DOI: 10.1002/adsc.200900309

# Palladium-Catalyzed Isomerization of *exo*-Methylenic Allylic Alcohols

Paul S. Fordred,[a] D. Gangani Niyadurupola,[a] Richard Wisedale,[b] and Steven D. Bull[a,*]

[a] Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, U.K.
Fax: (+44)-1225-386231; phone: (+44)-1225-383551; e-mail: s.d.bull@bath.ac.uk
[b] AstraZeneca, Global Process R&D, Avlon Works, Severn Rd., Hallen, Bristol, BS10 7ZE, U.K.

Received: May 1, 2009; Published online: October 1, 2009

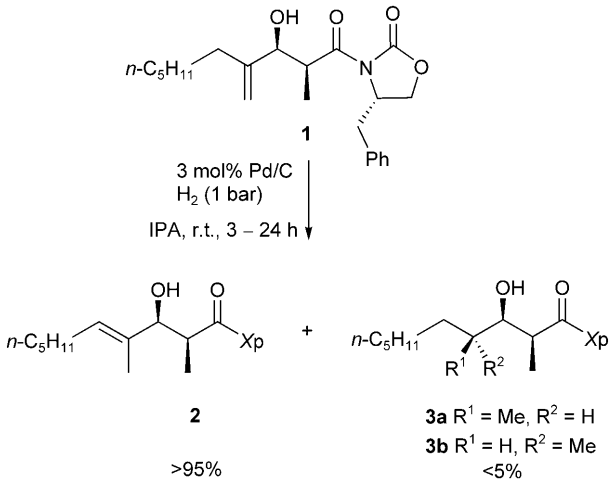
**Abstract:** Treatment of allylic alcohols containing a 1,1-disubstituted alkene with a palladium catalyst and hydrogen gas (1 bar) results in facile isomerization to their corresponding trisubstituted (*E*)-allylic alcohols, along with small amounts of the corresponding hydrogenated products.

**Keywords:** alkenes; allylic alcohols; hydrogenation; isomerization; palladium

The ability of transition metal complexes to catalyze the isomerization of olefinic compounds is well documented, with the alkene bonds of hetero-allylic systems representing a common target. Selected examples include: transition metal-catalyzed conversion of allylic alcohols to saturated aldehydes or ketones;[1] nickel-catalyzed isomerization of *O*-allyl ethers to enol ethers;[2] rhodium-catalyzed isomerization of allyl silyl ethers to silyl enol ethers;[3] ruthenium-mediated conversion of *N*-allylic amines to their corresponding enamines;[4] iron-catalyzed isomerization of *N*-allylamides to enamides;[5] ruthenium-catalyzed alkene migration of allylic sulfides, sulfones and sulfoxides to afford their corresponding vinylic species;[6] palladium-catalyzed formation of α,β-unsaturated esters from unconjugated species;[7] and ruthenium-catalyzed deconjugation of α,β-unsaturated esters.[8] Consequently, we now report herein on the palladium-catalyzed hydrogenolytic isomerization of *exo*-methylenic allylic alcohols to give their corresponding trisubstituted (*E*)-allylic isomers in good yield.

We have recently introduced the concept of using temporary stereocentres to efficiently relay stereochemical information to create remote stereogenic centres.[9] As part of an investigation employing hydroxyl-directed catalytic hydrogenation reactions for the asymmetric synthesis of chiral α-methyl aldehydes,[10] we required authentic samples of aldol diastereoisomers **3a** and **3b**. Therefore, *exo*-methylenic allylic alcohol **1** in isopropyl alcohol (IPA) was treated with 3 mol% Pd/C under one bar of hydrogen for three hours, which did not afford the expected diastereoisomeric hydrogenated products **3a**/**3b**, but instead gave the isomerized trisubstituted (*E*)-allylic alcohol **2** in >95% yield (Scheme 1). This result was unexpected, since palladium catalysts had been used previously to reduce the alkene functionality of related allylic alcohols,[11] as well as catalyzing isomerization to their corresponding ketones.[12]

This type of isomerization reaction has been proposed to explain the poor diastereoselectivity observed in rhodium-mediated hydrogenation reactions of related *exo*-methylenic allylic alcohols at low hydrogen pressure.[13] In this case, it was demonstrated that a cationic rhodium catalyst was capable of facilitating the isomerization reaction to afford mixtures of starting *exo*-methylenic allylic alcohol, its corresponding trisubstituted allylic alcohol and a β-keto imide.




