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In Situ Generated Bulky Palladium Hydride Complexes as Catalysts for the Efficient Isomerization of Olefins. Selective Transformation of Terminal Alkenes to 2-Alkenes

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Abstract: Application of an in situ generated bulky palladium(II) hydride catalyst obtained from a 1:1:1 mixture of $Pd(dba)_2$, $P(t\text{Bu})_3$, and isobutyryl chloride provides an efficient protocol for the isomerization and migration of a variety of olefins. In addition to the isomerization of (*Z*)- to (*E*)-olefins, the conjugative migration of allylbenzenes, allyl ethers, and amines was effectively achieved in near-quantitative yields and with excellent functional group tolerance. Catalyst loadings in the range of 0.5−1.0 mol % were typically applied, but even loadings as low as 0.25 mol % could be achieved when the reactions were performed under neat conditions. More interestingly, the investigated catalyst proved to be selective for converting terminal alkenes to 2-alkenes. This one-carbon migration process for monosubstituted olefins provides an alternative catalyst, which bridges the gap between the allylation and propenylation/vinylation protocols. Several substrates, including homoallylic alcohols and amines, were selectively transformed into their corresponding 2-alkenes, and examples using enantiomerically enriched substrates provided products without epimerization at the allylic stereogenic carbon centers. Finally, some mechanistic investigations were undertaken to understand the nature of the active in situ generated Pd−H catalyst. These studies revealed that the catalytic system is highly dependent on the large steric demand of the $P(t\text{Bu})_3$ ligand. The use of an alternative ligand, cataCXium PinCy, also proved effective for generating an active catalyst, and it was demonstrated in some cases to display better selectivity for the one-carbon shifts of terminal olefins. A possible intermediate involved in the preparation of the active catalyst was characterized by its single-crystal X-ray structure, which revealed a monomeric tricoordinated palladium(II) acyl complex, bearing a chloride ligand.

Introduction

Olefins represent key structural features in a plethora of naturally and non-naturally occurring compounds, as well as being precursors for the industrial synthesis of polymers.[1,2] This unsaturation occupies an important position in organic synthesis, since it can readily be transformed into a wide variety of other functionalities, as well as being a substrate for the metathesis reaction for the generation of new carbon−carbon double bonds.[2,3] In addition to the direct application of olefins in organic synthesis, they can also serve as protecting groups masking heteroatom-containing functionalities such as acids, amides, alcohols, amines, thiols, and others.[4] Despite a large variety of synthetic methods for the introduction of C−C double bonds into a number of molecular structures, such transformations are not always straightforward. An alternative way of positioning an unsaturation is to transpose a pre-existing carbon−carbon double bond with control of the stereochemistry. Consequently, the transformation of alkenes involving either the interconver-

(1) Kricheldorf, H. R.; Nuyken, O.; Swift, G. In *Handbook of Polymer Synthesis*, 2nd ed.; Marcel Dekker: New York, 2005.

(2) Selected examples: (a) Evans, D. A.; Trotter, B. W.; Côté, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2744. (b) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. *J. Am. Chem. Soc.* **2000**, *122*, 10033. (c) Ley, S. V.; Brown, D. S.; Clase, J. A.; Fairbanks, A. J.; Lennon, I. C.; Osborn, H. M. I.; Stokes, E. S. E.; Wadsworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2259. (d) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540. (e) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (f) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960.

(3) (a) Larock, R. C. In *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed.; VCH: New York, 1999; and references cited therein. (b) Mackenzie, K. In *The Chemistry of Alkenes*; Patai, S., Ed.; Wiley: New York, 1964. For a review on the Wittig reaction, see: (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. For a review on olefin metathesis, see: (d) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (e) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vols. 1−3.

(4) (a) Kocienski, P. J. In *Protecting Groups*, 3rd ed.; Thieme Verlag: Stuttgart, Germany, 2005. (b) Wuts, P. G. M.; Greene, T. W. In *Green's Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: New York, 2006. (c) Guibé, F. *Tetrahedron* **1998**, *54*, 2967. (d) Guibé, F. *Tetrahedron* **1997**, *53*, 13509. (e) Escoubet, S.; Gastaldi, S.; Bertrand, M. *Eur. J. Org. Chem.* **2005**, 3855.

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sion of (*E*)- and (*Z*)-alkenes or the controlled migration of this functionality along a carbon chain is of high importance.[5−10]

Recently, the selective transformation of terminal alkenes into 2-alkenes has received increased attention, since such migrations allow the conversion of products obtained from a C−C bond-forming allylation to the corresponding adducts of vinylation or propenylation. This one-carbon shift protocol was recently highlighted by Donohoe and co-workers,[11] stating: "Allyl groups have the advantage that they can be installed readily in procedures that are more convenient than the addition of a vinyl group, for example, through a radical Keck-type allylation of haloalkanes the allylation of an enolate, or the addition of an allylic organometallic reagent to a carbonyl group. Subsequent isomerization of the terminal olefin to the internal position affords a propenyl group, which can be further functionalized. Therefore, this sequence builds a bridge between the chemistry of an allyl group and that of a vinyl group; this tactic is particularly useful in synthesis."

One-carbon migrations of alkenes have in the past few years been successfully performed, exploiting a ruthenium hydride based complex derived from a Grubbs generation II metathesis catalyst.[9t−x,10i,11−14] Migration of the unsaturation does not proceed further, despite the fact that additional isomerization of the unsaturation would afford products of higher thermodynamic stability (conjugation or increased substitution pattern of the olefin). Impressive examples on the use of this Ru-based catalyst have been reported in the literature with catalyst loadings generally in the range of 5−10 mol % and sometimes with the necessity for stoichiometric additives.[12,14] These catalysts are, however, not without some drawbacks, as they also can promote unwanted side reactions such as reduction and self-dimerization of the olefin.[11,15] In the end, this leads to depletion of the overall yield of the transformation in combination with potentially difficult purification steps.

Just recently, the RajanBabu group reported the use of another interesting class of catalysts for this valuable single-carbon migration reaction derived from $[(allyl)PdCl]_2$, a triarylphosphine, and silver triflate.[16] Although the transformation of terminal olefins to 2-alkenes was successfully achieved with the few examples tested, the *E*:*Z* ratio of the newly formed disubstituted olefin was moderate. Hence, the identification of alternative catalysts which can not only promote this interesting migration reaction but also provide products with control of the C═C bond geometry could be of significant importance.

(5) For representative examples of *E*/*Z* interconversions, see the following. Isomerizations based on acids: (a) Gibson, T. W.; Strassburger, P. *J. Org. Chem.* **1976**, *41*, 791. Isomerizations based on halogens: (b) Hepperle, S. S.; Li, Q.; East, A. L. L. *J. Phys. Chem. A* **2005**, *109*, 10975. (c) Kodomari, M.; Sakamoto, T.; Yoshitomi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 4053. Isomerizations based on photochemistry: (d) Sairre, M. I.; Araújo, L. F. N.; Silva, R.; Donate, P. M.; Silvério, C. A.; Okano, L. T. *J. Braz. Chem. Soc.* **2008**, *19*, 194. (e) Dugave, C.; Demange, L. *Chem. Rev.* **2003**, *103*, 2475. (f) Baag, M. M.; Kar, A.; Argade, N. P. *Tetrahedron* **2003**, *59*, 6489. (g) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinéz, L. E. *Tetrahedron* **1994**, *15*, 4323. (h) Iranpoor, N.; Mottaghinejad, E. *J. Organomet. Chem.* **1992**, *423*, 399. Isomerizations based on radical processes: (i) Bosanac, T.; Yang, J.; Wilcox, C. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1875. (j) Ali, M. A.; Tsuada, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2842.

(6) For representative examples of *E*/*Z* interconversions, using palladium, see: (a) Canovese, L.; Santo, C.; Visentin, F. *Organometallics* **2008**, *27*, 3577. (b) Kim, I. S.; Dong, G. R.; Jung, Y. H. *J. Org. Chem.* **2007**, *72*, 5424. (c) Yu, J.; Gaunt, M.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627.

(7) For representative examples of migrations in allyl groups, see migrations based on bases: (a) Catozzi, N.; Edwards, M. G.; Raw, S. A.; Wasnaire, P.; Taylor, R. J. K. *J. Org. Chem.* **2009**, *74*, 8343. (b) Böhrsch, V.; Blechert, S. *Chem. Commun.* **2006**, 1968. (c) Sagoet, O.; Monteux, D.; Langlois, Y.; Riche, C.; Chiaroni, A. *Tetrahedron Lett.* **1996**, *37*, 7019.

(8) For reviews of migrations in *O*-allyl systems, see: (a) Kuźnik, N.; Krompiec, S. *Coord. Chem. Rev.* **2007**, *251*, 222. (b) Uma, R.; Crévisy, C.; Grée, R. *Chem. Rev.* **2003**, *103*, 27. (c) van der Drift, R. C.; Bouwmann, E.; Drent, E. *J. Organomet. Chem.* **2002**, *650*, 1.

