DOI: 10.1002/adsc.201100953

Modular Palladium Bipyrazoles for the Isomerization of Allylbenzenes – Mechanistic Considerations and Insights into Catalyst Design and Activity, Role of Solvent, and Additive Effects

Markus J. Spallek,[a] Skrollan Stockinger,[a] Richard Goddard,[b] and Oliver Trapp[a,*]

[a] Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
Fax: (+49)-6221-544-904; e-mail: trapp@oci.uni-heidelberg.de
[b] Department for Chemical Crystallography and Electron Microscopy, Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim a.d. Ruhr, Germany

Received: December 6, 2011; Revised: February 23, 2012; Published online: May 15, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100953.

Abstract: The catalytic activity of novel bidentate *N,N*-chelated palladium complexes derived from electron excessive, backbone fused 3,3′-bipyrazoles in the selective isomerization of terminal arylpropenoids and 1-alkenes is described. The catalysts are easily modified by appropriate wing tip substitution, while maintaining the same bulky, rigid unreactive aliphatic backbone. Eleven novel palladium complexes with different electronic and steric properties were investigated. Their performance in the palladium(II)-catalyzed isomerization of a series of substituted allylbenzenes was evaluated in terms of electronic as well as steric effects. Besides the clear finding of a general trend towards higher catalyst activity with more electron-donating properties of the coordinated *N,N*-bidentate ligands, we found that the catalytic process strongly depends on the choice of solvents and additives. Extensive solvent screening revealed that reactions run best in a 2:1 toluene-methanol mixture, with the alcohol employed being a crucial factor in terms of electronic and steric factors. A reaction mechanism involving a hydride addition–elimination mechanism starting with a palladium hydride species generated *in situ* in alcoholic solutions, as corroborated by experiments using deuterium labeled allylbenzene, seems to be most likely. The proposed mechanism is also supported by the observed reaction rate orders of κ_{obs}[cat.]$\approx$1 (0.94), κ_{obs} [substrate]$=0.20\rightarrow1.0$ ($t\rightarrow\infty$) and κ_{obs} [methanol]$=-0.51$ for the isomerization of allylbenzene. Furthermore, the influence of acid and base, as well as the role of the halide coordinated to the catalyst, are discussed. The system catalyzes the isomerization of allylbenzenes very efficiently yielding high *E*:*Z* selectivities under very mild conditions (room temperature) and at low catalyst loadings of 1 mol% palladium even in unpurified solvents. The integrity and stability of the catalyst system were confirmed by multiple addition reaction cycles, successive filtration and isolation experiments, and the lack of palladium black formation.

Keywords: alcohols; bipyrazoles; camphor; electronic effects; homogeneous catalysis; isomerization; palladium; reaction mechanism

Introduction

The catalytic isomerization of olefins is an important and widely established process in industry and is broadly employed in petrochemical refining processes, mostly in combination with heterogeneous catalysts.[1–3] There is a large variety of existing synthetic methods for the construction of carbon-carbon double bonds or the introduction of an unsaturated functionality, many of which deal with mixtures of (*E*)- and (*Z*)-isomers. The controlled migration of a pre-existing unsaturated functionality is a very elegant, alternative route of transformation.[4] In particular, the isomerization of carbon-carbon double bonds obeys the sustainability criteria in that it is a 100% atom efficient reaction and has widespread application, either for interconversion of (*E*)- and (*Z*)-alkenes[5–7] or for stereocontrolled rearrangement of functionality along

the carbon chain. This reaction is extensively deployed in the preparation of commodities for polymer synthesis, pharmaceuticals and fine chemicals, such as fragrances.[8–11] The selective isomerization of terminal allylbenzenes into their internal counterpart compounds represents a benchmark reaction for this kind of transformation, since the latter are common starting materials in the flavor and fragrance industry. Since (*Z*)-isomers are mostly characterized by an unpleasant odor and taste and are even toxic in some cases, processes with high yields, as well as high (*E*)-selectivity, are an attractive goal, but still remain a challenge. Nowadays, procedures range from heterogeneous catalysts on suitable supports at high temperatures to simple base-catalyzed isomerizations, used for the conversion of estragol to (*E*)-anethol in KOH at 200 °C. The low yields of below 60% and only moderate *E*/*Z* selectivities (*dr* = 82:18) of this process require additional separation steps and therefore many fragrances such as eugenol, estragol and safrol, as well as their internal alkenes, are still obtained by classical extraction techniques from natural sources with several million metric tons capacity per year.[10,12]

Despite the popularity of heterogeneous catalysts, which are known to be critically affected by the presence of water at high temperatures,[1,3] the use of homogeneous catalysts presents an attractive alternative.[8] The isomerization of terminal alkenes can be accomplished by employing various transition metals, e.g., Pd,[13–17] Pt,[18–20] Ru,[21–24] Rh,[15,25,26] Ir[27–29] or Ni,[2,30] which generally afford significant amounts of the thermodynamically more stable (*E*)-isomers. Since olefin isomerization is a kinetic phenomenon, the thermodynamic driving forces, in particular the steric and electronic factors that control the β-H elimination, can be investigated by following the kinetic distribution of *cis* and *trans* isomers early in the reaction process for various catalysts. The thermodynamic equilibrium ratio between (*E*) and (*Z*) may be tuned, especially by running the reactions at higher temperatures and using catalysts with long lifetimes.[31,32] Unfortunately, when transition metals catalyze the isomerization process, side-reactions with the carbon-carbon double bond occur, the kinetics and the product distribution are affected and hence the selectivity of the reaction changes. Examples, for which such side-reactions occur, include Grubbs-type hydride complexes, which can be modified in alcoholic solutions, with hydrogen, inorganic hydrides or alkoxides. They afford very active isomerization catalysts, which are usually accompanied by olefin self-dimerization, cross-metathesis and hydrogenation of the terminal alkene functionality[33–35] or transition metals in combination with additives, such as trialkylsilanes,[22] boron or aluminium hydrides.[6,33,34,36] Besides isomerization these reactions sadly also lead to significant amounts of undesired hydrogenated side-products. To date there is no clear pathway for isomerization reactions, owing to the large variety of different catalysts, metals and ligands available for this kind of transformation.[14] This being said, Pd^{2+} catalysis, is an area worth pursuing, since upon complexation with the appropriate ligands Pd^{2+} compounds are generally stable to air and moisture.

In the present work, we wished to contribute to this important field of research, by looking at isomerizations using *N,N*-coordinated Pd(II) catalysts in alcoholic solutions. Deploying a novel, modular and rigid ligand class of backbone fused 3,3′-bipyrazoles (bicamphorpyrazoles, bcpz) developed by our group, we tested in total eleven Pd(II) halide complexes (Cl, Br) for the selective isomerization of terminal alkenes. Allylbenzenes were chosen as benchmark substrates, since they are commonly employed in preliminary studies and have important widespread application in industry, as outlined above. The following benefits of this class of *N,N*-bidentate ligands (bcpz) rendered them very suitable for our studies.

(i) They exhibit a modular ligand pattern, which can be easy modified by wingtip substitution providing catalysts with different electronic and steric (e.g., alkyl *vs.* aryl substitution) properties, together with *cis*-coordination.[17]

(ii) The central coordination cavity and ligand pattern of the 3,3′-bipyrazole core structure is maintained, avoiding direct interference between ligand shape and catalyst performance.[24]

(iii) The *N,N*-bidentate ligand pattern exhibits good thermal stability and integrity up to 363 K compared to ordinary *N*-monodentate ligands (e.g., simple nitrile coordination), as observed by our group.[37]

(iv) The bulkiness of the ligand (backbone and wingtips) is able to suppress single-side *N*-decoordination and out-of-plane rotation of the ligand, as well as avoiding any catalyst dimerization processes, whether as the catalytically active species or as causing the catalyst termination step.[17,38]

(v) Flexible wingtip substituents and extended backbone facilitate excellent solubility in most solvents including ethers, alcohols, nitriles, ketones and hydrocarbons (e.g., compared to 2,2′-bipyridines).

(vi) The high electron donor capability and π-excessive nature of 3,3′-bipyrazoles, combined with a straightforward, high yielding preparation of catalysts and facile ligand synthesis provides an entirely new approach.

In the following, we describe the results we obtained in the selective Pd(II)-catalyzed isomerization of alkenes for the synthesis of fragrances under very mild and economical experimental conditions, employing media that did not need to be purified or dried, and using low catalyst loadings. In addition, the role of the solvent in terms of electronic and steric

factors, as well as the influence of the halide concentration and the pH value on the reaction progress when using bases and acids as additives was investigated. A possible reaction mechanism based on our observations and the results of deuterium labeling studies is also discussed.

Results and Discussion

Bicamphorpyrazole-Type Catalysts

As shown in Figure 1 all catalysts are mononuclear, neutral Pd(II) soft Lewis acids, with the *N*-2,*N*-2′-nitrogen atoms of the 3,3′-bipyrazole unit coordinated *via* κ^2. The catalysts can be divided into two distinctive groups depending on the nature of the wingtip substitution, either alkyl or benzylic residues. The ligands were chosen in order to be able to investigate and compare catalytic performance with steric factors and electronic properties within the group, while maintaining the same ligand geometry and metal-coordination cavity.

Overall eleven ligands of this family were tested in the isomerization reactions of allylpropenoids. The syntheses of the Pd(II)chloride complexes have already been reported by our group.[37] The novel palladium dibromide complex **10-Br** was prepared using $PdBr_2(MeCN)_2$ as precursor, following our standard procedure (see Experimental Section). Complete characterization and analytical data obtained for this compound are in agreement with those obtained for the corresponding dichloride complex **10-Cl**. The coordination of the bcpz ligand to Pd(II) was conveniently monitored by ^{1}H-NMR spectroscopy. Complexation results in a distinctive pattern for the *cisoid*-fixed structure.