**Scheme 1.** Palladium-catalyzed isomerization of *exo*-methylenic allylic alcohol **1** to afford trisubstituted (*E*)-allylic alcohol **2**.

Contrastingly, in our case, palladium-mediated isomerization of allylic alcohol **1** had occurred to selectively afford trisubstituted (*E*)-allylic alcohol **2**, with retention of its β-hydroxy stereocentre, as the major product.[14]

The mechanism of this palladium-catalyzed isomerization reaction was then investigated.[15] Firstly, it was shown that hydrogen was necessary for the isomerization reaction to occur, since treatment of **1** with 3 mol% Pd/C in IPA under nitrogen gave only unreacted starting material after 24 h. A series of deuterium labelling experiments were then carried out to determine where deuterium would be incorporated into **2**. Carrying out the isomerization reaction in IPA-$d_8$ only resulted in exchange of the hydroxylic proton, with no other deuterium atoms being incorporated into trisubstituted allylic alcohol **2**. Treatment of **1** with 3 mol% Pd/C in IPA under a balloon of deuterium gas for three hours resulted in very little isomerization occurring (<10% conversion), which we proposed was due to the presence of a large kinetic isotope effect. Consequently, this deuterium isomerization reaction was repeated over a period of 16 h which resulted in 50% conversion of aldol **1** to its isomerized aldol **2**. $^1$H and $^2$H NMR spectroscopic analysis revealed that two deuterium atoms had been incorporated into the trisubstituted allylic alcohol $d_2$-**2** (100% deuterium incorporation at allylic methyl position, 70% deuterium incorporation at vinylic position).[16] From these results a potential mechanism was proposed, in which a palladium deuteride species first adds across the alkene functionality of **1** to afford intermediate *d*-**4**, which selectively eliminates a palladium hydride species to afford the thermodynamically favoured trisubstituted alkene *d*-**2**.[17] Hydrogen-deuterium exchange of the palladium catalyst, followed by addition of palladium deuteride to *d*-**2**, then forms $d_2$-**5**, which eliminates a palladium hydride species to afford the observed trisubstituted allylic alcohol $d_2$-**2** (Figure 1).[18] It was also shown that 3 mol% $Pd(OAc)_2$ could be used to catalyze formation of trisubstituted allylic alcohol **2**, thus enabling this isomerization reaction to be carried out under either heterogeneous or homogeneous catalytic conditions.

It was then decided to optimize this palladium-catalyzed isomerization reaction using a pair of simplified *exo*-methylenic allylic alcohols **6a**, **6b** as substrates (Table 1). Treatment of allylic alcohol **6a** with 10 mol% $Pd(OAc)_2$ in IPA under one bar of hydrogen[19] for 20 min successfully afforded trisubstituted allylic alcohol **7a** [(*E*):(*Z*)=8:1] and the fully hydrogenated alcohols **8a**/**9a**[20] in a ratio of 77:23 (Table 1, entry 1). Evidently, the alkene bonds of allylic alcohols **6a**/**7a** were more susceptible to hydrogenation than the alkene bonds of allylic alcohols **1**/**2**, which we presumed was due to the presence of their less

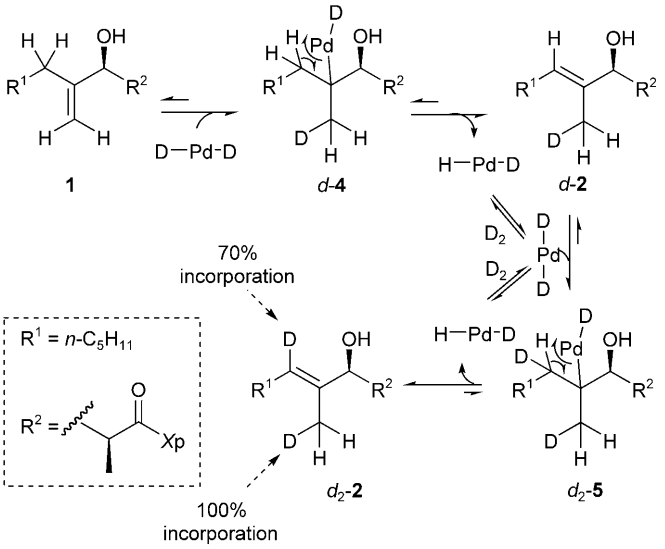
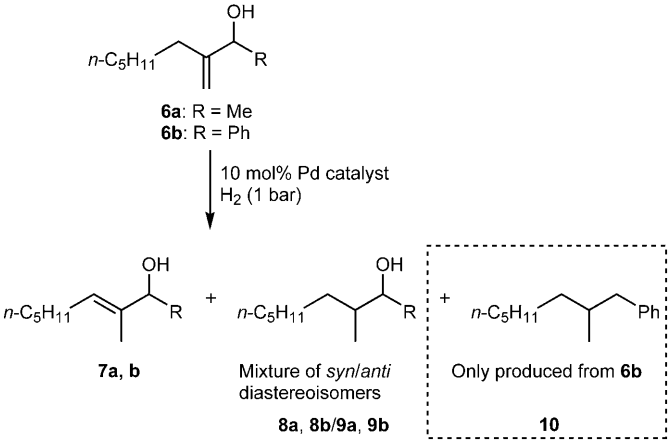