(9) For representative examples of migrations in allyl groups using transition metals, see the following. For Fe: (a) Crivello, J. V.; Kong, S. *J. Org. Chem.* **1998**, *63*, 6745. For Ir: (b) Baxendale, I. R.; Lee, A.-L.; Ley, S. V. *Synlett* **2002**, *3*, 516. For Rh: (c) Boons, G.-J.; Burton, A.; Isles, S. *Chem. Commun.* **1996**, 141. (d) Corey, E. J.; Suggs, W. *J. Org. Chem.* **1973**, *38*, 3224. (e) Galbe, K. P. *Tetrahedron Lett.* **1991**, *32*, 23. (f) Gent, P. A.; Gigg, R. *J. Chem. Soc., Chem. Commun.* **1974**, 227. (g) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027. (h) van Boeckel, C. A. A.; Oltvoort, J. J.; van Boom, J. H. *Tetrahedron* **1981**, *37*, 3751. (i) Strohmeier, W.; Weigelt, L. *J. Organomet. Chem.* **1975**, *86*, C17. (j) Kloosterman, M.; van Boom, J. H.; Chatelard, P.; Boulanger, P.; Descotes, G. *Tetrahedron Lett.* **1985**, *26*, 5045. (k) Gilbertson, S. R.; Hoge, G. S. *Tetrahedron Lett.* **1998**, *39*, 2075. (l) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139. For Pd: (m) Golborn, P.; Scheinmann, F. *Adv. Catal.* **1969**, *20*, 291. (n) Stork, G.; Atwal, K. S. *Tetrahedron Lett.* **1982**, *23*, 2073. (o) Carless, H. A. J.; Haywood, D. J. *J. Chem. Soc., Chem. Commun.* **1980**, 980. (p) Boss, R.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 558. (q) Moreau, B.; Lavielle, S.; Marquet, A. *Tetrahedron Lett.* **1977**, *18*, 2591. For Ni: (r) Taniguchi, T.; Ogasawara, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1136. (s) Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 4679. For Ru: (t) Donohoe, T. J.; Flore, A.; Bataille, C. J. R.; Churruca, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6507. (u) Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahdron Lett.* **2002**, *43*, 1839, and references cited therein. (v) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781. (w) Wang, D.; Chen, D.; Haberman, J. X.; Li, C.-J. *Tetrahedron* **1998**, *54*, 5129. (x) Zoran, A.; Sasson, Y.; Blum, J. *J. Org. Chem.* **1981**, *46*, 255. For Zr: (y) Gibson, T.; Tulich, L. *J. Org. Chem.* **1981**, *46*, 1821.

(10) For representative examples of migrations applying transition metals, see the following. For Mo: (a) Joe, D.; Overmann, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635. For Cr: (b) Sodeoka, M.; Yamada, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4906. For Rh: (c) Matsuda, I.; Kato, T.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1986**, *27*, 5747. For Pd: (d) Sen, A.; Lai, T. W. *Inorg. Chem.* **1984**, *23*, 3257. (e) Sen, A.; Lai, T. W. *Inorg. Chem.* **1981**, *20*, 4036. For Ni: (f) Lochow, C. F.; Miller, R. G. *J. Org. Chem.* **1976**, *41*, 3020. For Ru: (g) Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A. *J. Am. Chem. Soc.* **2007**, *129*, 9592. (h) Yue, C. J.; Liu, Y.; He, R. *J. Mol. Catal. A: Chem.* **2006**, *259*, 17. (i) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865. (j) Wakamatsu, H.; Nishida, M.; Adachi, N.; Mori, M. *J. Org. Chem.* **2000**, *65*, 3966. (k) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(11) Donohoe, T. J.; O'Riordan, T. J. C.; Rosa, C. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1014.

(12) For reviews on double-bond isomerizations with Ru hydride catalysts, see: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (b) Naota, T.; Takaya, H.; Murahahsi, S.-I. *Chem. Rev.* **1998**, *98*, 2599.

(13) (a) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem.* **2002**, *114*, 4926; *Angew. Chem., Int. Ed.* **2002**, *41*, 4732. (b) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. *J. Org. Chem.* **2006**, *71*, 4255. (c) Terada, Y.; Arisawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4063. (d) Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153. (e) Lee, H. M.; Smith, D. C., Jr.; He, Z.; Stevens, E. D.; Yi, C. S.; Nolan, S. P. *Organometallics* **2001**, *20*, 794. (f) Dharmasena, U. L.; Foucault, H. M.; dos Santos, E. N.; Fogg, D. E.; Nolan, S. P. *Organometallics* **2005**, *24*, 1056. (g) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T.-L.; Ding, S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 2546. (h) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414.

(14) (a) Alcaide, B.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817, and references therein. (b) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089. (c) Dinger, M. B.; Mol, J. C. *Eur. J. Inorg. Chem.* **2003**, 2827. (d) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481. (e) Donohoe, T. J.; Rosa, C. P. *Org. Lett.* **2007**, *9*, 5509. (f) Donohoe, T. J.; Chiu, J. Y. K.; Thomas, R. E. *Org. Lett.* **2007**, *9*, 421.

(15) Hong, S. H.; Snaders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

(16) Lim, H. J.; Smith, C. R.; RajanBabu, T. V. *J. Org. Chem.* **2009**, *74*, 4565.

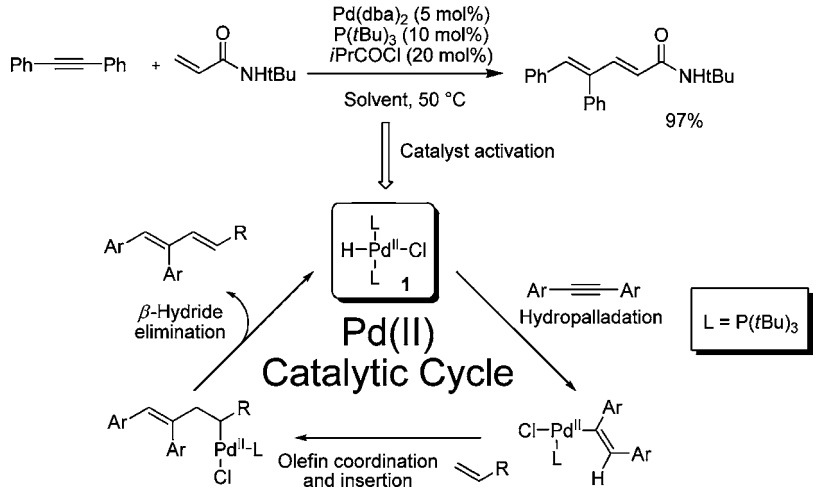


Figure 1. Direct intermolecular ene-yne coupling and its catalytic cycle.

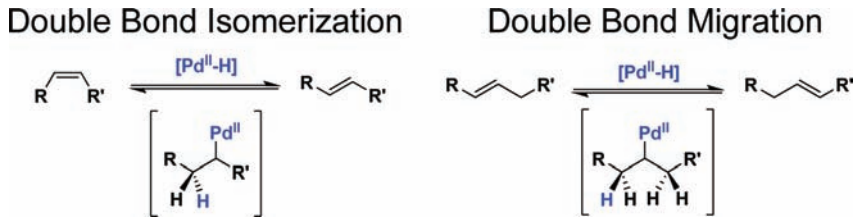


Figure 2. Isomerization/migration of C−C double bonds catalyzed by Pd−H complexes.

Previously, we reported the direct intermolecular coupling of alkynes to alkenes via a proposed palladium(II) hydride catalyzed Mizoroki−Heck (MH) type mechanism (Figure 1).[17,18] We proposed that the complex **1** was formed in situ from a mixture of $Pd(dba)_2$, $P(t\text{Bu})_3$, and isobutyryl chloride, and in all steps of the catalytic cycle, palladium was retained in the oxidation state II (Figure 1). Hills and Fu have previously isolated this complex and suggested it to be a potential MH-coupling resting state strongly dependent on the choice of base.[19] The increased stability of **1** compared to that of other Pd−H complexes is explained by the large steric bulk of the two coordinating $P(t\text{Bu})_3$ ligands, forcing them to be placed trans to each other in the square-planar structure of the Pd(II) complex, thereby retarding decomposition via reductive elimination.[19] Furthermore, it is a well-known problem in MH couplings that a palladium hydride resting state can initiate double-bond isomerizations by a repeated olefin addition/β-hydride elimination mechanism, leading to the undesired formation of byproducts (Figure 2).[20] With the apparent stability of palladium hydride complexes such as **1** and with a protocol leading to the possible in situ formation of such complexes, we sought to investigate their application in alkene isomerization/migration processes.