Whereas the free *N*-1,*N*-1′-benzyl-substituted ligands show a significant singlet between 5.0 and 5.6 ppm for the benzylic methylene group of the wingtips (enantiotopic protons), this signal splits into a set of

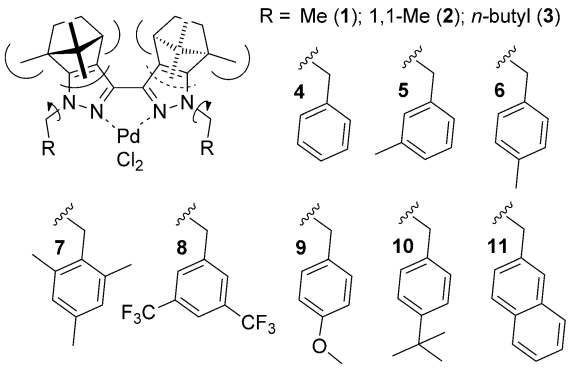


Figure 1. Catalysts for investigations of the Pd(II)-catalyzed isomerization of terminal allylic compounds.

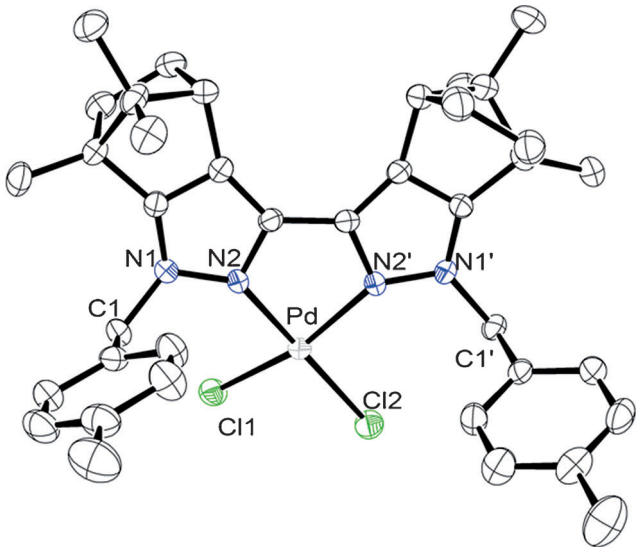


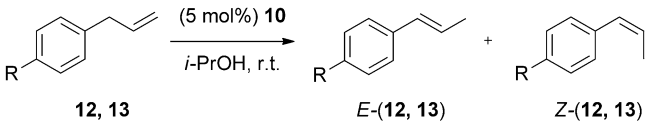
Figure 2. X-Ray crystal structure of palladium-3,3'-bipyrazole complex **6**, showing the *cisoid* structure. Thermal ellipsoids are plotted at 50% probability level and hydrogen atoms are omitted for clarity. Selected bond lengths (pm) and angles (deg) for one of the independent molecules in the unit cell: Pd–N2 208.1(2), Pd–N2′ 207.1(2), Pd–Cl1 228.8(1), Pd–Cl2 229.1(1), N1–N2 137.5(3), N1′–N2′ 137.9(3), N1–C1 148.3(3), N1′–C1′ 147.8(4), N1–Pd–N2 78.64(8), Cl1–Pd–Cl2 86.65(3).

two upon complexation, as expected for two groups of diastereotopic protons. The geminal coupling of the dibromide complex of **10** ($^2J_{C,H}$ = 15.9 Hz) and a downfield shift to 5.8 and 6.2 ppm are in agreement with the range and shift generally observed for these type of complexes ($^2J_{C,H}$ = ~13.8–14.1 Hz; Δ_{ppm} = ~0.8 ppm for dichloride complexes). The molecular structure of the palladium dichloride complex **6** obtained by single crystal structure analysis using synchrotron radiation is depicted in Figure 2. It provides an example for the eleven bcpz-derived catalysts. The dichloro-palladium unit is coordinated *via* *N*-2,*N*-2′ in a bidentate fashion. The coordination plane of the Pd atom is not exactly planar, and the Pd atom is located 0.3 Å out of the bipyrazole plane, away from the two methylbenzyl substituents. In addition, the $PdCl_2$ moiety is tilted to that of the PdN_2 unit by 14°. Slightly elongated Pd–N–bonds [average 2.078(15) Å] reflect the electron donating nature of the ligand (see Figure 2).

Isomerization of Allylbenzene – A Benchmark

In order to evaluate the performance of the catalysts in the Pd(II)-mediated selective isomerization of terminal alkenes a set of two arylpropenes (allylbenzene **12**; estragol **13**) was chosen as starting materials. Initially, the reactions were carried out using 5 mol% of

Table 1. Pd(II)-catalyzed selective isomerization of allylbenzene **12** and estragol **13**.[a]



Entry	Substrate (R=)	Reaction time [h]	Yield of *E* [%][b]	*E*/*Z*[b]
1	H	5	80	97:3
		26	96	97:3
2	OMe	5	57	95:5
		26	93	97:3
3[c]	H	3	98	96:4

[a] *Reaction conditions:* catalyst **10** (5 mol%), substrates (89 mM), *n*-undecane (10.0 μL) as internal standard in a cap sealed vial at room temperature. Average outcome of two repetitions.

[b] Reactions were monitored and yields determined by GC analysis on a 25 m HP-5MS column. Product assignment determined by GC-MS and ^{1}H NMR analysis of isolated products.

[c] Reaction at 70 °C.

Pd catalyst **10**, substrate (0.09 M) in 2-propanol (HPLC grade) and undecane (10 μL) as internal standard. The reactions were monitored and yields determined by GC, GC-MS[39–42] and ^{1}H NMR spectroscopy of isolated products.

All starting materials were readily isomerized under very mild conditions in air at room temperature, giving the (*E*)-isomers in high yields with high *E*/*Z*-selectivities of 97:3 for *trans*-allylbenzene and *trans*-anethol (*dr* = 97:3). Reactions were complete after 26 h at the latest by raising the temperature to 70 °C. All reactions were carried out in unpurified solvent. Allylbenzene **12** was isomerized in three hours in 98% yield with an *E*/*Z* ratio remaining almost constant at 96:4 (*dr* = 96%), which is noteworthy since isomerizations are known to be critically affected by water and impurities (see Table 1, Figure 3).

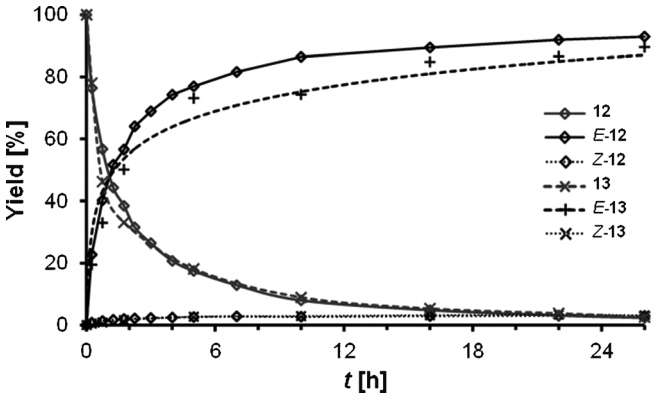


Figure 3. Isomerization of allylbenzene **12** (×) and estragol **13** (◇) in *i*-PrOH at room temperature.

Promising conversions were even observed on lowering the catalytic amount of Pd to 1 mol%. These results encouraged us to investigate the role of the solvent more deeply. Interestingly, under the chosen reaction conditions almost no conversions were obtained in non-polar solvents (diethyl ether, toluene) as well as in aprotic polar solvents (acetonitrile, tetrahydrofuran, acetone, chloroform). We therefore first considered the influence of the alcohol in terms of steric as well as electronic factors. Metal hydrides are known to be generated *in situ* by the use of additives, such as inorganic hydrides or, more recently, by weak acids, in particular alcohols, as is the case in the present study.[21] Only absolute solvents of high purity were used for the tests and no conversions were observed without the addition of Pd(II) catalysts, as proven by blank samples. Besides linear, monofunctional alcohols, such as MeOH, EtOH and *n*-PrOH, and secondary alcohols, such as *i*-PrOH, cyclohexanol as well as *t*-BuOH, 1,5-pentanediol, 1-propanethiol and 1-aminoheptane and glycerol, as a trifunctional alcohol, were employed. To complete the set also fluorinated alcohols were used, because remarkable effects have been reported for these substances.[43–45] The results are depicted in Figure 4. Besides the need for a protic solvent, the electronic character is highly important as there is clear evidence for rate acceleration in the range of MeOH > EtOH > *n*-PrOH > *i*-PrOH > *t*-BuOH. This result is in line with the pK_a values of the alcohols (Table 2).[46,47]

Nevertheless, besides inductive effects, steric bulk doubtless also has a significant influence on the pK_a

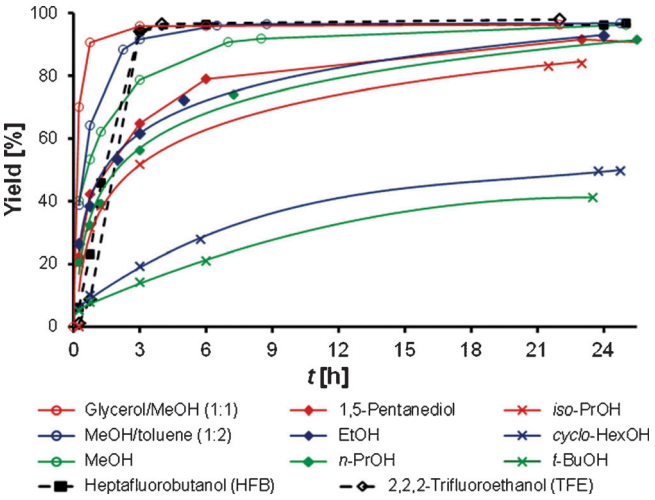


Figure 4. Solvent influence on the Pd(II)-catalyzed isomerization of allylbenzene **12** displaying the time-resolved formation of the *trans*-methylstyrene over time. *Reaction conditions:* 1 mol% catalyst **10**, substrate (89 mM) under air. *t*-BuOH at 70 °C.