**Figure 1.** Palladium-catalyzed isomerization of *exo*-methylenic allylic alcohol **1** to afford trisubstituted (*E*)-allylic alcohol **2**.

**Table 1.** Palladium-catalyzed isomerization of *exo*-methylenic allylic alcohols.

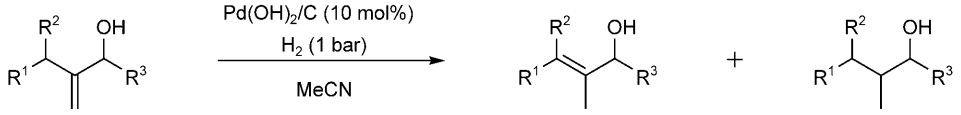



| Entry | Substrate | Solvent/ Additive | Time [min] | Product ratio [%][a] 7[b] | 8/9 |
|---|---|---|---|---|---|
| 1[c] | **6a** | IPA | 20 | 77 (8:1) | 23 |
| 2[c,d] | **6b** | IPA | 60 | 55 (9:1) | 15 |
| 3[c] | **6b** | IPA/$Cs_2CO_3$ | 60 | 80 (14:1) | 20 |
| 4[c] | **6b** | EtOAc | 90 | 83 (12:1) | 7 |
| 5[e] | **6a** | MeCN/$Cs_2CO_3$ | 15 | 90 (21:1) | 10 |

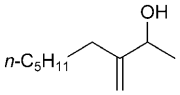
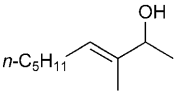
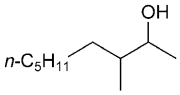
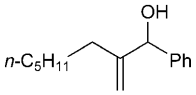
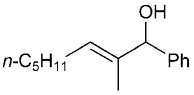
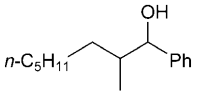
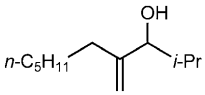
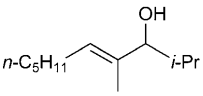
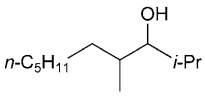
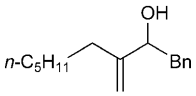
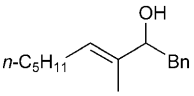
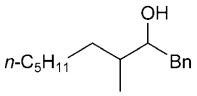
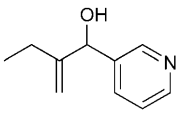
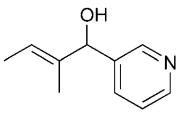
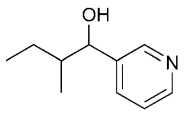
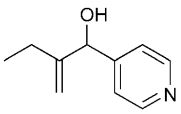
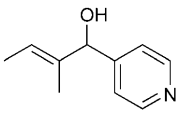
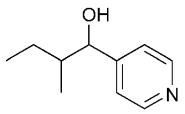
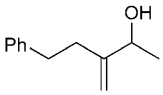
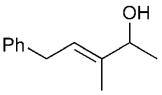
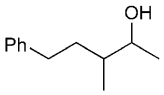
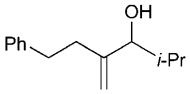
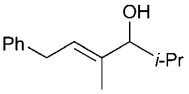
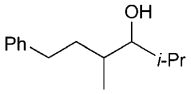
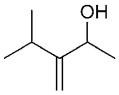
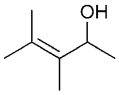
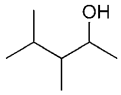
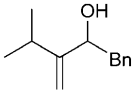
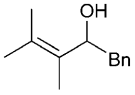
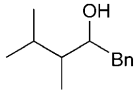
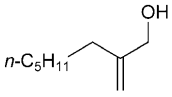
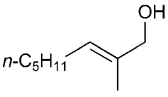
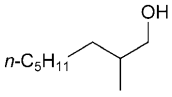
[a] Ratios determined by $^1$H NMR spectroscopic analysis.
[b] Numbers in brackets denote (*E*):(*Z*) ratios.
[c] Reactions carried out using $Pd(OAc)_2$ at room temperature.
[d] Remaining mass balance comprised of (2-methyloctyl)-benzene **10**.
[e] Reaction carried out using $Pd(OH)_2$/C at 0 °C.

