salguero, F. J. *Catal. Today* **2010**, *149*, 275−280. (e) Harmer, M. A.; Sun, Q.; Vega, J. A.; Farneth, W. E.; Heidelcum, A.; Hoelderich, W. F. *Green Chem.* **2000**, *2*, 7−14. (f) Marković, D.; Varela-Álvarez, A.; Sordo, J. A.; Voge, P. *J. Am. Chem. Soc.* **2006**, *128*, 7782−7795. (g) Kaskel, S.; Schichte. *J. Catal.* **2001**, *201*, 270−274. (h) Ono, Y.; Baba, T. *Catal. Today* **1997**, *38*, 321−337. (i) Koenigsmann, L.; Schwab, E.; Hahn, T.; Kons, G. Isomerizing Linear Olefins, W.O. Patent 2011076718, June 30, 2011. (j) Iselborn, S.; Heidemann, T. Method for Isomerizing Olefins, W.O. Patent 2009050194, April 23, 2009.

(3) (a) Sherrington, D. C.; Tang, H. *J. Mol. Catal.* **1994**, *94*, 7−17. (b) Freeman, M. B.; Patrick, M. A.; Gates, B. C. *J. Catal.* **1982**, *73*, 82−90. (c) Motoyama, Y.; Abe, M.; Kamo, K.; Kosako, Y.; Nagashima, Y. *Chem. Commun.* **2008**, 5321−5323. (d) Augustine, R. L.; Jiwan, L. *J. Mol. Catal.* **1986**, *37*, 189−200. (e) Lau, C.; Chang, B.; Grubbs, R. H.; Brubaker, C. H., Jr. *J. Organomet. Chem.* **1981**, *214*, 325−337. (f) Bergbreiter, D. E.; Parsons, G. L. *J. Organomet. Chem.* **1981**, *208*, 47−53. (g) Baxendale, I. R.; Lee, A. L.; Ley, S. V. *Synlett* **2001**, *9*, 1482−1484. (h) Baxendale, I. R.; Lee, A. L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850−1857.

(4) (a) Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A. *J. Am. Chem. Soc.* **2007**, *129*, 9592−9593. (b) Grotjahn, D. B.; Larsen, C. R.; Erdogan, G.; Gustafson, J. L.; Nair, R.; Sharma, A. *Catal. Org. React.* **2009**, *123*, 379−390.

(5) Erdogan, G.; Grotjahn, D. B. *J. Am. Chem. Soc.* **2009**, *131*, 10354−10355.

(6) (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149−2154. (b) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275−3300. (c) Cole-Hamilton, D. J. *Science* **2003**, *299*, 1702−1706.

(7) Seki, M. *Synthesis* **2006**, *18*, 2975−2992 and ref 11 therein.

(8) (a) De Vos, D. E.; Dams, M.; Sels, B. F.; Jacobs, P. A. *Chem. Rev.* **2002**, *102*, 3615−3640. (b) Djakovitch, L.; Rollet, P. *Adv. Synth. Catal.* **2008**, *350*, 1816−1822. (c) Kohler, K.; Wagner, M.; Djakovitch, L. *Catal. Today* **2001**, *66*, 105−114. (d) Sheils, R. A.; Venkatasubbaiah, K.; Jones, C. W. *Adv. Synth. Catal.* **2008**, *350*, 2823−2834.

(9) Hodge, P.; Sherrington, D. C. *Polymer-Supported Reactions in Organic Synthesis*; John Wiley & Sons: Toronto, 1980; p 249.

(10) Larsen, C. R.; Erdogan, G.; Moore, C. E.; Grotjahn, D. B.; Rheingold, A. L. *manuscript in progress*.

(11) (a) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147−4154. (b) Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *J. Catal.* **2003**, *215*, 199−207.

(12) (a) Atrash, B.; Reader, J.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 4779−4782. (b) Frechet, M. J. J.; Darling, G. D.; Itsuno, S.; Lu, P. Z.; de Meftahi, M. V.; Rolls, W. A., Jr. *Pure Appl. Chem.* **1988**, *60*, 353−364.

(13) For pyridylphosphine on a support, see: Doherty, S.; Knight, J. G.; Betham, M. *Chem. Commun.* **2006**, 88−90.

(14) Detection limits are estimated as 0.5% for reactions conducted wholly in NMR tubes and 2% for vial reactions from which aliquots were removed, followed by dilution for analysis by ^{1}H NMR spectroscopy.

(15) (a) Epiotis, N. D.; Bjorkquist, D.; Bjorkquist, L.; Sarkanen, S. *J. Am. Chem. Soc.* **1973**, *95*, 7558−7562. (b) Bingham, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 535−540. (c) Knorr, R. *Chem. Ber.* **1980**, *113*, 2441−2461. (d) Larsen, C. R.; Grotjahn, D. B. *J. Am. Chem. Soc.* **2012**, *134*, 10357−10360. (e) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413−416.

(16) (a) Kaspar, J.; Spogliarich, R.; Graziani, M. *J. Organomet. Chem.* **1985**, *281*, 299−304. (b) Qian, Y.; Zhuang, J.; Lu, J.; Huang, Q.; Wu, W. *J. Mol. Catal.* **1986**, *38*, 331−335. (c) Qian, Y.; Li, G. *J. Mol. Catal.* **1990**, *60*, 19−30.

(17) Clark, J. H.; Macquarrie, D. J. *Handbook of Green Chemistry and Technology*; Blackwell: Oxford, 2002.

(18) Jinesh, C. M.; Rives, V.; Carriazo, D.; Antonyraj, C. A.; Kannan, S. *Catal. Lett.* **2010**, *134*, 337−342.

(19) (a) Brennan, M. C. *A Practical Approach to Quantitative Metal Analysis of Organic Matrices*; Wiley: Chichester, U.K., 2008. (b) Keraani, A.; Fischmeister, C.; Renouard, T.; Le Floch, M.; Baudry, A.; Bruneau, C.; Rabiller-Baudry, M. *J. Mol. Catal. A: Chem.* **2012**, *357*, 73−80. (c) Yang, L.; Mayr, M.; Wurst, K.; Buchmeiser, M. R. *Chem.—Eur. J.* **2004**, *10*, 5761−5770.

(20) (a) Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W. W.; Fong, H. H. S.; Farnsworth, N. R.; Kinghorn, D. A.; Mehta, N. R.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218−220. (b) Rayne, S.; Goss, C. D.; Forest, K.; Friesen, K. J. *Med. Chem. Res.* **2010**, *19*, 864−901. (c) Ferré-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. *Eur. J. Org. Chem.* **2005**, 3319−3325.

(21) Berlo, V. B.; Houthoofd, K.; Sels, B. F.; Jacobs, P. A. *Adv. Synth. Catal.* **2008**, *350*, 1949−1953.

(22) Vankelecom, I. F. J.; Jacobs, P. A. in *Chiral Catalyst Immobilization and Recycling*; De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; Wiley-VCH: Weinheim, 2000; pp 22−28.