Table 2. pK_a values of selected solvents.[a]

Compound	pK_a[a]
H_2O	15.74
MeOH	15.54
EtOH	15.9
i-PrOH	16.5
t-BuOH	17.0
$HOCH_2CH(OH)CH_2OH$	4.4
$CH_3(CH_2)_2SH$	13.24
CF_3CH_2OH	12.37[b]
$C_3F_7CH_2OH$	11.4[c]

[a] In H_2O; compiled and listed as reported by R. Williams;[46,47] significant digits left uncorrected.
[b] pK_a of 11.3 in 50% aqueous EtOH.[47]
[c] In 50% aqueous MeOH.[47]

values (due to disturbance of solvation and H-bonding). A drop of about 45% yield when comparing *i*-PrOH and cyclohexanol underlines these aspects, although the electronic properties of these two compounds tend to be quite similar. Whereas all other solvents and solvent mixtures lead to almost equal conversions over time, a reaction progress analysis revealed a significant retardation of the reaction rate as the reaction proceeded (50% conversion after 24 h in *cyclo*-hexanol and 27% conversion after 23 h in *t*-BuOH, both at room temperature). Although decomposition of the catalyst provides an inadequate explanation, since only the type of alcohol for the given reaction conditions was changed, unknown inhibition effects of the catalyst cannot be ruled out.

Surprisingly, no conversions were observed in more acidic 1-propanethiol ($pK_a = 13$) and, as expected, no reaction occurred when using the more basic 1-aminoheptane as a solvent.

Although, no isomerization occurred in pure acetonitrile due to its coordination capability, no inhibition was observed in MeOH when adding 0.5–10 mol% acetonitrile, showing that low concentrations are still tolerated by the catalyst system. Two hydroxy functionalities, as present in 1,5-pentanediol, had no significant effect and rates similar to those for EtOH were obtained. Even an increased acceleration compared to MeOH was observed when 2,2,2-trifluoroethanol (TFE) and 2,2,3,3,4,4,4-heptafluorobutanol (HFB) were used as solvents, which is consistent with the higher pK_a values of fluorinated alcohols.

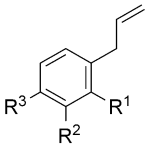
If one takes a closer look at the time-resolved conversion, a slightly different ascending slope bisecting the alcohol-mediated isomerization rate after an average of three hours, depending on the alcohol, can be detected for the fluorinated solvents. However, very high conversions and consistent diastereoselectivities are still maintained. It is worth mentioning that, by further optimization of the reaction conditions, fast conversions, similar to the results in fluorinated solvents, can be achieved using a 1:2 mixture of MeOH and toluene. Since all catalysts are easily soluble in alcohols as well as in most aliphatic solvents, we attribute this observation to matching effects between solvent, starting materials (allylbenzene **12**) and catalyst shape (bipyrazole-core and wingtip-arylation). Operating with this solvent mixture, allylbenzene conversion to the internal *E*-isomer was still very effective with catalyst loadings as low as 0.5 mol% Pd (92% yield, $dr = 96{:}4$ after 6 h at room temperature) and even 0.1 mol% Pd (35% yield, $dr = 96{:}4$ at room temperature; 70% yield, $dr = 95{:}5$ at 60 °C; both measured after 6 h) with almost no decrease in diastereoselectivity. Remarkably, by using a solvent mixture (1:1) of glycerol and MeOH at room temperature and catalyst loadings of 1 mol% the isomerization rate was even further accelerated (91% yield, $dr = 95.5{:}4.5$ after 45 min) compared to the reaction in the toluene-MeOH (2:1) solvent mixture (64% yield, $dr = 96.5{:}3.5$ after 45 min). This is again in agreement with the low pK_a value of glycerol, but may also be affected by the pronounced mesomeric stabilization capability within glyceric aldehyde. In summary, rate acceleration was obtained in the range of: glycerol/MeOH (1:1) > HFB ≈ TFE ≈ MeOH/toluene (1:2) > MeOH > 1,3-pentanediol > EtOH > *n*-PrOH > *i*-PrOH > *cyclo*-$C_6H_{10}OH$ > *t*-BuOH.

Substrate and Catalyst Screening

With the optimized conditions in hand we focused on the scope of the isomerization reaction by employing different starting materials, as well as the previously developed catalysts.

In order to get reliable results before varying the catalyst, the previous set of tests was extended to allylbenzenes with different functional groups at the aryl terminus (CF_3, OH, OAc, OMe; see Table 3).

Table 3. Substrates used for catalyst screening.



Entry	R^1	R^2	R^3	Compound
12	H	H	H	allylbenzene
13	H	H	OMe	4-allylanisol/estragol
14	OMe	H	H	2-allylanisol
15	OH	H	H	2-allylphenol
16	H	H	CF_3	4-(trifluoromethyl)allylbenzene
17	H	OMe	OH	eugenol
18	H	OAc	OH	eugenyl acetate
19	H	OMe	OMe	4-allyl-1,2-dimethoxybenzene

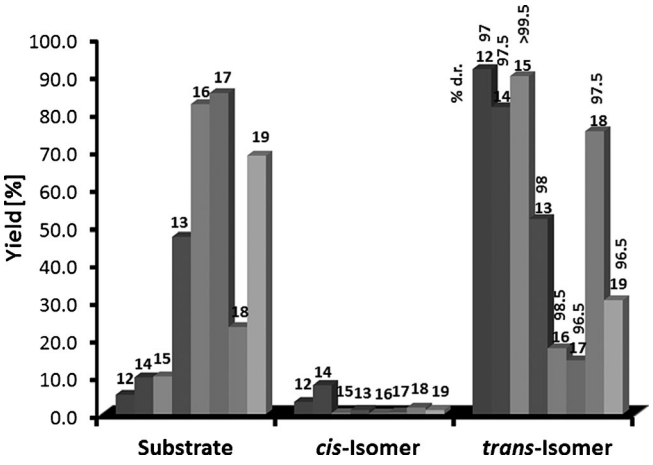


Figure 5. Conversion of allylbenzenes to internal alkenes after 3 h using catalyst **10**. *Reaction conditions:* 1 mol% catalyst **10**, substrate (89 mM) in MeOH/toluene (1:2) at room temperature under air. Conversions monitored and product assignment determined by GC and GC-MS. Average outcome of three runs. Substrate order (left to right): 4-allylbenzene **12**, 2-allylanisol **14**, 2-allylphenol **15**, estragol **13**, 4-(trifluoromethyl)allylbenzene **16**, eugenol **17**, eugenyl acetate **18**, 4-allyl-1,2-dimethoxybenzene **19**.

Applying the optimized reaction conditions (1 mol% Pd, 1:2 mixture MeOH/toluene, air, room temperature) samples were taken and analyzed after 3 h. It has to be pointed out that the reactions were not allowed to run to completion in order to be able to evaluate the catalyst performance on the substrates regarding electronic properties and functional group tolerance. Several functionalities proved compatible to the catalytic conditions and after three hours 90% of allylbenzene **12** and 2-allylphenol **15** were converted to their corresponding *E*-isomers, followed by 2-allylanisol **14** (80%), eugenyl acetate **18** (75%), estragol **13** (50%), 4-(trifluoromethyl)allylbenzene **16** (20%) and eugenol **17** (15%) (Figure 5). Low conversions of challenging, electron-deficient starting materials, e.g., for fluorinated compounds, is a common phenomenon.[17]

As evidenced by the substrates, the catalyst is compatible with donor heteroatoms, such as phenols and acetates and the overall high selectivities of 96.5–99% *dr* are among the highest ratios comparable to other well-studied systems.[13,17,21,23,26,31,48] The excellent selectivity for *trans*-4-hydroxyallylbenzene (exclusively, >99.5% *dr*) is particularly remarkable and represents the highest diastereoselectivity reported so far.[13,31] We attribute this effect to the 2-hydroxy functionality being in close proximity to the reaction center. A similar effect was observed recently and led to increased product formation and high selectivities in the Pd(II)-catalyzed double bond isomerization of 2-(but-3-enyl)phenols over two carbon atoms.[16] On the basis of the results obtained from the substrates, we then focused on the electronic and steric influence of the catalysts outlined in Figure 1 on the isomerization reaction. With *N*-1,1′-alkylated bipyrazole catalysts **1–3** and their arylated counterparts **4–11** in hand, we had two types of Pd(II)-catalysts characterized by different steric demands for investigation, and within each group, catalysts with different electronic properties. To obtain meaningful data for evaluation of the catalyst performance, the less reactive eugenyl acetate **18** was chosen as a benchmark. The reactions were performed under the optimized reaction conditions (89 mM, 1:2 mixture methanol/toluene, 1 mol% Pd, room temperature) and samples were taken after three and six hours. For the *N*-1,1′-alkylated catalysts (**1–3**) increased activity was observed for **2** (R = *i*-Pr), followed by **3** (R = *n*-Pent) and the lowest conversions to the *E*-isomer was obtained by using catalyst **1** (R = Me).

The results are indicative of a trend correlating higher electron-donating properties and catalyst activity, since oxidative addition of substrates should be enhanced by higher electron density located at the metal center.[49] For further evaluation, catalysts **4–11** were tested under equal conditions and showed a similar trend towards higher activity with increased electronic density at the 3,3′-bipyrazole core. After six hours Pd(II) catalyst **7** (R = Mes) showed the overall highest conversion of eugenyl acetate **18** (96%), followed by **10** [R = *p*-(*t*-Bu)C_6H_4, 90%], **6** (R = *p*-Tol, 87%), **11** (R = naphthyl, 79%), **4** (R = Ph, 65%), **5** (R = *m*-Tol, 62%) and **8** [R = 3,5-$(CF_3)_2C_6H_3$, 4%]. This is in good agreement with the electron-donor capability of aryl substituents and verifies the results obtained for the *N*-1,1′-alkylated Pd(II) catalysts. Surprisingly, catalyst **9** (R = OMe), with the most activat-

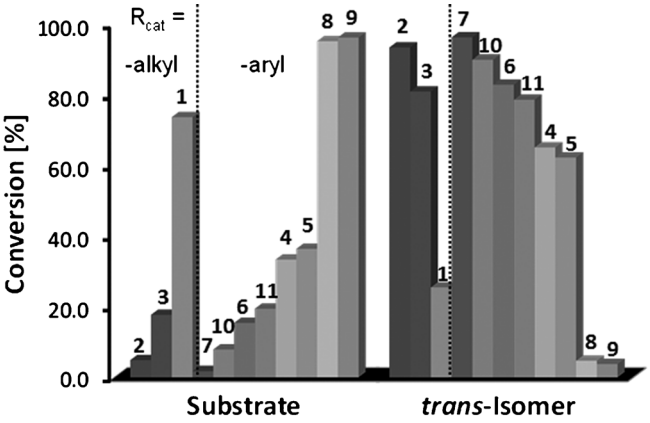


Figure 6. Catalyst performance evaluated in the selective isomerization of less reactive eugenyl acetate **18**. *Reaction conditions:* 1 mol% catalyst, eugenyl acetate **18** (89 mM) in MeOH/toluene (1:2) at room temperature under air. Conversions monitored and product assignment determined by GC and GC-MS. Average outcome of two repetitions. Catalyst order (left to right): **2**, **3**, **1**, **7**, **10**, **6**, **11**, **4**, **5**, **8**, **9**.