**Table 2.** Palladium-catalyzed isomerization of allylic alcohols **6a–k** under hydrogenolytic conditions.




**6a – k** **7a – k** **8a – k/9a – k**

| Entry | Allylic alcohol **6** | Temp. [°C][a] | Time [min] | Product ratio [%][b] **7**[c] | **8/9**[20] |
|---|---|---|---|---|---|
| 1 | **6a**  | 0 | 15 | **7a**: 90 (21:1)  | **8a/9a**: 10  |
| 2 | **6b**  | 20 | 30 | **7b**: 87 (8:1)  | **8b/9b**: 13  |
| 3 | **6c**  | 20 | 40 | **7c**: 96 (17:1)  | **8c/9c**: 4  |
| 4 | **6d**  | 0 | 60 | **7d**: 80 (7:1)  | **8d/9d**: 20  |
| 5[d] | **6e**  | 20 | 15 | **7e**: 83 (10:1)  | **8e/9e**: 17  |
| 6[d] | **6f**  | 20 | 15 | **7f**: 83 (10:1)  | **8f/9f**: 17  |
| 7 | **6g**  | 0 | 60 | **7g**: 55 (6:1)  | **8g/9g**: 45  |
| 8 | **6h**  | 20 | 60 | **7h**: 75 (8:1)  | **8h/9h**: 25  |
| 9 | **6i**  | 20 | 15 | **7i**: 61  | **8i/9i**: 39  |
| 10 | **6j**  | 20 | 25 | **7j**: 58  | **8j/9j**: 42  |
| 11[e] | **6k**  | 20 | 15 | **7k**: 65 (4:1)  | **8k/9k**: 21  |

[a] Temperature chosen to maximize yield of **7** and ensure isomerization reaction proceeded to completion within one hour.
[b] Ratios determined by $^1$H NMR spectroscopic analysis.
[c] Numbers in brackets denote (*E*):(*Z*) ratios.
[d] Reactions carried out in IPA because alcohols **6e**/**6f** are not soluble in MeCN.
[e] Remaining mass comprised of aldehyde **11**.

sterically demanding methyl substituents. We then investigated isomerization of allylic alcohol **6b** under these conditions, which gave a 55:15:30 ratio of trisubstituted allylic alcohol **7b** [(*E*):(*Z*)=9:1], hydrogenated alcohols **8b**/**9b**[20] and (2-methyloctyl)benzene **10** (Table 1, entry 2). We considered that formation of **10** might be facilitated by protonation of its hydroxy group by the IPA solvent. Consequently, we carried out the isomerization reaction in the presence of one equivalent of $Cs_2CO_3$ which served to completely sup-

press formation of **10**, but still gave 20% of the unwanted hydrogenated alcohols **8b/9b** (Table 1, entry 3). Alternatively, repeating the isomerization reaction of **6b** in an aprotic polar solvent such as EtOAc resulted in only 10% of **10** being formed, as well as producing significantly less amounts of the unwanted hydrogenated alcohols **8b/9b**[20] (7%) (Table 1, entry 4). At this stage, a full catalyst/solvent screen was carried out to maximize the yield of trisubstituted allylic alcohol **7a**. This resulted in $Pd(OH)_2/C$ in MeCN being identified as the catalyst/solvent system of choice, which in the presence of one equivalent of $Cs_2CO_3$ gave trisubstituted allylic alcohol **7a** in 90% yield, with only 10% of the hydrogenated alcohols **8a/9a**[20] being formed (Table 1, entry 5).