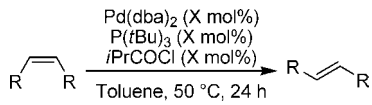
Herein, we wish to report on the application of a highly effective catalytic system composed of a 1:1:1 ratio of $Pd(dba)_2$, $P(t\text{Bu})_3$, and isobutyryl chloride for the isomerization of double bonds with excellent functional group tolerance. Not only does this catalyst perform simple and selective *Z* to *E* isomerizations of 1,2-disubstituted olefins in almost quantitative yields but it can efficiently catalyze the migration of a variety of terminal olefins such as heteroatom-substituted allylic systems and allylbenzenes to their corresponding 1-propenyl derivatives under mild reaction conditions,[21] in which for the latter a high selectivity for the *E* isomer was achieved. Furthermore, we demonstrate that the combination of these three reagents generates a catalyst, which can successfully migrate various terminal olefins by one carbon to 2-alkenes, even though further migration would lead to products of higher thermodynamic stability through conjugation with other functional groups. This method represents thereby a viable alternative to the Ru-based catalysts. A detailed study on the factors which govern the activity of this catalyst revealed that an alternative phosphine, cataCXium PinCy, proved in some cases to be superior to $P(t\text{Bu})_3$. Finally, studies were undertaken to provide information about the mechanism of formation and structure of the active catalyst.

Results and Discussion

***Cis−Trans* Isomerizations.** Initial screenings revealed that direct transfer of the catalytic system applied to the intermolecular ene-yne coupling using $Pd(dba)_2$ (5 mol %), $P(t\text{Bu})_3$ (10 mol %), and isobutyryl chloride (10 mol %) in toluene at 50 °C overnight afforded full isomerization of (*Z*)-stilbene (**2**) and

(17) Lindhardt, A. T.; Mantel, M. L. H.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2668.
(18) For a review on palladium hydride complexes, see: (a) Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011. (b) Hii, K. K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002; Chapter II.2.5.
(19) Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178.
(20) Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley-Interscience: New York, 2002, Chapter IV.2.
(21) For examples of the relevance of propenylbenzenes, see: (a) Bauer, K.; Garbe, D.; Surberg, H.; In *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley: New York, 2002. (b) Luu, T. X. T.; Lam, T. T.; Le, T. N.; Duus, F. *Molecules* **2009**, *14*, 3411. (c) Sharma, S. K.; Srivastava, V. K.; Pandya, P. H.; Jasra, R. V. *Catal. Commun.* **2005**, *6*, 205. (d) Sharma, S. K.; Srivastava, V. K.; Jasra, R. V. *J. Mol. Catal. A: Chem.* **2006**, *245*, 200.

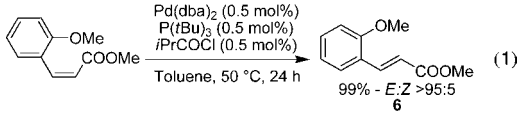
Table 1. Catalyst Optimization



Entry	$Pd(dba)_2$:$P(tBu)_3$:isobutyryl chloride X:X:X mol %	Ph, Ph **4** Conversion (yield)	MeOOC, COOMe **5** Conversion (yield)
1	5 : 10 : 10	>95%	>95%
2	1 : 2 : 2	>95%	>95%
3	1.0 : 1.0 : 1.0	>95%	>95%
4	0.5 : 0.5 : 0.5	>95% (97%)	>95% (96%)
5	0.1 : 0.1 : 0.1	87%	>95% (96%)

[a] Conversion determined by ^{1}H NMR analysis of the crude product mixture. [b] Isolated yield after chromatography.

(*Z*)-dimethyl maleate (**3**) to their corresponding *E* isomers **4** and **5** (Table 1, entry 1). Control experiments proved that the palladium source, the phosphine, or the acid chloride individually or in combinations of two could not catalyze the *cis*−*trans* double-bond isomerization. Apart from DMF, other solvents such as EtOAc, dioxane, and THF did not seem to affect the catalytic activity (see the Supporting Information), and hence toluene was therefore chosen as a representative solvent for further screening. Lowering of the catalyst loading to $Pd(dba)_2$ (1 mol %), $P(tBu)_3$ (2 mol %), and isobutyryl chloride (2 mol %) afforded the same high conversion (entry 2). Changing the catalyst composition to a 1:1:1 ratio of the $Pd(dba)_2$:$P(tBu)_3$: isobutyryl chloride mixture (1 mol % of each) provided the same activity, and even an amount as low as 0.5 mol % allowed the reaction to be completed within 24 h with almost quantitative yields of the isolated products (entries 3 and 4). Applying a 0.1 mol % catalyst loading promoted the quantitative isomerization of (*Z*)-dimethyl maleate, but only an 87% conversion was detected for (*Z*)-stilbene after 24 h (entry 5). When methyl (*Z*)-3-(2-methoxyphenyl)-2-propenoate was tested with the same catalyst loading, a 99% isolated yield of the *E* isomer **6** with a >95:5 *E:Z* ratio was obtained (eq 1).



(1)

Migration of Allylic Alcohols and Amines and Allylbenzenes. With these conditions in hand, we decided to investigate the catalyst's reactivity on terminal olefins in examples where migration to internal alkenes is possible. Initially, the allylbenzenes were subjected to conditions operating with a 0.5 mol % catalyst loading in toluene. When the temperature was increased from 50 to 80 °C, we were pleased to find that all the allylbenzenes tested underwent isomerization, affording the more stable conjugated trans isomer in high isolated yields ranging from 84 to 99% (Scheme 1). Several functionalities proved compatible to the catalytic conditions, including tosylates (**9**), phenols (**10**, **11**, **13** and **14**), heteroaromatic cores (**13**), and even a free aromatic carboxylic acid (**14**). The presence of a free alcohol positioned ortho to the allylic chain resulted in a lower *E:Z* ratio, but this effect was remedied upon functionalization of the alcohol as its benzylic ether instead (**11** and **12**). Isomerization of safrole to isosafrole (**15**) was accomplished in a 96% isolated yield under the standard conditions described above. On the other hand, performing the reaction under neat conditions using 0.25 mol% catalyst on a 27.8 mmol scale (4.5 g of safrole) resulted in quantitative isolation of the migrated product with the same high stereoselectivity favoring the trans isomer **15**. Conjugative migration of the electron-deficient allylpentafluorobenzene again performed well under neat conditions, furnishing **16** in an 84% isolated yield.[22]

Allylic ethers and amines were also susceptible to the migration protocol at hand, and the results are depicted in Scheme 2. In order for the double-bond migration to reach completion, the catalyst loading was increased to 1.0 mol %. Once again, the catalytic system proved effective in the presence of a range of sensitive functional groups, including aromatic aldehydes and aliphatic alcohols as for compounds **17** and **18**, respectively, and all migrated compounds could be isolated in yields ranging from 92% to quantitative yield, although with a drop in the *E:Z* selectivity in most cases. The loss of stereoselectivity observed in these systems was not considered problematic, since a typical procedure would involve one-pot migration followed by acidic treatment in order to remove the resulting vinyl ether protecting group.[22,23] The double migration of 1-allyl-2-(allyloxy)benzene afforded **20** in a 99% isolated yield using the same catalyst loading of 1 mol %.

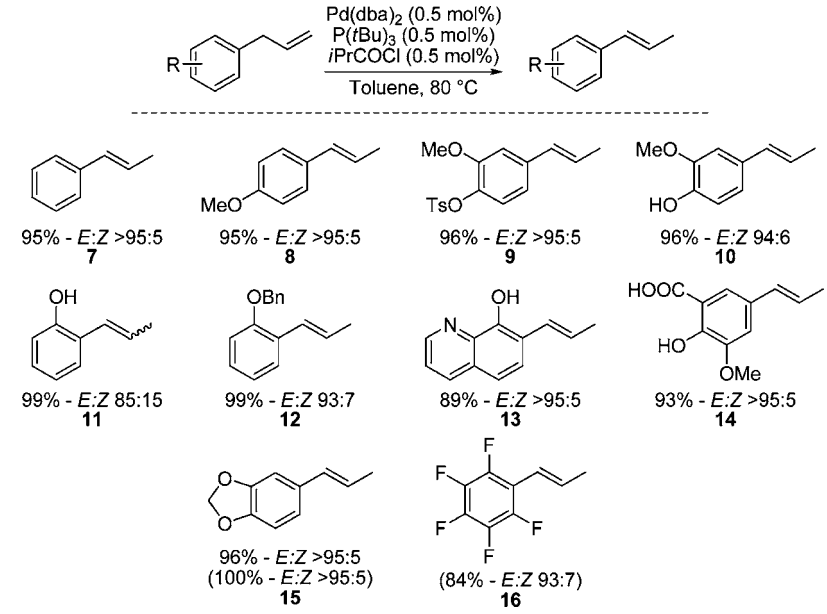
Three different O-allylic glycosides of protected glucosamine, **21**−**23**, were also tested.[23c] Addition of dioxane as a cosolvent proved helpful in order to ensure a homogeneous solution of the glycosides, and all products were isolated in yields ranging from 95% to 97%. Finally, a few N-allylated compounds were screened, and again all proved to be successful substrates for these isomerization conditions. This led to the formation of the products **24**−**27**, which included both a simple and a functionalized indole,[9v] the latter of which was isolated in a 99% yield with an overall 90:10 *E:Z* stereoselectivity. At this point, it should be mentioned that basic allylamines proved detrimental for the catalyst, with full recovery of the starting material. This observation will be addressed in further detail in Mechanistic Considerations.