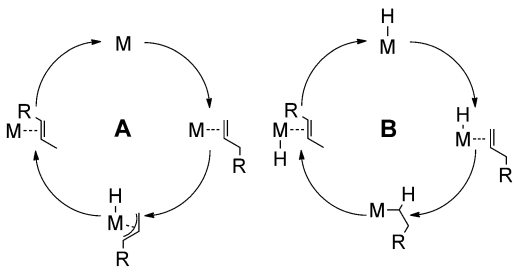
ing substituent pattern, did not fit into the trend (5% yield), but it represents the only catalyst exhibiting a heteroatom functionality at the wingtip position. However, the reason is still unclear. Within the given ligand pattern a significant steric influence on the isomerization reaction was not observed and the high *E*/*Z*-selectivities (97–98.5% *dr*) achieved for eugenyl acetate **18** were comparatively similar and remained almost constant during the reaction progress, as shown by variation of the catalysts. In summary, increased catalyst activity was obtained for Pd(II)(bcpz)-catalysts exhibiting a higher electron density within the 3,3′-bipyrazole core induced by the substituents in the range of ($R_{wingtip}$ =): *i*-Pr > *n*-Pent > Me and Mes > *p*-(*t*-Bu)C_6H_4 > *p*-Tol > naphthyl > Ph > *m*-Tol ⩾ 3,5-$(CF_3)_2C_6H_3$ (Figure 6).

Mechanistic Studies

Generally, two main reaction pathways for the isomerization of alkenes can be envisaged. The transition metal catalyst can operate *via* a π-allyl mechanism (**A**) or a hydride addition-elimination mechanism (**B**) (Scheme 1).

The metal hydride complex can be initially present as catalyst or generated *in situ*, whereas the other mechanism features a rearrangement through a transitory π-allyl intermediate upon alkane coordination, which is followed by a reversible hydride transfer to form the π-allyl metal hydride species. Overall olefin isomerization follows the thermodynamic driving forces, reaching an equilibrium distribution, with the thermodynamically more stable *E*-isomer being favored.[6,15,33,50] In particular, the kinetic distribution of the isomers depends on the electronic and steric factors controlling the β-elimination process. Moreover, the kinetics and product distribution, and thus the selectivity of the reaction, are affected, when the transition metal catalyzes the isomerization as well as reaction at the double bond. Generally, the π-allyl intermediate mechanism has a dramatic effect on the distribution of isomers giving rise to high *E*/*Z* selectivities, and *E*/*Z* ratios greater than 4:1 will be generally observed.[2] An interesting class of catalysts capable of this type of terminal olefin isomerization was derived from $[(allyl)PdCl]_2$, a triarylphosphine and silver triflate. Although the transformation was successfully achieved with the substrates employed, the *E*:*Z* ratios of the newly formed olefins were only moderate.[15] Recently, ruthenium hydride species, derived from thermally modified Grubbs 2nd generation metathesis catalysts have been developed and successfully applied in the isomerization of terminal olefins.[21] However, the reactions are commonly accompanied by unwanted side reactions, such as reduction or self-dimerization.[32,35] Palladium(II) hydride complexes are known to be generated *in situ* by addition of alcohols, which undergo oxidation upon β-H-elimination.[38,49] Some peculiarities regarding the metal hydride formation should be noted. Alcohols bearing no β-H atom, such as MeOH or BnOH, are dehydrated (β-H atom) to their corresponding carbonyl derivatives, suggesting that β-elimination of water is not involved, whereas the reaction in *t*-BuOH is likely to proceed *via* β-H atom and hydroxy group elimination forming a water molecule.[38] Since the solvent screening revealed the necessity of alcoholic additives for the catalytic cycle to operate and the fact that Pd-assisted proton migration *via* a π-allyl mechanism is favored in non-polar aprotic media, as shown for $PdCl_2(PhCN)_2$,[51] a hydride addition–elimination mechanism seems to be most conceivable for our catalyst system. The robustness of our catalysts is also in agreement with this mechanism, because π-allyl type based Pd isomerization reactions usually require purified, dry aprotic solvents[52–57] and our catalyst system performed very well even in unpurified, non-anhydrous solvents under air. A complete lack of methoxylated and acetalized side products, which may arise from nucleophilic attack of the solvent at the carbon double bond is a further indication for a mechanism involving a hydride addition–elimination mechanism, instead of a π-allylic pathway.[58,59]

To get further insight into the reaction mechanism, isotopic labeling studies were performed. Even though both the metal hydride addition–elimination and the π-allyl hydride mechanisms result in the same product, the two mechanistic pathways can be distinguished by looking at the hydrogen shift of the deuterium labeled starting materials upon isomerization and at incorporation of deuterium into the substrates when the reactions are run in deuterated solvents. The π-allyl mediated mechanism initially involves a "*hydride-free*" metal precursor featuring two empty coordination sites. Coordination of the free olefin followed by oxidative addition of the allylic carbon-hydrogen bond would form the π-allyl metal hydride catalyst, which transfers the hydride to the terminal position by reductive elimination yielding the isomer-



Scheme 1. Isomerization of terminal alkenes via π-allyl intermediate (A) and hydride addition elimination (B) reaction mechanism.

ized alkene. Therefore, a formal [1,3-H] shift within the substrates should be observed for a π-allyl mechanism. If one considers the hydride which originates from the approaching olefin, the active catalyst is thus generated by an *intra*molecular reaction. The metal hydride mechanism on the other hand involves a distinct metal hydride complex being initially present before entering the catalytic cycle and can therefore be called *inter*molecular, because hydrides are successively displaced between catalyst and new incoming substrates during catalysis. In this case, the olefin coordinates to form a hydrido π-alkene complex, followed by β-addition, generating a σ-alkyl intermediate (hydropalladation) and finally β-H-elimination furnishes the isomerized olefin. The Markovnikov and *anti*-Markovnikov hydropalladation step across the double bond are both reversible and only Markovnikov addition leads to the isomerized product. This process results in a characteristic [1,2-H] shift when the metal hydride mechanism is active. Although both reaction pathways proceed along different hydrogen shifts, only the observation of a [1,2-H] shift is sufficient proof of the hydride addition–elimination mechanism, because deuterium scrambling between the alkene hydrogens and subsequent isomerization thereof by a hydride addition–elimination reaction results in a formal [1,3-H] shift as well, and thus preventing distinction. For this investigation we prepared 1,1-d_2-prop-1-en-3-ylbenzene by Wittig reaction of d_3-methyl iodide and phenylethanal. Applying our standard reaction conditions using 1 mol% catalyst **10** in a 0.89 mM solution of 1,1-d_2-prop-1-en-3-ylbenzene in MeOH afforded the isomerized *E*-isomer as the major-product. By constant, careful monitoring of the starting materials, the reaction progress and the products by GC-MS measurements, a characteristic key fragment of the deuterated starting material and the products could be identified (Figure 7).

This allowed for a clear differentiation as to whether deuterium incorporation at C-2 took place or not. Even though starting materials and products exhibit the same molecular ion in the higher, and benzyl fragmentation in the lower mass region, the initial fragmentation of 1,1-d_2-prop-1-en-3-ylbenzene generates fragment $m/z = 104.1$ by loss of the d_2-methylene group whereas $m/z = 103.1$ is expected for the product, regardless of isomer configuration. This fragment originates from α-methyl cleavage of the terminal methyl group within the product. Contrary to this an $m/z = 104.1$ for the initial fragment of the *E*- and the *Z*-product was detected, which clearly demonstrates deuterium incorporation at the C-2 position of propenylbenzene. It has to be pointed out that during fragmentation of allyl systems in the gas phase, metastable ions induce carbon skeleton rearrangements and hydrogen migrations, which lead to complex mixtures of interconverting structures prior to further decomposition. Consequently, the identification of characteristic fragments and isomer assignment is quite difficult, as shown for the molecular ions of linear octene isomers. However, it has been previously demonstrated that scrambling of terminal hydrogens does not occur over the entire time range.[60] Furthermore, it is important to check, whether the catalyst employed is capable of *trans*-isomerization. During multiple addition-reaction cycles a constant amount of *cis*-isomer was produced (kinetic distribution). On the account of this, the observed initial fragment ($m/z = 104.1$) of *trans*-propenylbenzene originates from a [1,2-H] shift thus proving that only the hydride addition-elimination mechanism is active (Figure 7). Fragmentation patterns of undeuterated starting material and isolated products were cross validated in MeOH and MeOH-d_4. Deuterium scrambling between starting materials and substrates was not observed and at low catalyst loadings in MeOH-d_4, no deuterated *E*-/*Z*-propenylbenzenes arising from initial deuterium transfer from the solvent to the catalyst, were detected. Finally, the here proposed [1,2-H] shift was experimentally corroborated by unambiguous characterization of 1,1-d_2-prop-1-en-3-ylbenzene and the isomerization product 2,3-d_2-(*E*)-prop-1-en-1-ylbenzene by NMR spectroscopy (see the Supporting Information).