The scope and limitation of this palladium-catalyzed isomerization reaction was then investigated by applying the optimal conditions of 10 mol% $Pd(OH)_2/C$, $H_2$ (1 bar), $Cs_2CO_3$ (1 equiv.), [substrate] = 1 mol dm$^{-3}$ to a range of eleven *exo*-methylenic allylic alcohols **6a–k** (Table 2) in MeCN.[21–23] These isomerization reactions gave eleven trisubstituted allylic alcohols **7a–k** in moderate to high yields (55–96%) with good to excellent (*E*):(*Z*) ratios (ranging from 4:1 to 21:1),[24] as well as producing varying amounts (4–45%) of their corresponding hydrogenated alcohol products **8a–k/9a–k**.[20] This isomerization reaction was successful for the preparation of trisubstituted allylic alcohols **7a–f** bearing a range of aliphatic and aromatic substituents at their carbinol carbon, with ≥80% yields being obtained in each case (Table 2, entries 1–6). However, isomerization of *exo*-methylenic allylic alcohols **6g**, **6h** containing benzylic substituents at their allylic position proved less efficient, affording trisubstituted allylic alcohols **7g**, **7h** in 55–75% yield accompanied by significant amounts (25–45%) of hydrogenated alcohols **8g**, **8h/9g**, **9h** (Table 2, entries 7 and 8).

Similarly, palladium-catalyzed isomerization of *exo*-methylenic allylic alcohols **6i**, **6j** gave allylic alcohols **7i**, **7j** containing a tetrasubstituted alkene functionality in only 58–61% yield, with significant amounts of reduced alcohols **8i**, **8j/9i**, **9j** (39–42%) being produced (Table 2, entries 9 and 10). In these cases it is likely that significant steric interactions disfavour the *syn*-periplanar conformation required for palladium hydride elimination to occur [see Figure 2a for formation of (*E*)-**7i**], resulting in higher proportions of the hydrogenated alcohols **8i**, **8j/9i**, **9j** being produced. Isomerization of primary allylic alcohol **6k** gave a 65% yield of trisubstituted allylic alcohol **7k**, a 21% yield of its corresponding hydrogenated alcohols **8k/9k**[20] and a 14% yield of 2-methyloctanal **11** (Table 2, entry 11). This aldehyde is likely to be formed from palladium-catalyzed isomerization of **6k** to an unstable enol which subsequently tautomerizes to the carbonyl compound. Attempts to isomerize tertiary allylic alcohol **12** (Figure 2b) proved unsuccessful with prolonged reaction times being required to afford large amounts of its corresponding hydrogenated alcohol, with <20% of its isomerized trisubstituted allylic alcohol being formed.

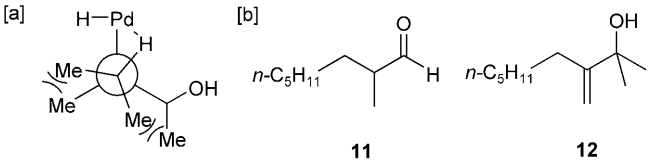



**Figure 2.** [a] Significant steric interactions disfavour the *syn*-periplanar conformation required for elimination to afford (*E*)-**7i**; [b] Aldehyde **11** and tertiary allylic alcohol **12**.

In summary, we have shown that treatment of allylic alcohols containing a 1,1-disubstituted alkene with a palladium catalyst and hydrogen gas (1 bar) results in facile isomerization to their corresponding trisubstituted allylic alcohols, along with small amounts of their corresponding hydrogenated products.

## Experimental Section

### Procedure for the Synthesis and Isomerization of Allylic Alcohol 6c

**2-Methyleneoctanal**:[25] Into a 100-mL flask, fitted with a reflux condenser, were placed *n*-octanal (8.2 g, 64.0 mmol), dimethylamine hydrochloride (6.89 g, 84.4 mmol) and 37% aqueous formaldehyde solution (6.3 mL, 84.4 mmol). The resulting mixture was heated at 70 °C with stirring for 24 h. After cooling to room temperature, the reaction mixture was neutralized with $NaHCO_3$ solution and the aqueous layer extracted with hexane (3×10 mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent removed under vacuum to afford the title compound as a colourless oil; yield: 6.9 g (77%); $^1$H NMR ($CDCl_3$): $\delta$ = 9.47 (1H, s), 6.19–6.16 (1H, m), 5.92–5.90 (1H, m), 2.21–2.12 (2H, m), 1.44–1.14 (8H, m), 0.81 (3H, t, $J$ = 6.8 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 195.2, 150.9, 134.2, 32.0, 29.3, 28.1, 28.0, 22.9, 14.4.