During the study on the allylic ethers, another allyl derivative was tested, which led to an interesting observation. Protecting eugenol with 3-chloro-2-methyl-1-propene and a base afforded the O-alkylated derivative **28** (Scheme 3). When **28** was subjected to our isomerization conditions, migration was predominantly observed for the simple allyl functionality rather than for the 1,1-disubstituted olefin, leading to a 95:5 mixture of **29** and **30** in a 92% isolated yield. This result was also noted for the doubly functionalized 1,7-naphthalenediol **31**, in which selective shift of the C−C double bond of the allylic ether took place, providing exclusively the vinyl ether **32** in a 96% yield.

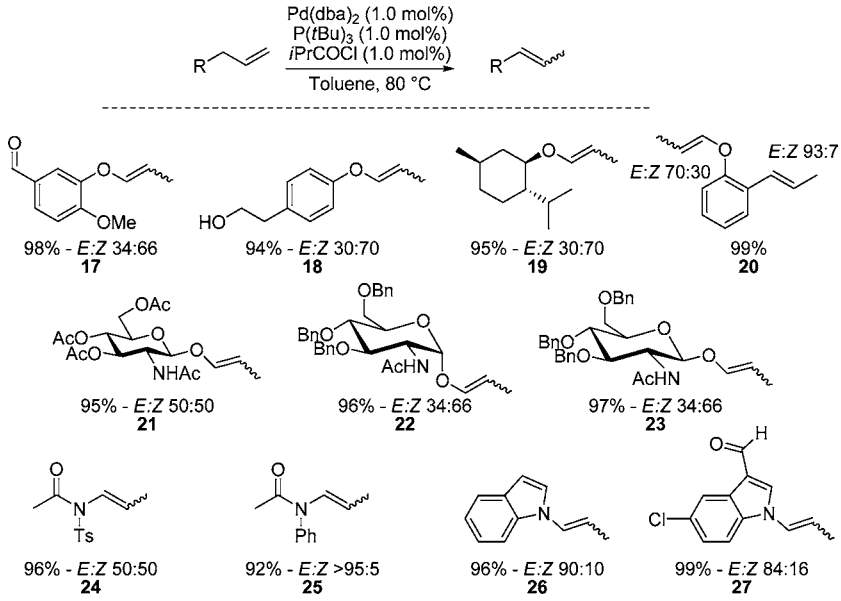
One-Carbon Migrations of Terminal Olefins. Interestingly, when *N*-Boc-*N*-tosyl-4-pentenamine (**33**) was subjected to the catalytic conditions at 50 °C in toluene, isomerization to the 3-pentenyl amine isomer **34** was the only product observed for this reaction instead of complete migration with the formation of the vinyl amide derivative (Scheme 4). Inspired by these

(22) Baxendale, I. R.; Lee, A.-L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850.
(23) (a) Wille, A.; Tomm, S.; Frauenrath, H. *Synthesis* **1998**, 305. (b) Davies, S. G. In *Organotransition Metal Chemistry: Applications To Organic Synthesis*; Pergamon: Oxford, U.K., 1982. (c) Christensen, H.; Christiansen, M. S.; Petersen, J.; Jensen, H. H. *Org. Biomol. Chem.* **2008**, *6*, 3276.

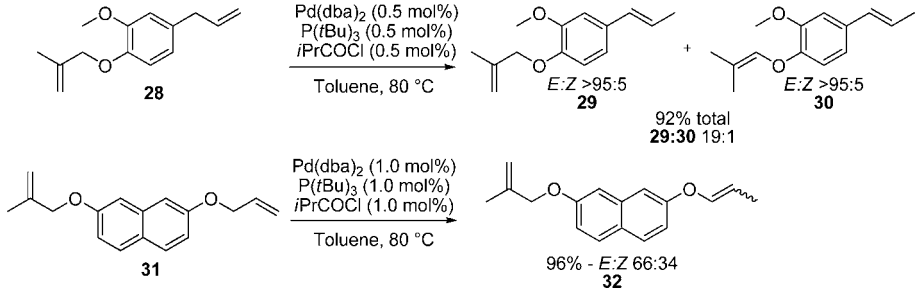
Scheme 1. Conjugative Migrations of Allylbenzenes



Scheme 2. Conjugative Migrations of Allylic Ethers, Amines, and Indoles



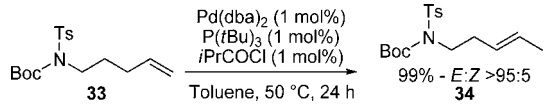
Scheme 3. Examples of Regioselective C−C Double-Bond Migration



findings, we decided to screen more substrates, including homoallylic amines and alcohols, the results of which are presented in Table 2. This same one-carbon migration was observed in these similar systems, even though further migration in general would lead to products of higher stability.

Applying the catalytic system directly to the nonprotected homoallylic alcohol **35** at 80 °C afforded an approximately 90% conversion to **43** with an isolated yield of 73% and a *E:Z* ratio of 90:10.[24] In contrast to that observed for the pentenyl amine **33**, attempted migration at 50 °C only led to lower conversions.

Scheme 4. Olefin Migration Studies with *N*-Boc-*N*-tosyl-4-pentenamine



Silylation or benzylation of the free hydroxyl group had a significant effect on the conversion efficiency. For example, in the case of the benzyl ether **37**, selective migration of the terminal olefin led to an improved level of conversion and the alcohol derivative **45** could be secured in an excellent 92% yield. Exchange of the homoallylic side chain from an alkyl to a phenyl group proved also equally rewarding, providing selectively **46** in a satisfactory 91% yield, even though the driving force for conjugation would be greater for this substrate. In addition to the homoallylic alcohols, a few enantiomerically pure homoallylic amines were tested. Again, the same high selectivity for the one-carbon migration was observed, and in both examples examined, **47** and **48** were obtained in good yields. Importantly, chiral HPLC analysis of the products revealed that no epimerization of the nitrogen-bearing stereogenic carbon centers had occurred.

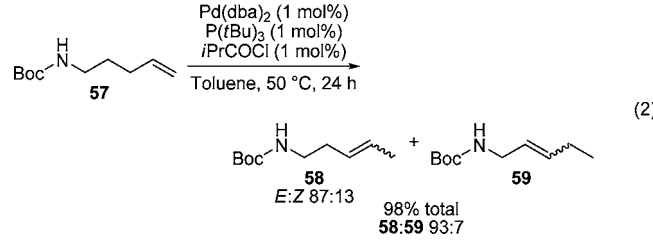
Finally, subjecting substrates derived from either the stereoselective allylation of glutamate or Evans *N*-acyl oxazolidinone to our conditions provided the desired 1,2-disubstituted olefins **49** and **50** in good yields without sign of products derived from conjugation of the C−C double bond. Again, epimerization of the stereogenic carbon centers was not observed.

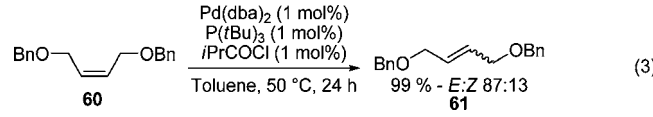
Whereas the conversions were high in all cases, for some substrates the reaction ceased after approximately 90% conversion.[25] Whether this was the result of catalyst decomposition or the attainment of an equilibrium between reactant and product was examined with the pure *E* isomer of the allylic alcohol **43**. Subjecting this substrate to the same reaction conditions led to an identical 9:1 product distribution of the internal and terminal alkenes, exactly as observed for the migration reaction of **35**, suggesting that indeed the aforementioned migrations had reached thermodynamic equilibrium. Nevertheless, as illustrated with **37**, benzylation of the homoallylic alcohol can influence this equilibrium in favor of the allylic alcohol formation.

The selective one-carbon migration observed for the substrates in Scheme 4 and Table 2 also matches with the observations made for compounds **28** and **31** in Scheme 3. Here selective migration of the simple allyl functionality over the 1,1-disubstituted olefin occurred. This reactivity discrepancy may originate in the energy differences between the intermediate alkyl−palladium complexes obtained after the hydropalladation step. It would be expected that a tertiary alkyl−palladium species carrying a bulky P(*t*Bu)$_3$ ligand is higher in energy compared to a secondary alkyl−palladium species, hence accounting for the observed selectivity.