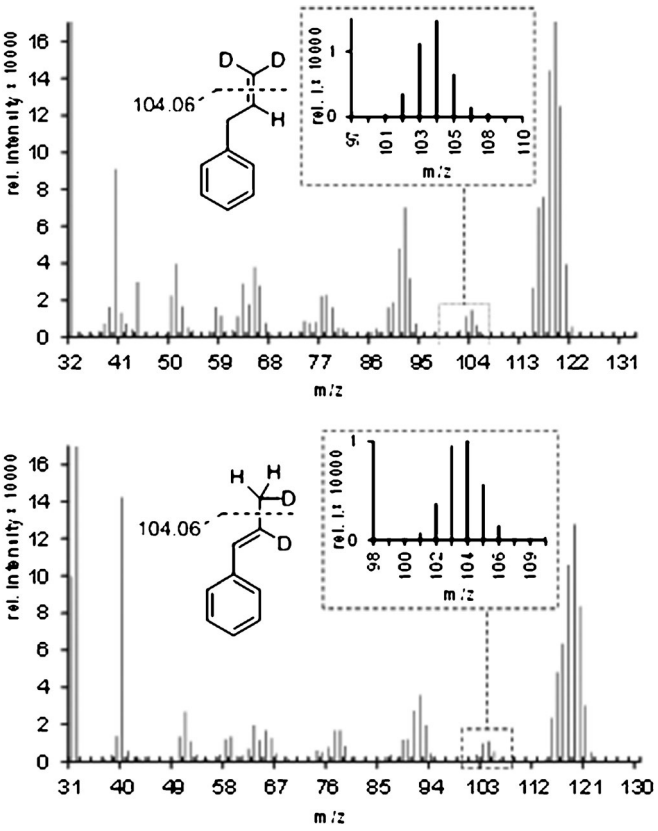


Figure 7. Mass spectra showing the characteristic fragments of 1,1-d_2-prop-1-en-3-ylbenzene (*top*) and 2,3-d_2-(*E*)-prop-1-en-1-ylbenzene (*bottom*).

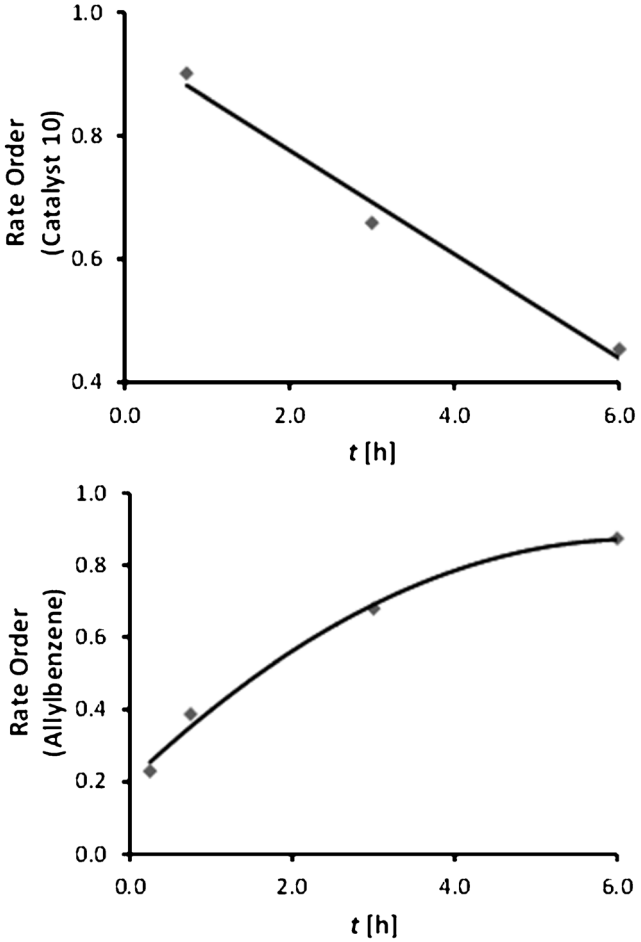


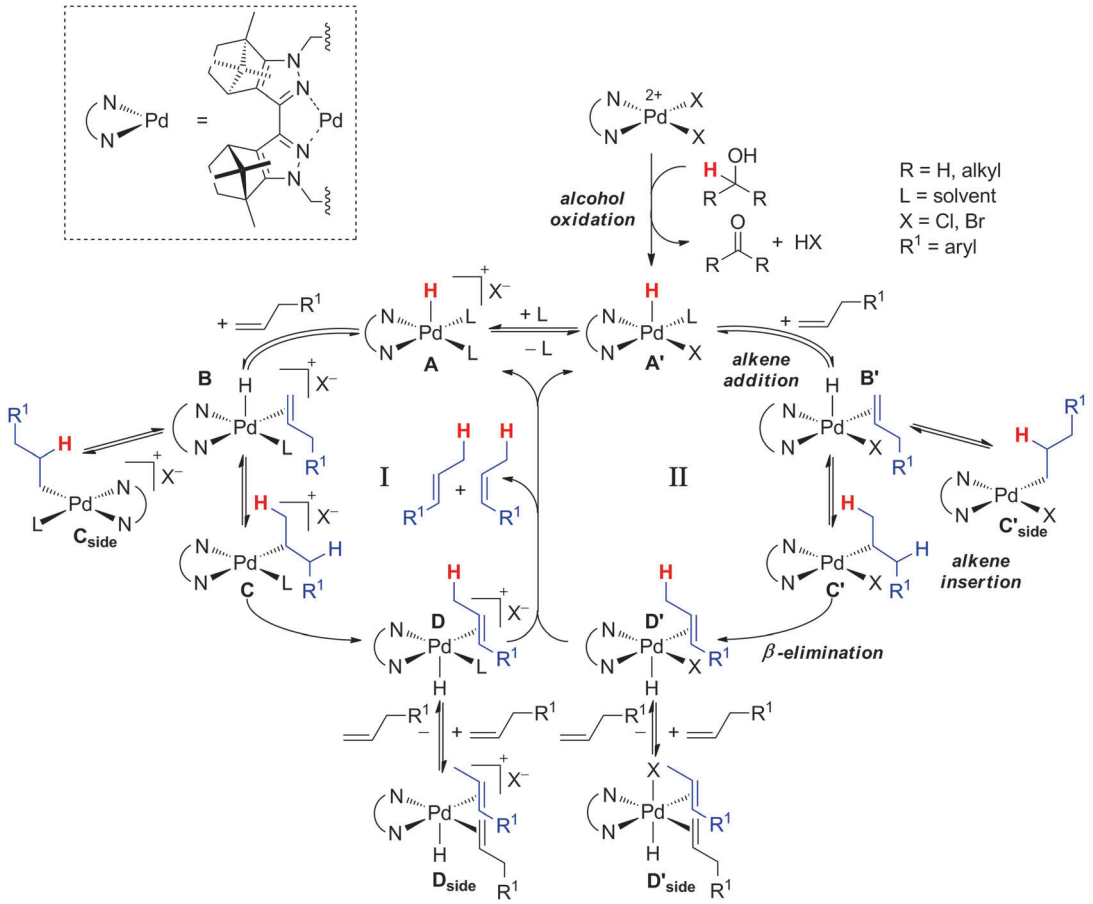
Figure 8. Effect of the concentration of catalyst **10** (*top*) and allylbenzene **12** (*bottom*) on the rate of isomerization. *Conditions:* $[sub]_0$ 89 mM or, respectively, $[cat]_0$ 0.089 mM (1 mol%) in MeOH/toluene mixture (1:2) at room temperature.

To gain further insight into the catalytic cycle, the kinetics and the reaction order of the isomerization were investigated using catalyst **10**. Performing the reactions at catalyst loadings of 0.1 mol%, 0.5 mol% and 1 mol% showed a first-order dependence on the initial catalyst concentration (Figure 8, *top*). With constant catalyst loadings of 1 mol% a sub-first-order dependence on the initial (high) substrate concentration of about 0.20 was observed. During reaction progress the sub-first-order dependence on the initial substrate concentration changes and approximates 1.0 at very low substrate concentration, which indicates substrate inhibition. For the solvent combination MeOH/toluene, employing concentrations of 1:2, 1:1 and 1:0, a negative sub-first order dependence of −0.5 was obtained (Figure 8, *bottom*), leading to the following rate expression:

$$rate = k(T)\frac{[Pd]^{1.0}\,[substrate]^{0.2\rightarrow 1.0\ (t\rightarrow\infty)}}{[MeOH]^{\approx 0.5}}$$

The results are indicative of an inhibition effect of the starting materials. Methanol at higher concentrations shows a decelerating effect. However the concentration of the solvent was not investigated in depth, because a solvent effect cannot be ruled out. The reaction order on the products was not assigned, but neither rate deceleration nor inhibiting effects were observed by the external addition of pure *trans*- or *cis*-propenylbenzene to the reaction. Increased product concentration over time by performing the reaction over multiple substrate addition-reaction cycles had no effect on the conversion rates. The catalyst activity remained constant, thus proving catalyst stability and the inhibitive effect of the starting material (allylbenzene **12**) concentration. No kinetic isotope effect was detected with undeuterated allylbenzene **12** in MeOH and MeOH-d_4 leading to comparable reaction rates, yields and selectivities. Thus, generation of the metal hydride complex is not the rate-limiting step, if one assumes that the formation of only small amounts of active hydride species is insufficient for catalysis. In contrast, using 1,1-d_2-prop-1-en-3-ylbenzene as starting material in MeOH and MeOH-d_4 resulted in a large kinetic isotope effect ($k_H/k_D = 6.7$) being observed. No H/D-exchange was observed between starting materials and solvent at low catalyst loadings suggesting that the isomerization mechanism is an inner sphere interconversion after initial metal hydride formation.[38] With catalyst **10** and allylbenzene **12** or 4-allylanisol **13** the ^{1}H NMR spectra did not show the presence of any Pd−H species up to −100 ppm, which is usually observed at high-field resonances ($\delta < 0$ ppm). The same was true under substrate inhibition conditions. Indeed, many hydride catalysts are too reactive to be observed by spectroscopic measurements. Scheme 2 suggests a possible reaction pathway that is in accordance with the spectrometric and kinetic evidence given above. Initially the alcohol present in the reaction media is oxidized and thus generates the active palladium hydride species **A′**, which then enters the catalytic cycle. Upon oxidation of the alcohol, a vacant coordination site is exposed at the electron-deficient palladium center owing to liberation of HX, which may be occupied by solvent molecules. The hydride then moves to the axial position of the metal complex to furnish a *cis*-coordination site for the incoming olefin, a necessary prerequisite for the hydropalladation step.