**2-Methyl-4-methylenedecan-3-ol** (**6c**): THF (80 mL) and *i*-PrMgCl (19.6 mL, 2.0 M in THF) were placed into a 250-mL round-bottom flask and the resulting solution cooled to 0 °C. 2-Methyleneoctanal (5 g, 35.7 mmol) was then added dropwise. After stirring at this temperature for a further 15 min, the reaction was quenched by cautious addition of saturated potassium sodium tartrate solution, filtered through Celite® and the solvent removed under vacuum. The residue was redissolved in $Et_2O$ (100 mL), washed successively with 1.0 M aqueous HCl (30 mL), $H_2O$ (2×30 mL) and brine (30 mL), dried ($MgSO_4$) and the solvent removed under vacuum. The crude product was purified by silica gel column chromatography to afford the title compound as a colourless oil; yield: 4.54 g (69%); $^1$H NMR ($CDCl_3$): $\delta$ = 4.91 (1H, s), 4.82–4.79 (1H, m), 3.68 (1H, d, $J$ = 6.5 Hz), 2.07–1.80 (2H, m), 1.80–1.66 (1H, m), 1.47–1.16 (8H, m), 0.86 (3H, d, $J$ = 6.7 Hz),

0.82 (3H, obs. t), 0.81 (3H, d, $J=6.8$ Hz); $^{13}$C NMR ($CDCl_3$): $\delta=151.7$, 110.5, 81.5, 32.2, 31.8, 31.5, 29.7, 28.3, 23.0, 20.1, 17.7, 14.5; HR-MS (ESI): $m/z=183.1739$, calcd. for $C_{12}H_{24}O$ [$M^-$] :183.1749.

### (*E*)-2,4-Dimethyldec-4-en-3-ol (7c)

2-Methyl-4-methylenedecan-3-ol (**6c**) (184 mg, 1 mmol) was dissolved in MeCN (0.2 mL) and then added *via* syringe to a Schlenk tube containing $Pd(OH)_2$/C (125.2 mg, 0.1 mmol Pd), $Cs_2CO_3$ (325.8 mg, 1 mmol) in MeCN (0.8 mL) under one bar of hydrogen. The reaction mixture was then stirred at 20 °C for 40 min, filtered through Celite® and the solvent removed under vacuum to afford the title compound. $^1$H NMR ($CDCl_3$); $\delta=5.38$ (1H, t, $J=7.1$ Hz), 3.59 (1H, d, $J=8.3$ Hz), 2.11–1.98 (3H, m), 1.87–1.68 (1H, m), 1.43–1.22 (8H, m), 1.00 (3H, d, $J=6.6$ Hz), 0.91 (1H, t, $J=6.7$ Hz), 0.80 (3H, d, $J=6.8$ Hz); $^{13}$C NMR ($CDCl_3$): $\delta=136.6$, 128.5, 84.7, 31.9, 31.5, 29.6, 22.9, 19.8, 19.2, 19.1, 14.5, 11.6; HR-MS (ESI): $m/z=207.1732$, calcd. for $C_{12}H_{24}NaO$ [$M^+$]: 207.1725.