Application of this catalytic system to the substrates **51** and **54**, in which the length between the olefin and the alcohol functionality has been extended by one methylene group, as well as to their corresponding benzyl- and TIPS-protected versions (**52**, **53** and **55**, **56** respectively) was attempted in order to establish the role of the alcohol or oxygen atom's position for the selective isomerization (Table 3). In contrast to the examples shown in Table 2, these homologues provided a mixture of products resulting from one- and two-carbon migration of the double bond. Nevertheless, it is interesting to note that again no ketone or aldehyde products were identified in the product mixtures from **51** and **54**. Protection of the alcohol functionality as the benzyl ether (**52** and **55**) or TIPS ether (**53** and **56**) did, however, reveal some perplexing results. Whereas, the amount of two-carbon migrated products doubled for the protected versions of **51** (entries 2 and 3) the opposite was observed for **55** and **56** (entries 5 and 6). One explanation for this decrease in two-carbon migration with **55** and **56** could be that protection of the alcohol retards the coordinating ability of the oxygen atom allowing the steric interaction with the 2-methyl side chain to influence the overall selectivity (entries 5 and 6).

Upon application of **57**, the nontosylated version of **33** in Scheme 4, a one-carbon shift of the double bond was primarily observed with only minor amounts of the two-carbon migrated product (eq 2). Notably, when dibenzylated *cis*-2-butene-1,4-diol (**60**; eq 3) was examined, under our conditions only the *Z* to *E* isomerization was observed, with no trace of products resulting from migration to the conjugated vinyl ether. When all these results are compared with the conjugative migrations in Table 2, it becomes clear that it is difficult to provide a concise model predicting the regioselectivity of this migration depending on the position or mode of protection on the heteroatom (oxygen or nitrogen) in these systems. However, it appears that the migration toward conjugation is impeded due to the presence of a secondary allylic heteroatom.



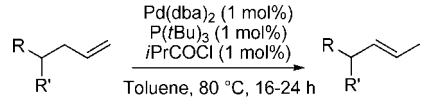


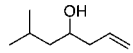
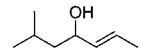
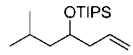
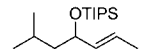
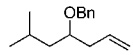
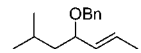
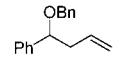
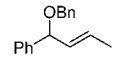
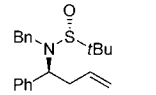
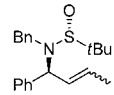
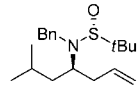
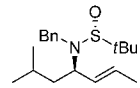
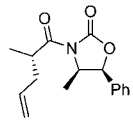
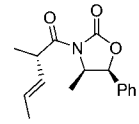
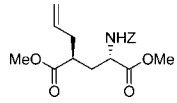
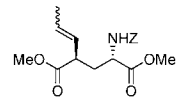
Influence of the Catalyst Composition. With these substrate effects in mind, it was therefore decided to further investigate the factors which influenced the catalytic system, including the palladium and hydride source, as well as to what extent P(*t*Bu)$_3$ was unique as the ligand. The silylated homoallylic alcohol **62** was chosen as the test substrate, and the results of this study are depicted in Table 4. Applying Pd(PPh$_3$)$_4$ as the palladium precursor only affected the yield and the product distribution marginally, despite the presence of extra triphenylphosphine in the catalyst mixture (entry 2). The importance of the structure of the dba ligand in Pd(dba)$_2$ was also investigated. Modified dba ligands represented by their corresponding 4,4′-MeO and 4,4′-fluoro derivatives on the aromatic rings were prepared as the Pd$_2$(dba-OMe)$_3$ and Pd$_2$(dba-F)$_3$ complexes according to Firmansjah and Fu.[26] Again, little difference was observed with these Pd(0) variations on the aptitude for migration, although the fluorine substitution showed a small drop in conversion

(24) Compound **43** could not be separated from the starting material **35** by column chromatography. See the Supporting Information.

(25) Subjecting 6-methyl-1-hepten-4-ol to another in situ generated Pd−H catalyst provided mainly the fully migrated ketone product or inferior conversion rates and yields; see: (a) Balraju, V.; Dev, R. V.; Reddy, D. S.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 3569. (b) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625. (c) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651.

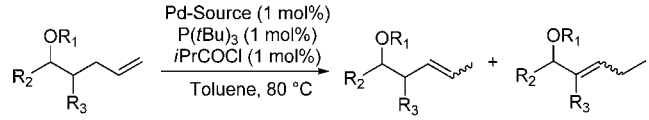
Table 2. Terminal Olefins Which Undergo a One-Carbon Migration

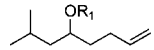


Entry	Substrate		Product		Yield[a]	*E*:*Z*[b]
1		**35**		**43**	73	90:10
2		**36**		**44**	85	90:10
3		**37**		**45**	92	90:10
4		**38**		**46**	91	>95:5
5		**39**		**47**	72	86:14
6		**40**		**48**	86	95:5
7		**41**		**49**	90	85:15
8		**42**		**50**	99	80:20

[a] Isolated yield after chromatography. [b] Ratio of isomers determined by ^{1}H NMR analysis of the crude product.

Table 3. Studying the Effect of the Alcohol or Ether Functionality



Entry	Substrate	R_1	Nr	Total yield [%][a]	**a**	**b** (*E*:*Z*)[b]	**c**
1		H	**51**	86	9	74 (80:20)	17
2		Bn	**52**	98	7	59 (64:36)	34
3		TIPS	**53**	99	10	56 (68:32)	34
4		H	**54**	87	4	78 (60:40)[c]	18
5		Bn	**55**	95	12	76 (87:13)	12
6		TIPS	**56**	98	7	85 (81:19)	8

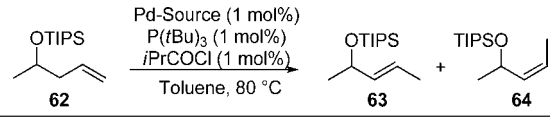
[a] Isolated yield after chromatography. [b] Ratio of isomers determined by ^{1}H NMR analysis of the crude product. [c] Formation of one unidentified product in minor proportion.

(entries 3 and 4). Once again the choice of solvent did not interfere with the catalytic system and all solvents tested, including EtOAc, dioxane, MeCN, THF, and dichloroethane, provided product mixtures nearly identical with that of toluene (Table 4, entry 1; see the Supporting Information).

Substituting *i*PrCOCl with an acetyl bromide or an acid fluoride did lead in both cases to the generation of an active catalyst, though with somewhat lower conversion for the acetyl bromide (Table 5, entries 2 and 3).[27] To avoid the possible removal of the TIPS group in our test substrate **62** under the acid fluoride conditions, the benzylated 4-penten-2-ol **65** was

(26) (a) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340. (b) Fairlamb, I. J. S.; Lee, A. F. *Organometallics* **2007**, *26*, 4087. (c) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; McGlacken, G. P.; Weissburger, F.; de Vries, A. H. M.; Schmieder-van de Vondervoort, L. *Chem. Eur. J.* **2006**, *12*, 8750. (d) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435. For an overview of the role of dba in palladium-catalyzed coupling reactions, see: (e) Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178*, 511.

Table 4. Effect of the Palladium Source on the One-Carbon Migration



Entry	Pd Source	Total yield (%)[a]	**62**:**63**:**64** (%)[b]
1	$Pd(dba)_2$	92	9:80:11
2	$Pd(PPh_3)_4$	93	13:78:9
3	$Pd_2(dba\text{-}OMe)_3$	91	9:80:11
4	$Pd_2(dba\text{-}F)_3$	93	14:76:10

[a] Isolated yield after chromatography. [b] Ratio of isomers determined by ^{1}H NMR analysis of crude product.

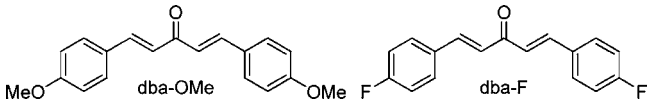
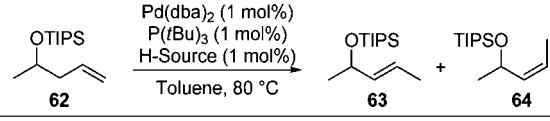


Table 5. Investigation of Different Hydride Sources



Entry	Acid-X	Total yield (%)[a]	**62**:**63**:**64** (%)[b]
1	*i*PrCOCl	92	9:80:11
2	AcBr	94	23:70:7
3	RF[c,d]	88	7:80:13
4	Ac_2O	nd[e]	nd
5	$TsOH\cdot H_2O$	nd[e]	nd

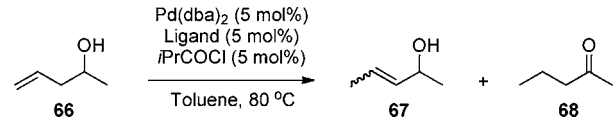
[a] Isolated yield after chromatography. [b] Ratio of isomers determined by ^{1}H NMR analysis of crude product. [c] 4-(1,3-Dioxoisoindolin-2-yl)butanoyl fluoride used as acid fluoride. [d] **65** was used instead of **62**; see the Supporting Information. [e] Formation of a complex mixture.

used instead (entry 3).[28] Also, acetic anhydride and *p*-toluenesulfonic acid were tested, but in both cases ^{1}H NMR analysis of the crude reaction mixtures were complex, with formation of several unidentifiable products (entries 4 and 5).