Whereas in **II** the catalytic cycle begins with the entering and coordination of the electron-rich olefin, complex **A′** is thought to be capable of losing its second halide in a reversible process, forming the cationic Pd(II) hydride complex **A**, which may be stabilized under protic polar conditions.[61,62] This intermediate offers a second vacant coordination site for incoming substrates. Considering cycle **I**, olefin addition to hydrido-π-alkene complex **B** occurs. β-Addi-



Scheme 2. Proposed mechanism for the isomerization reaction of terminal allylarenes to *E*- and *Z*-propenylarenes in alcoholic media using (bcpz)-type $PdCl_2$ catalysts.

tion, either in a Markovnikov or *anti*-Markovnikov fashion, results in the hydropalladated σ-alkyl intermediates **C** and $\mathbf{C_{side}}$, which are reversible steps and the reason for the [1,2-H] shift as previously described. The M-η^1-C(β)-intermediate undergoes *syn*-β-hydride elimination and the palladium hydride species **D** is regenerated, which liberates the *E*- and *Z*-isomers, respectively. Apart from retention of one halide coordinated to the metal center in cycle **II**, both mechanisms are equal and all catalytic species reported run through alternating 18 and 16 VE complexes. The transition states for both hydride transfers involve a *syn*-coplanar arrangement of the two carbon atoms, the metal center and the hydrogen participating and reductive elimination requires coordinative unsaturation of the Pd complex (16 VE).[49]

Although rhodium[63,64] and iridium dihydride[65] complexes have been reported for isomerization reactions, a palladium dihydride species[66,67] is improbable under the reaction conditions, since dihydride species are prone to decomposition and capable of hydrogenation reactions, which were not detected. To rule out the presence of Pd(0) species within the catalytic cycle, we tested $Pd_2(dba)_3$ as precursor, which is not a catalyst under the reaction conditions reported here. It is well known that dba forms relatively stable Pd complex precursors, which are unable to act as catalyst in the hydride transfer mechanism. It is interesting to note that eugenyl acetate **18** is tolerated under our reaction conditions using catalyst **10**. Furthermore, our catalyst system was still active after multiple addition–reaction cycles (10×) without any loss of activity, conversion or selectivity. Palladium black was not formed over prolonged reaction times, even at elevated temperatures (343 K). This was verified by careful monitoring of the reaction progress and fine filtration of the solution after each reaction cycle. When $Pd(MeCN)_2Cl_2$ was employed as catalyst, fast isomerization was also observed under our reaction conditions, but a substantial loss of activity was observed, as early as after seven cycles (53% *E*-isomer, 95% *dr*) and almost no conversions were detected after 21 cycles (11% *E*-isomer, 94% *dr*) (see the Supporting Information). Even under Wacker oxidation conditions, the formation of Pd(0) was not detected using bcpz-type catalysts, as has been reported.[37] Liberation of HX from metal hydride complex **A** to form a Pd(0) complex can be ruled out, since reductive

elimination is likely to occur from a *trans*-configuration, which is not favored for our neutral bidentate *N*-ligand as it is coordinated at the equatorial positions. This together with the chelating properties and the π-back-bonding character of the bispyrazole ligands may account for the observed integrity of the bcpz-alcohol-catalyst system and explain the observed precipitation of palladium black by using Pd-$(MeCN)_2Cl_2$ as catalyst (*trans*-coordinated MeCN and Cl). Since no kinetic isotope effect was observed in deuterated solvents but with deuterium labeled substrates, the rate-limiting step is thought to be the β-H-elimination reaction and not the initial formation of the metal hydride complex, or regeneration thereof. If we take the sub-first order on substrate and methanol concentration into account, inhibition of the catalytic cycle may take place by trapping of a catalytic species. As found, decomposition to Pd(0) does not occur and therefore cannot account for this observation. Poisoning of the catalyst by impurities within substrates or methanol can also be ruled out, since the catalyst maintained its activity through multiple substrate addition–reaction cycles and with the use of absolute solvents. Reasons for the observed rate deceleration may either originate from formation of inactive complexes, which would result in removal of catalytic species out of the catalytic pool, or be caused by a competitive reaction, because simple saturation in allylarenes would not account for the prolonged reaction times. Deactivation of a certain amount of catalyst is improbable, since the catalyst recovers its previous activity after a certain time. More conceivable, seems to be another reversible pathway, which becomes competitive at higher substrate and methanol concentrations. This may operate by occupation of a secondary vacant coordination site offered by the metal center leading to $\mathbf{D}_{\mathbf{side}}$ (see Scheme 2, route **I**, *bottom*). Related mechanisms, involving positively charged complex species due to loss of a secondary halide prior to olefin complexation, were recently proposed by Sigman et al. under Wacker oxidation conditions,[68] and for the Pd-catalyzed reductive cross-coupling of styrenes in 2-propanol, also involving Pd hydride π-alkene intermediates.[69] ^{1}H-NOESY, ^{13}C and ^{15}N HMBC NMR measurements did not show additional complex species present in solution, giving no evidence for a competitive pathway.

Additive Effects on the Reaction Progress and Role of the Halide

The results show a strong solvent effect on the isomerization, regarding first of all the pK_a and the steric encumbrance as well as electronic effects originating from ligand design. Bearing the envisaged reaction mechanism (route **I**) in mind, we decided to investigate further the role of the pH value and the halide on the catalyst (Figure 9). Clearly, a hydride-driven reaction mechanism would be influenced by the external addition of acid and base.[70,71] We therefore performed our standard reaction with 1 mol% **10**, allylbenzene **12** (89 mM) in a mixture of MeOH/toluene (1:2) at room temperature, combined with 10 mol% of an additive. As expected, the addition of sodium methanolate significantly slowed down the reaction rate, leading to lower conversions (48% *E*-isomer after 24 h, 96.5% *dr*) and with Cs_2CO_3 no reaction was observed. $Pd(OAc)_2$ and the corresponding Pd(II) diacetate of **10** did not promote the reaction either, regardless of ligand substitution, owing to the lack of metal hydride formation. The addition of toluenesulfonic acid monohydrate did not accelerate the reaction and after prolonged reaction times resulted in equal conversions as without additive. Interestingly, the observed reaction progress was almost identical with our results obtained for catalyst loadings between 0.5 mol% and 0.1 mol%. This is indicative of partial catalyst poisoning, which is generally attributed to sulfur containing substances,[1,72-74] and may account for no isomerization in 1-propanethiol (pK_a = 13.24) as well. Noteworthy, 10 mol% acetic acid did not have a positive influence on the outcome of the reaction and similar reaction rates, conversions and selectivities were observed as without additive. This brings to mind the facile, mild and effective catalyst preparation, which occurs without the formation of typical by-products arising from acid-catalyzed dehydration reactions (alkenes, ethers). For evaluation of the influence of the halide coordinated to the metal center on the isomerization, the dibromide palladium complex of **10** was prepared and tested under our

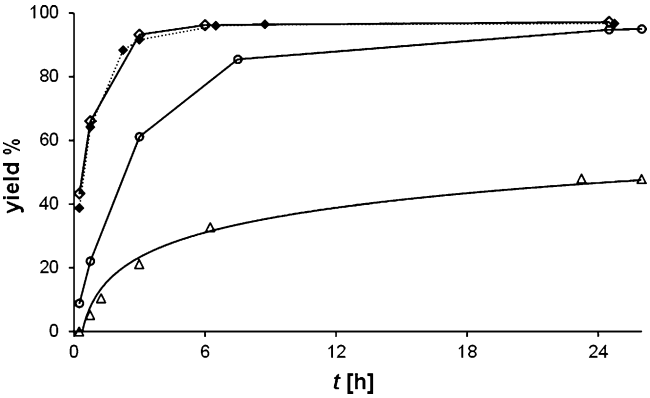


Figure 9. Influence of additives in the isomerization of allylbenzene **12** catalyzed by **10**. *Reaction conditions:* 1 mol% catalyst, 10 mol% additive [blank (◆), NaOMe (○), *p*-toluenesulfonic acid (△), acetic acid (◇)], allylbenzene **12** (89 mM) in MeOH/toluene (1:2) at room temperature. under air. Conversions monitored and product assignment determined by GC and GC-MS. Data points represent the mean of two repetitive experiments.

standard conditions (1 mol% catalyst, 89 mM substrate, 2:1 toluene/MeOH at room temperature). In order to effectively compare the catalyst performance, the less reactive eugenyl acetate **18** was chosen as the model substrate. Only small differences in the yield of *trans*-products were observed (77% for **10** and 70% for the dibromide complex after 3 h; 92% or respecrtively, 86% after 6 h). Selectivity was not affected, as expected, and finally almost equal conversions were obtained with both catalysts (99% for **10** or, respectively, 96% after 24 h). The decreased isomerization rate can be understood in terms of the lower π-donation ability of bromide compared to chloride.

Although less pronounced, the effect is in agreement with the results obtained for the iridium hydride-driven isomerization of allylbenzene **12**, whereby higher reaction rates were observed by stabilization of unsaturation at the metal center originating from more effective π-donation of the halide in the order: $I < Br < Cl < OH < F$.[65] Even further increased isomerization rates may therefore be realized with our catalyst system by fluoride substitution, an aspect that is still underestimated as a tunable parameter.

Conclusions

We describe a detailed experimental investigation of the activity of a series of novel backbone-fused bipyrazole (bcpz)-derived palladium catalysts, which are highly effective in the selective isomerization of arylpropenoids in alcoholic media. Catalyst screening revealed that the donor capability of the wingtip substitutents of the bidentate ligand has a strong influence on the activity. Catalyst integrity, a prerequisite for any application in homogeneous catalysis, was shown to be maintained, even at elevated temperatures (343 K) and over multiple addition–reaction cycles, with neither loss of activity nor degradation nor decomposition to metallic palladium. Deuterium-labeled mechanistic investigations revealed the formation of palladium hydride species under the reaction conditions, as evidenced by a characteristic [1,2-D] shift detected by MS fragmentation experiments, and indicated that these species are the active catalysts. Taking the observed reaction orders into account, a catalytic cycle, which proceeds *via* a metal hydride addition–elimination mechanism, is proposed. Solvent screening revealed that the pK_a has a strong influence on the reaction rate. The impact of acid and base additives was also addressed. The absence of side reactions, such as reduction or dimerizations and no precipitation of palladium metal, compared to reported catalyst systems employing acids or metal hydrides as co-reactants, highlights the mildness and effectiveness of our catalyst system, which operates in various alcoholic media at low catalyst loadings of 1 mol%. The investigation also shows how the bcpz class of ligands can be used for catalyst design. The effect of substitution pattern, combined with substrate and solvent screening, and a discussion of electronic and steric factors, as well a solvent polarity, pK_a value, the coordinated halide and additives, provide valuable information for future developments and improvements of related catalytic systems. In view of the positive results obtained with our catalysts in isomerization and oxidation reactions, research on hydroformylation and cyanohydrin formation is currently under investigation in our laboratory. Furthermore, modification of these neutral bidentate bcpz-ligands for asymmetric catalysis, taking advantage of their rigid nature and the chiral camphor-backbone, is also being undertaken.