## Acknowledgements

*We would like to thank the EPSRC and AstraZeneca for funding.*

## References

[1] R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27–51.
[2] A. Wille, S. Tomm, H. Frauenrath, *Synthesis* **1998**, 305–308.
[3] K. Hiroya, Y. Kurihara, K. Ogasawara, *Angew. Chem.* **1995**, *107*, 2445–2448; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2287–2289.
[4] B. Alcaide, P. Almendros, J. M. Alonso, *Chem. Eur. J.* **2003**, *9*, 5793–5799.
[5] S. Sergeyev, M. Hesse, *Synlett* **2002**, 1313–1317.
[6] N. Kuźnik, S. Krompiec, T. Bieg, S. Baj, K. Skutil, A. Chrobok, *J. Organomet. Chem.* **2003**, *665*, 167–175.
[7] X. Wang, L. K. Woo, *J. Mol. Catal. A: Chem.* **1998**, *130*, 171–176.
[8] H. Wakamatsu, M. Nishida, N. Adachi, M. Mori, *J. Org. Chem.* **2000**, *65*, 3966–3970.
[9] M. Cheeseman, F. J. P. Feuillet, A. L. Johnson, S. D. Bull, *Chem. Commun.* **2005**, 2372–2374.
[10] D. G. Niyadurupola, I. R. Davies, R. Wisedale, S. D. Bull, *Eur. J. Org. Chem.* **2007**, *33*, 5487–5491.
[11] A. Bouzide, *Org. Lett.* **2002**, *4*, 1347–1350.
[12] M. G. Musolino, P. De Maio, A. Donato, R. Pietropaolo, *J. Mol. Catal. A: Chem.* **2004**, *208*, 219–224.
[13] D. A. Evans, M. M. Morrissey, *J. Am. Chem. Soc.* **1984**, *106*, 3866–3868.
[14] For previous reports of rhodium-catalyzed isomerizations of *exo*-methylenic cyclohexanes, *exo*-methylenic ketones and *exo*-methylenic lactones, see: a) P. Stahl, L. Kissau, R. Mazitschek, A. Huwe, P. Furet, A. Giannis, H. Waldmann, *J. Am. Chem. Soc.* **2001**, *123*, 11586–11593; b) N. De Kimpe, W. Aelterman, *Tetrahedron* **1996**, *52*, 12815–12820; c) H. Takayama, R. Sudo, M. Kitajima, *Tetrahedron Lett.* **2005**, *46*, 5795–5797.
[15] A series of other transition metal complexes were unsuccessfully screened as catalysts for this isomerization reaction, including $Au(PPh_3)Cl$, $Rh(cod)_2OTf$, $RhCl_3\cdot 3H_2O$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$ and $PdCl_2(PhCN)_2$.
[16] A mechanism involving a π-allyl palladium intermediate would be likely to incorporate either one or four equivalents of deuterium.
[17] See also: a) J. Yu, J. B. Spencer, *J. Org. Chem.* **1997**, *62*, 8618–8619; b) J. Yu, P. S. Whitney, J. B. Spencer, *J. Mol. Catal. A* **1999**, *146*, 199–210.
[18] Treatment of trisubstituted allylic alcohol **2** with 3 mol% Pd/C in IPA under a balloon of deuterium gas for eight hours resulted in 60% incorporation of deuterium into its vinylic position.
[19] Experiments employing $<1$ bar of hydrogen resulted in competing oxidation of allylic alcohol **6a** to its corresponding ketone.
[20] All *syn*-/*anti*-hydrogenated alcohols **8**/**9** were formed in a ratio ranging from 1:1 to 2:1, with major isomers unassigned.
[21] Allylic alcohols **6a–d** and **6g–j** were prepared *via* α-methylenation of the appropriate aldehyde with formaldehyde and dimethylamine hydrochloride, followed by addition of the corresponding Grignard reagent; see: a) C. S. Marvel, R. L. Myers, J. H. Saunders, *J. Am. Chem. Soc.* **1948**, *70*, 1694–1699; b) Y. Nakao, Y. Hirata, M. Tanaka, T. Hiyama, *Angew. Chem.* **2008**, *120*, 391–393; *Angew. Chem. Int. Ed.* **2008**, *47*, 385–387.
[22] Allylic alcohols **6e**, **f** were prepared *via* addition of the appropriate pyridyl-Grignard reagent to 2-ethylacrolein; see: F. Trécourt, G. Breton, V. Bonnet, F. Mongin, F. Marsais, G. Quéguiner, *Tetrahedron* **2000**, *56*, 1349–1360.
[23] Allylic alcohol **6k** was prepared *via* reduction of 2-methyleneoctanal with $LiAlH_4$; see: K. Mori, *Tetrahedron: Asymmetry* **2007**, *18*, 838–846.
[24] The alkene protons of the (*E*)-isomers of trisubstituted allylic alcohols **7a–h**, **7k** appeared at a higher chemical shift in their $^1$H NMR spectra than the alkene protons of their corresponding (*Z*)-isomers.
[25] Y. Nakatsuji, T. Nakamura, M. Yonetani, H. Yuya, M. Okahara, *J. Am. Chem. Soc.* **1988**, *110*, 531–538.