Apart from the alternative activators of entries 4 and 5 in Table 5, the catalytic system proved to be adaptable to changes in all but one component of the catalyst mixture: namely, the ligand. To examine the effect of the ligand, it was decided to alter the screening protocol from the original TIPS-protected 4-penten-2-ol (**62**) to 4-penten-2-ol (**66**).[29] This modification was made in order to perform the study on a homoallylic alcohol with a minimum of steric hindrance adjacent to the hydroxy group, to ensure that any changes observed were the result of the phosphine ligand and were not due to the bulk of the substrate. Furthermore, the catalyst loading was increased to 5 mol % of all components. A selection of results from this ligand screening is depicted in Table 6.

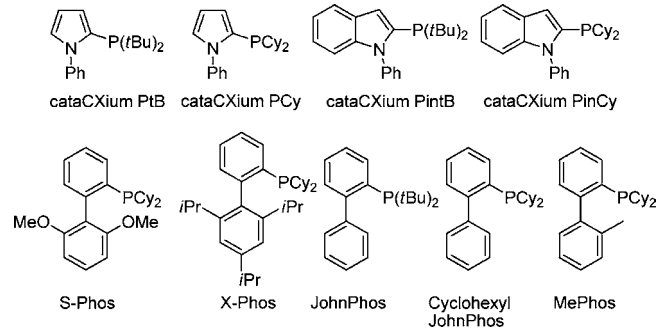
Once again the effect of the substrate became evident, since applying P(*t*Bu)$_3$ as the ligand provided the ketone product **68** in 30% yield as a result of a two-carbon migration (entry 1). Significant formation of **68** was also observed for several other ligands, but no general trend could be determined (entries 1, 3,

Table 6. Ligand Screening Studies in the Olefin Migration of 4-Penten-2-ol



		Yield (%)		
Entry	Ligand	**66**	**67** (*E*:*Z*)	**68**[a]
1	P(*t*Bu)$_3$	9	61 (91:9)	30
2	*n*BuP(Adm)$_2$	21	67 (88:12)	12
3[b]	PCy_3	47	26 (69:31)	27
4	P(2-furyl)$_3$	63	37 (66:33)	trace
5	PPh_3	18	76 (80:20)	6
6	P(*o*-Tol)$_3$	21	64 (81:19)	15
7[b]	cataCXium PtB	6	50 (88:12)	44
8	cataCXium PCy	12	88 (89:11)	
9	cataCXium PintB	13	57 (95:5)	30
10	cataCXium PinCy	4	96 (91:9)	
11	S-Phos	15	80 (85:15)	5
12	X-Phos	4	73 (88:12)	23
13[b]	JohnPhos	4	61 (97:3)	35
14	Cyclohexyl JohnPhos	12	78 (90:10)	10
15	MePhos	4	81 (94:6)	15

[a] Ratios **66**:**67**(*E*:*Z*):**68** determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Formation of several unidentified byproducts.

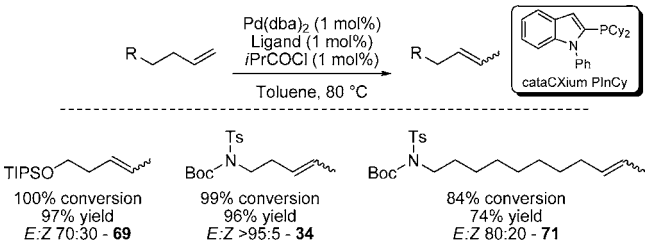


7, 9, 12, 13, and 15). Smaller cone angles of the ligands also had an influence on the reactivity of the system, providing lower conversion rates (entries 3−6). Only ligands with properties similar to those of P(*t*Bu)$_3$ showed promising results. Especially, PCy and PinCy of the cataCXium series performed well with good *E*:*Z* ratios and reasonable conversion rates, but importantly, only the desired one-carbon migration was observed (entries 8 and 10).[30,31] Especially the cataCXium PinCy ligand proved to be an excellent alternative, as shown in Scheme 5.

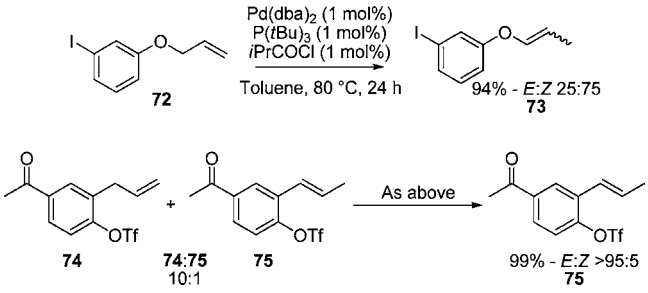
When both the protected 4-pentenol and 4-pentenamine were subjected to a catalyst generated from the cataCXium ligand at

(27) Carpino, L. A.; Sadat-Aalaee, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651.
(28) Applying 4-(1,3-dioxoisoindolin-2-yl)butanoyl chloride as the acid halide precursor afforded a product mixture comparable to that of *i*PrCOCl.
(29) 4-Penten-2-ol is commercially available.
(30) For representative references of CataCXium ligands, see: (a) Rataboul, F.; Zapf, A.; Jackstell, R.; Harkal, S.; Riermeier, T.; Monsees, A.; Dingerdissen, U.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 2983. (b) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38. (c) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem.* **2000**, *112*, 4315; *Angew. Chem., Int. Ed.* **2000**, *39*, 4153. (d) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209. (e) Stambuli, J. P.; Stauffer, S. R.; Shaugnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677. (f) Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056.
(31) P(*t*Bu$_3$), CataCXium PinCy,[30] and the Phos series of Buchwald's ligands are known to provide monodentate phosphine complexes. For P(*t*Bu)$_3$: (a) Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184. (b) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349. Buchwald's Phos ligands: (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, 1461.

Scheme 5. Selective One-Carbon Migrations using cataCXium PinCy as the Ligand



Scheme 6. Migration Experiments with Allylbenzenes Possessing an Iodide or Triflate Substituent



80 °C, the products **69** and **34** from the one-carbon migration could be isolated in good yields. Even more gratifyingly, the single-carbon shift of the double bond in the 10-undecenamine derivative **70** also proved possible, affording the desired disubstituted alkene **71** in a 74% yield. Repeating this experiment with P(tBu)$_3$ as the ligand provided product contaminated with significant amounts of products from further migration of the olefin unit at this reaction temperature, revealing the much higher selectivity of the cataCXium PinCy ligand.[32]

Mechanistic Considerations. Throughout this work on the migration of double bonds, some classes of substrates were of particular interest, as the results of the migration provided information toward a better understanding of the structure of the active catalyst. As mentioned previously, basic allylic amines failed to undergo isomerization, which is in accordance with the base-induced reductive elimination of the MH coupling depleting the catalytic palladium(II) hydride species.[20,33] Electrophiles such as the aryl iodide **72** and the activated aryl triflate **74** did not interfere with the catalytic isomerization, indicative of the mildness of the catalytic system and the fact that the catalytic cycle is devoid of Pd(0) intermediates (Scheme 6).