Experimental Section

Materials and Methods

All reagents and solvents were obtained from Acros, ABCR, Alfa Aesar, Sigma-Aldrich or VWR and were used without further purification unless otherwise noted. Deuterated solvents were purchased from Euriso-Top. NMR spectra were recorded on Bruker Avance 500, Bruker Avance 300 and Bruker ARX-250 spectrometers at room temperature. Chemical shifts (in ppm) were referenced to residual solvent protons.[75] GC- and GC-MS measurements were performed on a Thermo Trace-Ultra GC-MS, equipped with split injector (250 °C), FID (250 °C) and a quadrupole MS (Thermo, San Jose, CA). Mass spectra were recorded on a JEOL JMS-700 spectrometer. IR spectra were recorded on a Bruker Vector 22 FT-IR. Elemental analyses were performed by the analytical laboratories of the chemical institute of the University of Heidelberg. Melting points were determined on a Büchi melting point apparatus and temperatures were uncorrected. Intensity data for crystal structure analysis were measured on a Bruker APEX diffractometer.

Catalysis

General procedure for the palladium-catalyzed isomerization of terminal arylpropenoids: The catalyst (1 mol%) was dissolved in a mixture of 3 mL of toluene and methanol (1:2) in a cap-sealed vial and the appropriate allylbenzene (89 mM) and 10 μL of internal standard (undecane) were added. Reactions were carried out at given temperatures and control samples were taken of the solution in due course, filtered through a short plug of neutral alumina to remove the catalyst and analyzed by GC and GC-MS (ISQ Trace-Ultra GC-MS, Thermo, San Jose, CA) using a 25 m DB-5 column (Agilent Technologies, Palo Alto, CA, film thickness 250 nm).

Bcpz-palladium(II) bromide complex (10^{Br}): To a solution of the corresponding bipyrazole ligand[77] (27.1 mg, 77.8 μmol) in acetonitrile was added $Pd(MeCN)_2Br_2$[77] (50.0 mg, 77.8 μmol) and the solution was stirred for 20 h at room temperature. The solvent was evaporated under reduced pressure; the product was dissolved in a small

amount of chloroform and filtered through a short plug of silica. Evaporation and drying under high vacuum afforded dibromide complex **10^{Br}** as a deep orange microcrystalline solid ; yield: 47.7 mg (52.5 μmol, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.75$ (s, 6H), 0.92 (s, 6H), 1.11 (m, 4H), 1.24 (s, 6H), 1.29 (s, 18H), 1.75 (m, 2H), 2.00 (m, 2H), 2.87 (d, $J =$ 3.5 Hz, 2H), 5.85 (d, $J = 15.9$ Hz, 2H), 6.21 (d, $J = 15.9$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 4H), 7.32 (d, $J = 8.4$ Hz, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 11.1$, 19.3, 20.3, 26.8, 31.3, 32.7, 34.5, 47.9, 54.0, 63.1, 125.4, 125.5, 126.8, 133.8, 139.6, 150.7, 159.4; IR (KBr): $\nu = 2957$, 2866, 1700, 1514, 1455, 1414, 1390, 1364, 1312, 1269, 1247, 1204, 1182, 1123, 1047, 1015, 1000 cm^{-1}; anal. calcd. for $C_{44}H_{58}Br_2N_4Pd \cdot 1/100\,H_2O$: C 57.55, H 6.48, N 6.10; found: C 57.37, H 6.55, N 6.17; HR-MS (FAB$^+$): $m/z = 829.2903$, calcd. for $C_{44}H_{58}BrN_4Pd$ [M−Br$^-$]$^+$: 827.2880.

1,1-d_2-Prop-1-en-3-ylbenzene

To a solution of d_3-methyltriphenylphosphonium iodide[77] (1.7 g, 4.3 mmol) and potassium *tert*-butoxide (0.5 g, 4.3 mmol) in tetrahydrofuran was added phenylacetaldehyde (513.4 mg, 4.3 mmol) dropwise. The solution was stirred for 19 h at 70 °C. Aqueous hydrochloric acid was added to the reaction mixture at room temperature. The product was extracted with diethyl ether and washed with water. The dried and concentrated organic layer was purified by chromatography using *n*-pentane as eluent. Careful evaporation furnished 1,1-d_2-prop-1-en-3-ylbenzene as a colorless oil; yield: 61.5 mg (512 μmol, 12%). ^{1}H NMR (300 MHz, MeOH-d_4): $\delta = 3.37$ (d, $J = 6.7$ Hz, 2H), 5.08 (m, 2H), 5.96 (m, 1H), 7.17 (m, 3H), 7.25 (m, 2H); ^{13}C NMR (151 MHz, MeOD-d_4): $\delta =$ 41.1, 115.9, 127.0, 129.4, 129.6, 138.9, 141.4; GC-MS (EI): $t_R = 12.81$ min, $m/z = 120.1$ [M]$^+$, 119.1 [M−D]$^+$, 118.1 [M−2D]$^+$.

General Procedure for the Preparation of Reference Samples for the Gas Chromatographic Assignment of Diastereomers

To a solution of catalyst (1 mol%) in 2,2,3,3,4,4,4-heptafluorobutanol the substrate (89 mM) was added and the isomerization was allowed to proceed to completion at room temperature. The solution was extracted three times with small amounts of *n*-pentane, the organic layers were combined, dried over sodium sulfate and filtered. Careful evaporation according to the general low boiling points of arylpropenoids yielded reference samples of isomerized compounds for GC and NMR analysis.

Determination of Time-Independent Reaction-Rate Orders

Isomerization was carried out under standard reaction conditions using catalyst **10** (1 mol%), allylbenzene (89 mM) and 10 μL of *n*-undecane as internal standard in a mixture of toluene/methanol (2:1) at room temperature under variation of the substrate (89 mM, 444 mM, 1 M), catalyst (0.1 mol%, 0.5 mol%, 1.0 mol%) and methanol concentrations (33%, 50%, 100%). Samples were taken after 0.25 h, 0.75 h, 3 h and 6 h, filtered through a short pad of silica and analyzed by GC measurements. Consecutive plotting of concentrations *versus* yields furnished the corresponding reaction-rate orders.[78]

X-Ray Crystallography

Crystal data for **10**: $C_{38}H_{46}Cl_2N_4Pd$, $M_r = 736.09$, $0.15 \times 0.14 \times$ 0.01 mm^3, monoclinic, space group $P2_1$, $a = 16.196(5)$ Å, $b =$ 10.248(3) Å, $c = 21.795(7)$ Å, $\beta = 96.143(4)°$, $V = 3596.6(19)$ Å^3, $Z = 4$, $\rho_{calcd.} = 1.36$ g/cm^3, synchrotron radiation, $\lambda = 0.8$ Å, $T = 150$ K, $\Theta_{range} = 1.86$–$31.57°$. Reflections measured 97835, independent 15609, $R_{int} = 0.040$. Final R indices: $R1 =$ 0.027 [$I > 2\sigma(I)$], $wR2 = 0.061$ (all data). Details of data collection, structure solution and refinement of the crystal structures of **6** are contained in CCDC 852494. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre v*via* www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information

NMR data, results of the crystal structure analysis of **6**, additional material related to rate-order determination, deuterium-labeling and catalyst evaluation experiments are available in the Supporting Information.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (DFG SFB 623 Molecular Catalysts: Structure and Functional Design) for generous financial support and a doctoral fellowship (M.J.S., DFG GK 850 Molecular Modeling). We thank the Synchrotron Light Source ANKA for measuring time at the SCD beamline and Christian Lothschütz for fruitful discussions.

References

[1] G. Ertl, H. Knözinger, F. Schüth, J. Weitkamp, *Handbook of Heterogeneous Catalysis*, 2nd edn., Wiley-VCH, Weinheim, Germany, **2008**, p 4016.
[2] G. W. Parshall, S. D. Ittel, *Homogeneous Catalysis*, 2nd edn., Wiley, New York, **1992**, pp 2-24.
[3] J. Hagen, *Industrial Catalysis: A Practical Approach*, 2nd edn., Wiley-VCH, Weinheim, Germany, **2006**, p 507.
[4] R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd edn., Wiley-VCH, New York, **1999**, p 2619.
[5] L. Canovese, C. Santo, F. Visentin, *Organometallics* **2008**, *27*, 3577–3581.
[6] I. S. Kim, G. R. Dong, Y. H. Jung, *J. Org. Chem.* **2007**, *72*, 5424–5426.
[7] J. Yu, M. J. Gaunt, J. B. Spencer, *J. Org. Chem.* **2002**, *67*, 4627–4629.
[8] B. Cornils, W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds: A Comprehensive Handbook in Three Volumes*, 2nd edn., Wiley-VCH, New York, **2002**, pp 980–991.