The ^{31}P NMR spectrum of the catalyst mixture obtained only a few minutes after its preparation at room temperature in THF indicated the formation of the known Pd(II)−H complex **1** residing at 83.1 ppm.[19] In THF, a minor species was also detected at 77.5 ppm in a 1:4 relation with **1** as the major species, along with free P(tBu)$_3$ ligand (63.4 ppm). The complex at 77.5 ppm was obtained selectively by reacting the commercially available complex Pd[P(tBu)$_3$]$_2$ with 3 equiv of isobutyryl chloride in THF at room temperature. This reaction released 1 equiv of free P(tBu)$_3$ (δ 63.4 ppm), measured by the integration of the two signals formed in the ^{31}P NMR spectrum.[19] The single-crystal X-ray structure of this unknown

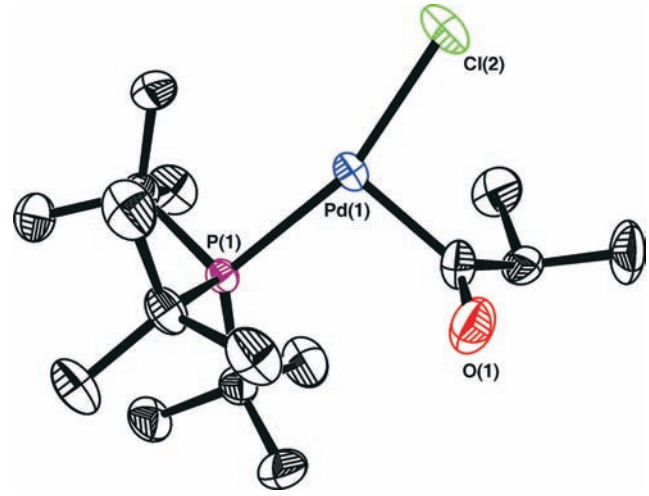


Figure 3. ORTEP diagram of acylpalladium complex **76**.

species revealed the tricoordinated Pd(II) complex **76** formed by the oxidative addition of *i*PrCOCl to PdP(tBu)$_3$ (Figure 3).

Compound **76** represents an example of a monomeric tricoordinated acylpalladium(II) complex carrying a chloride ligand. It is interesting to compare this structure with the crystal structures of related Pd(II) complexes bearing a P(tBu)$_3$ ligand, such as those described by Hartwig[34] and Beller.[35] The Hartwig group has earlier observed that oxidative addition of an aryl chloride to the Pd−P(tBu)$_3$ complex leads to the formation of a dimeric Pd(II) complex,[34] rather than a monomeric structure, as in our observations using an acid chloride. On the other hand, Beller and co-workers reported the structure of the monomeric acylpalladium complex [Pd(Br)(p-CF$_3$C$_6$H$_4$CO)(PtBu$_3$)], bearing a bromide ligand.[35] As with the complex **76**, the acyl group is oriented *trans* to the empty site of the metal nucleus. The reason for this particular configuration, according to Beller et al., is presumably not due to steric effects, since the bulky phosphine ligand is placed *cis* to the acyl moiety and not *cis* to the smaller chlorine atom.[35] Instead, a strong trans effect of the acyl moiety has been suggested for this particular configuration, placing this group opposite to the empty site on the palladium center.

Although the formation of **1** and **76** occurred rapidly, the stability of the catalyst mixture was inadequate for further ^{1}H NMR and ^{31}P NMR studies, with formation of new unidentified phosphorus-containing species within 10−15 min in combination with palladium precipitation.[36] Changing the solvent to safrole seemingly increased the stability of the catalyst, and the formation of both **1** and **76** could be followed by ^{31}P NMR, as shown in Figure 4. **1** and **76** were formed almost exclusively after 30 min in safrole at room temperature from a 1:1:1 mixture of Pd(dba)$_2$, P(tBu)$_3$, and *i*PrCOCl using a 25% aqueous solution of H_3PO_4 as the external reference. Although **76** is rapidly formed in safrole (5 min by ^{31}P NMR; Figure 1) compared to THF as the solvent, there is a continuous buildup of this species until all P(tBu)$_3$ is consumed (see the Supporting Information).

The shaded squares in Figure 4, labeled a−d, depict ^{31}P NMR spectra of the individual species **1**, **76**, [P(tBu)$_3$]$_2$Pd, and P(tBu)$_3$

(32) Work regarding the optimization of the one-carbon migration using cataCXium PinCy as ligand is currently ongoing in our laboratories and will be reported in due time.

(33) Whitcombe, N. J.; Hii, K. K. M.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449.

(34) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141.

(35) Sergeev, A. G.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2008**, *130*, 15549.

(36) (a) Clark, H. C.; Goel, A. B.; Goel, S. *Inorg. Chem.* **1979**, *18*, 2803. (b) Goel, R. G.; Ogini, W. O. *Organometallics* **1982**, *1*, 654. (c) Dùravilà, V.; Mingos, D. M. P.; Vilar, R.; White, A. J. P.; Williams, D. J. *J. Organomet. Chem.* **2000**, 198.

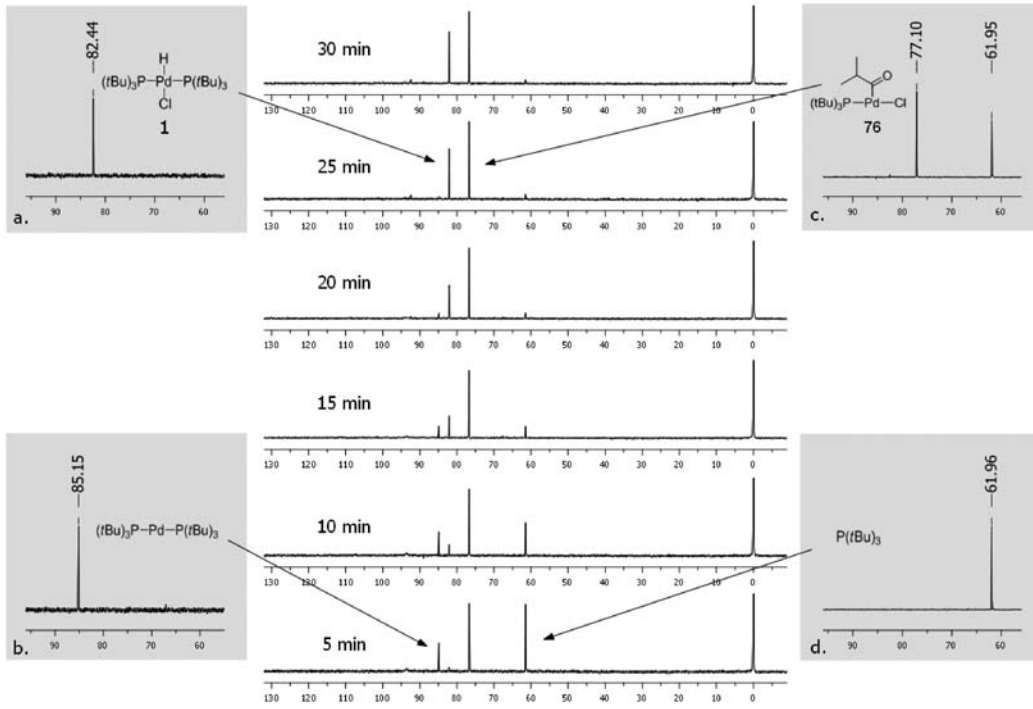


Figure 4. ^{31}P NMR spectra of the catalyst mixture in safrole and its evolution over time.

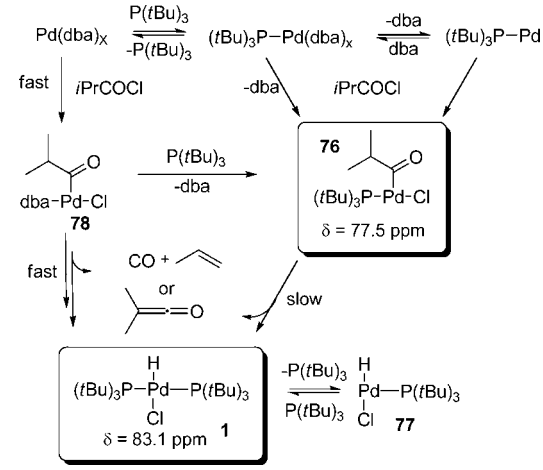
in safrole. This example serves to show the rapid formation of **1** and **76**, although the individual ratios of the final catalytic mixture should not be compared with reactions performed in other solvents such as THF, toluene, and dioxane.

Slow decomposition of pure **76** into the Pd−H complex **1** was detected after 24 h at room temperature in THF.[37] This decomposition could potentially occur via two possible pathways, due to the T-shaped nature of the tricoordinated complex. First, this Pd complex must isomerize, placing the acyl group *cis* to the vacant coordination site. Subsequent formation of a palladium hydride species could be envisaged to take place either by β-elimination of the acyl α-hydrogen, forming the corresponding ketene, or by decarbonylation followed by a β-hydride elimination releasing carbon monoxide and propene, with the eventual formation of **1** upon coordination of one extra P(tBu)$_3$. An indication of this decomposition pathway leading from **76** to **1** was observed by heating a solution of **76** in benzene-d_6 at 50 °C. After 2 h, the specific ^{1}H NMR shifts for the hydride of **1** were observed in combination with the shifts for propene residing at 5.67 ppm (ddq, 1H, J = 16.8, 10.0, 6.8 Hz), 4.96 ppm (ddq, 1H, J = 16.8, 2.4, 1.6 Hz), and 4.90 ppm (ddq, 1H, J = 10.0, 2.4, 1.2 Hz) (see the Supporting Information). However, complex **1** is formed rapidly upon mixing of Pd(dba)$_2$, P(tBu)$_3$, and isobutyryl chloride at room temperature, suggesting that an alternative pathway leading to **1** is operating.