[9] P. Kraft, K. A. D. Swift, *Current Topics in Flavour and Fragrance Research*, 1st edn., Helv. Chim. Acta, Zürich and Wiley-VCH, Weinheim, Germany, **2008**, p 400.
[10] K. Bauer, D. Garbe, H. Surburg, *Common Fragrance and Flavour Materials: Preparation, Properties and Uses*, 5th edn., Wiley-VCH, Weinheim, Germany, **2006**, p 318.
[11] H. R. Kricheldorf, O. Nuyken, K. A. D. Swift, *Handbook of Polymer Synthesis*, 2nd edn., Marcel Dekker, New York, **2005**, p 984.
[12] S. K. Sharma, V. K. Srivastava, R. V. Jasra, *J. Mol. Catal. A* **2006**, *245*, 200–209.
[13] D. Gauthier, A. T. Lindhardt, E. P. K. Olsen, J. Overgaard, T. Skrydstrup, *J. Am. Chem. Soc.* **2010**, *132*, 7998–8009.
[14] R. Jennerjahn, I. Piras, R. Jackstell, R. Franke, K.-D. Wiese, M. Beller, *Chem. Eur. J.* **2009**, *15*, 6383–6388.
[15] H. J. Lim, C. R. Smith, T. V. RajanBabu, *J. Org. Chem.* **2009**, *74*, 4565–4572.
[16] J. Fan, C. Wan, Q. Wang, L. Gao, X. Zheng, Z. Wang, *Org. Biomol. Chem.* **2009**, *7*, 3168–3172.
[17] A. Scarso, M. Colladon, P. Sgarbossa, C. Santo, R. A. Michelin, G. Strukul, *Organometallics* **2010**, *29*, 1487–1497.
[18] B. Lastra-Barreira, J. Francos, P. Crochet, V. Cadierno, *Green Chem.* **2011**, *13*, 307–313.
[19] S. Krompiec, N. Kuznik, M. Urbala, J. Rzepa, *J. Mol. Catal. A* **2006**, *248*, 198–209.
[20] A. Salvini, F. Piacenti, P. Frediani, A. Devescovi, M. Caporali, *J. Organomet. Chem.* **2001**, *625*, 255–267.
[21] T. J. Donohoe, T. J. C. O'Riordan, C. P. Rosa, *Angew. Chem.* **2009**, *121*, 1032–1035; *Angew. Chem. Int. Ed.* **2009**, *48*, 1014–1017.
[22] T. C. Morill, C. A. D'Souza, *Organometallics* **2003**, *22*, 1626–1629.
[23] I. R. Baxendale, A.-L. Lee, S. V. Ley, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1850–1857.
[24] C. J. Yue, Y. Liu, R. He, *J. Mol. Catal. A* **2006**, *259*, 17–23.
[25] J. Zhang, H. Gao, Z. Ke, F. Bao, F. Zhu, Q. Wu, *J. Mol. Catal. A* **2005**, *231*, 27–34.
[26] S. K. Sharma, V. K. Srivastava, P. H. Pandya, R. V. Jasra, *Catal. Commun.* **2005**, *6*, 205–209.
[27] A. Quintard, A. Alexakis, C. Mazet, Angew. Chem. **2011**, *123*, 2402–2406; *Angew. Chem. Int. Ed.* **2011**, *50*, 2354–2358.
[28] L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Angew. Chem.* **2009**, *121*, 5245–5249; *Angew. Chem. Int. Ed.* **2009**, *48*, 5143–5147.
[29] L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem. Eur. J.* **2010**, *16*, 12736–12745.
[30] R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, 4th edn., Wiley, New Jersey, **2005**.
[31] S. Hanessian, S. Giroux, A. Larsson, *Org. Lett.* **2006**, *8*, 5481–5484.
[32] B. Schmidt, *Chem. Commun.* **2004**, 742–743.
[33] M. Mirza-Aghayan, R. Boukherroub, M. Bolourtchian, *Appl. Organomet. Chem.* **2006**, *20*, 214–219.
[34] M. Mirza-Aghayan, R. Boukherroub, M. Bolourtchian, M. Moseini, K. Tabar-Hydar, *J. Organomet. Chem.* **2003**, *678*, 1–4.
[35] S. H. Hong, D. P. Snaders, C. W. Lee, R. H. Grubbs, *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.
[36] P. S. Fordred, D. G. Niyadurupola, R. Wisedale, S. D. Bull, *Adv. Synth. Catal.* **2009**, *351*, 2310–2314.
[37] M. J. Spallek, S. Stockinger, R. Goddard, O. Trapp, *Eur. J. Inorg. Chem.* **2011**, in press.
[38] I. I. Moiseev, T. A. Stromnova, M. N. Vargaftik, *J. Mol. Catal. A* **1994**, *86*, 71–94.
[39] O. Trapp, *J. Chromatogr. A* **2008**, *1184*, 160–190.
[40] O. Trapp, *Chem. Today* **2008**, *26*, 26–28.
[41] O. Trapp, S. K. Weber, S. Bauch, T. Bäcker, W. Hofstadt, B. Spliethoff, *Chem. Eur. J.* **2008**, *14*, 4657–4666.
[42] O. Trapp, S. K. Weber, S. Bauch, *Angew. Chem.* **2007**, *119*, 7447–7451; *Angew. Chem. Int. Ed.* **2007**, *46*, 7307–7310.
[43] S. Liu, J. Xiao, *J. Mol. Catal. A* **2007**, *270*, 1–43.
[44] I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* **2007**, 2925–2943.
[45] J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, 18–29.
[46] P. Ballinger, F. A. Long, *J. Am. Chem. Soc.* **1960**, *82*, 795–798.
[47] P. Ballinger, F. A. Long, *J. Am. Chem. Soc.* **1959**, *81*, 1050–1053.
[48] G. Erdogan, D. B. Grotjahn, *J. Am. Chem. Soc.* **2009**, *131*, 10354–10355.
[49] J. Tsuji, *Palladium Reagents and Catalysts – New Perspectives for the 21st Century*, John Wiley & Sons Ltd., Chichester, England, **2004**, p 656.
[50] W. A. Herrmann, B. Cornils, *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley-VCH, New York, **2000**, p 1450.
[51] D. Bingham, B. Hudson, D. E. Webster, P. B. Wells, *J. Chem. Soc. Dalton Trans.* **1974**, 1521–1524.
[52] F. Ding, Y. Sun, F. Verpoort, *Eur. J. Inorg. Chem.* **2010**, 1536–1543.
[53] P. Kisanga, L. A. Goj, R. A. Widenhoefer, *J. Org. Chem.* **2001**, *66*, 635–637.
[54] K. L. Bray, J. P. H. Charmant, I. J. S. Fairlamb, G. C. Lloyd-Jones, *Chem. Eur. J.* **2001**, *7*, 4205–4215.
[55] K. L. Bray, I. J. S. Fairlamb, G. C. Lloyd-Jones, *Chem. Commun.* **2001**, 187–188.
[56] M. M. Kabat, L. M. Garofalo, A. R. Daniewski, S. D. Hutchings, W. Liu, M. Okabe, R. Radinov, Y. Zhou, *J. Org. Chem.* **2001**, *66*, 6141–6150.
[57] A. Heumann, L. Giordano, A. Tenaglia, *Tetrahedron Lett.* **2003**, *44*, 1515–1518.
[58] T. Hosokawa, T. Yamanaka, M. Itotani, S.-I. Murahashi, *J. Org. Chem.* **1995**, *60*, 6159–6167.
[59] E.-i. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 2, John Wiley & Sons, New York, **2002**, p 3424.
[60] F. Borchers, K. Levsen, H. Schwarz, C. Wesdemiotis, H. U. Winkler, *J. Am. Chem. Soc.* **1977**, *99*, 6359–6365.
[61] J. Tsuji, *Palladium in Organic Synthesis*, in: *Topics in Organometallic Chemistry*, Vol. 14, Springer, Berlin, **2005**, p 329.
[62] J. F. Hartwig, *Organotransition Metal Chemistry – From Bonding to Catalysis*, University Science Books, Sausalito, **2010**, p 1127.
[63] T. C. Morrill, C. A. D'Souza, *Organometallics* **2003**, *22*, 1626–1629.

[64] K. Burgess, W. A. Donk, T. B. Marder, S. A. Westcott, T. A. Baker, J. C. Calabrese, *J. Am. Chem. Soc.* **1992**, *114*, 9350–9359.
[65] A. C. Cooper, K. G. Caulton, *Inorg. Chim. Acta* **1996**, *251*, 41–51.
[66] S. Fantasia, J. D. Egbert, V. Jurcik, C. S. J. Cazin, H. Jacobsen, L. Cavallo, M. Heinekey, S. P. Nolan, *Angew. Chem.* **2009**, *121*, 5284–5288; *Angew. Chem. Int. Ed.* **2009**, *48*, 5182–5186.
[67] K. Kudo, M. Hidai, Y. Uchida, *J. Organomet. Chem.* **1973**, *56*, 413–418.
[68] B. J. Anderson, J. A. Keith, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 11872–11874.
[69] K. M. Gligorich, S. A. Cummings, M. S. Sigman, *J. Am. Chem. Soc.* **2007**, *129*, 14193–14195.
[70] P. M. Henry, *J. Am. Chem. Soc.* **1972**, *94*, 7316–7322.
[71] R. Cramer, R. V. Lindsey, *J. Am. Chem. Soc.* **1966**, *88*, 3534–3544.
[72] S. Bhaduri, D. Mukesh, *Homogeneous Catalysis – Mechanisms and Industrial Applications*, John Wiley & Sons, New York, **2000**, p 239.
[73] D. D. Beck, J. W. Sommers, C. L. DiMaggio, *Appl. Catal. B* **1994**, *3*, 205–227.
[74] P. Albers, J. Pietsch, S. F. Parker, *J. Mol. Catal. A* **2001**, *173*, 275–286.
[75] H. E. Gottlieb, V. Kotlyar, A. Nudelmann, *J. Org. Chem.* **1997**, *62*, 7512–7515.
[76] L. Ademi, E. C. Constable, C. E. Housecroft, M. Neuburger, S. Schaffner, *Acta Cryst.* **2006**, *E62*, m1059–m1061.
[77] 1,1′-Bis(4-methylbenzyl)-4,8,8′-trimethylbicyclo[2.2.1]-4,4′,5,5′,6,6′,7,7′-octahydro-1*H*,1′*H*-3,3′-biindazole was prepared as reported[37] and $PdBr_2(MeCN)_2$ was synthesized according to a procedure described in the literature.[76] d_3-Methyltriphenylphosphonium iodide was synthesized by adding d_3-methyl iodide (1.0 g, 6.0 mmol) to a solution of triphenylphosphine (1.8 g, 6.0 mmol) in anhydrous tetrahydrofuran. The reaction mixture was stirred for 4 h at room temperature. The resulting white solid was washed with tetrahydrofuran and diethyl ether, dried under high vacuum and used without further purification.
[78] For detailed information and additional graphs see the Supporting Information.