The active catalyst which promotes these isomerizations could be represented by the Pd(II) hydride complex **77** depicted in Scheme 7, carrying one phosphine ligand and a free site for the coordination of the olefinic moiety prior to isomerization. Scheme 7 illustrates possible pathways leading to the formation of all the discussed complexes.

Since Pd(dba)$_2$ and P(tBu)$_3$ are mixed in a 1:1 ratio and only the bis-coordinated species Pd[P(tBu)$_3$]$_2$, **1**, **76**, and free ligand

Scheme 7. Plausible Pathway Leading to **1**, **76**, and **77**



are observable by ^{31}P NMR, this implies that palladium(0) is still left in the mixture without phosphine coordination. The remainder of the added palladium is likely to participate in equilibrium with several Pd species only stabilized by dba as the ligand. Oxidative addition of *i*PrCOCl to Pd(dba)$_n$ followed by dba dissociation, if required, would lead to an acyl tricoordinated palladium(II) complex (**78**).[38,39] This complex also contains a vacant coordination site on the palladium and an elimination pathway similar to those suggested above, leading to a hydride species, could be envisaged. Replacement of the dba ligand(s) by P(tBu)$_3$ would then provide the stable and detectable Pd−H complex **1**.[40]

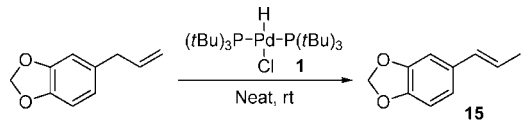
Neither of the two suggested pathways for the hydride formation from **78**, being either direct β-hydride elimination

(37) It should be noted that heating a solution of complex **76** in safrole at 80 °C effectively promotes the migration to isosafrole, as observed for the mixture Pd(dba)$_2$:P(tBu)$_3$:*i*PrCOCl.

(38) Personal correspondence with Anny Jutand (Ecole Normale Supérieure, Département de Chimie, URA CNRS 1679, 24 rue Lhomond, 75231 Paris, Cedex 05, France).

(39) The presence of dba might not be essential, since Pd(PPh$_3$)$_4$ also provided an active catalyst (Table 4, entry 2).

Scheme 8. Isomerization of Safrole Catalyzed by $[P(t\text{Bu})_3]_2PdHCl$ (**1**)



1 (X mol%)	Time	Yield	*E*:*Z*	TON
0.1 mol%	15 min	98%	>95:5	1000
0.01 mol%	160 min	98%	>95:5	10.000

forming the ketene or decarbonylation followed by β-hydride elimination releasing propene and CO, can be excluded at the present time, since both acetyl chloride and pivaloyl chloride afforded **1**. Importantly, substituting isobutyryl chloride with benzoyl chloride, an acid chloride devoid of hydrogens for β-hydride elimination, only led to a phosphorus species residing at 72.2 ppm in benzene-d_6, presumably the benzoyl derivative of **76**, with no formation of **1** even after 14 h at room temperature (see the Supporting Information).[41]

Furthermore, attempts to isolate products from these processes with high-molecular-weight acid chlorides have so far been unrewarding. Since the reaction of isobutyryl chloride with $Pd[P(t\text{Bu})_3]_2$ only leads to **76**, the formation of **1** does not originate from trace water present in the reaction medium, leading to HCl by reaction with the acid chloride.[19] The Hartwig group has previously described the formation of a palladium hydride by β-hydride elimination of a Mizoroki−Heck (MH) intermediate formed upon carbopalladation of an arylpalladium halide complex to dba.[34] Similar products obtained by MH reactions with dba could not be observed or isolated from our catalyst mixtures, and hence this pathway to **1** does not seem plausible in the case of an acylpalladium(II) complex. Furthermore, the transformations of **76** to **1** in THF at room temperature with or without added dba occur at similar rates (results not shown).

To test the hypothesis of **1** being a precursor for the active catalyst, this metal hydride complex was prepared according to the protocol of Fu and co-workers.[19] Applying this catalyst to safrole under neat conditions gratifyingly provided a highly active catalyst with TON's of 1000 to 10 000 in 15−160 min at room temperature (Scheme 8).

If **77** represents the catalytically active species, then the addition of excess $P(t\text{Bu})_3$ to the reaction mixture should slow the migration reactions by shifting the equilibrium between **1** and **77** illustrated in Scheme 7 in favor of the tetracoordinated Pd complex **1**. To test this hypothesis, the isomerization of safrole to isosafrole (**15**) was followed by ^{1}H NMR at 65 °C using a premixed 1:1:1 $Pd(dba)_2$:$P(t\text{Bu})_3$:*i*PrCOCl catalyst mixture followed by the addition of $P(t\text{Bu})_3$ (Figure 5).

Ligand addition significantly reduced the reaction rate, even after the addition of only 1 equiv of $P(t\text{Bu})_3$. A similar experiment catalyzed by the addition of the isolated Pd−H complex **1** proved even more sensitive to the phosphine addition, as performing the isomerization at room temperature in the presence of an extra 1 equiv of $P(t\text{Bu})_3$ completely quenched the reaction. Furthermore, premixing **1** with dba and adding this mixture to safrole slowed the rate of reaction. This effect was also noted previously, since the formation of **1** occurs at room temperature from the 1:1:1 $Pd(dba)_2$:$P(t\text{Bu})_3$:*i*PrCOCl catalyst mixture but does not initiate the double-bond isomerization before heating. Only in the case with direct application of **1** as in Scheme 8 did the reaction occur without the need for external warming.

Conclusion

In conclusion, a highly efficient catalytic protocol for the isomerization of olefins was presented using a catalyst generated from the premixing of $Pd(dba)_2$, $P(t\text{Bu})_3$, and *i*PrCOCl. Apart from simple *Z* to *E* isomerization, the conjugative migration of allylbenzenes and heteroatom-substituted allyl groups was performed with excellent functional group tolerance and the products were furnished in high isolated yields. Furthermore, the in situ formed bulky palladium(II) hydride catalyst was able to catalyze a highly selective one-carbon migration of a variety of substrates, including homoallylic alcohols and amines, without epimerization at adjacent stereogenic centers. Finally, the factors controlling these double-bond shifts were investigated and revealed that the presence of bulky monodentate phosphine ligands capable of forming tricoordinated complexes was necessary for high catalytic activity. An alternative phosphine ligand, cataCXium PinCy, proved in certain cases to be superior to $P(t\text{Bu})_3$, and further work with this ligand is currently under investigation in our laboratories. Finally, some mechanistic studies were undertaken, during which a novel monomeric tricoordinated acylpalladium(II) complex was isolated and characterized by X-ray crystallographic analysis. Additional investigations are ongoing in order to obtain better conversion levels for the selective one-carbon migration of terminal olefins, as well as to obtain an in-depth understanding regarding the formation of the palladium(II) hydride catalyst.

Experimental Section

General Methods. Solvents were dried according to standard procedures. Flash chromatography was performed on silica gel 60 (230−400 mesh). The chemical shifts of the NMR spectra are reported in ppm relative to the solvent residual peak.[42] MS spectra were recorded on a LC TOF (ES) apparatus. All isomerizations/migrations were carried out in 7.0 mL sample vials with a Teflon sealed screwcap in a glovebox under an argon atmosphere. All purchased chemicals were used as received without further purification.

(*E*)-7-(1-Propenyl)-8-quinolinol (13) (Scheme 1).[43] General Procedure for the Conjugative Migration. 7-Allyl-8-quinolinol (185.2 mg, 1.0 mmol) dissolved in toluene (2.5 mL), $Pd(dba)_2$ from a 0.01 mg μL^{-1} stock solution in toluene (288.0 μL, 5.0 μmol), $P(t\text{Bu})_3$ from a 0.02 mg μL^{-1} stock solution in toluene (50.6 μL, 5.0 μmol), and isobutyryl chloride from a 0.01 mg μL^{-1} stock solution in toluene (53.3 μL, 5.0 μmol) were reacted for 21 h at 80 °C. The crude product was purified by flash chromatography on silica gel using CH_2Cl_2 as eluent. This afforded 164.2 mg of (*E*)-7-(1-propenyl)-8-quinolinol (**13**) (89% yield, *E*/*Z* > 95:5) as a pale yellow solid. ^{1}H NMR (400 MHz, C_6D_6): δ 9.06 (bs, 1H), 8.35 (dd, 1H, J = 4.4, 1.6 Hz), 7.45 (d, 1H, J = 8.8 Hz), 7.42 (dd, 1H, J = 8.0, 1.6 Hz), 7.17 (dq, 1H, J = 16.0, 1.6 Hz), 6.91 (d, 1H, J = 8.8 Hz), 6.64 (dd, 1H, J = 8.4, 4.4 Hz), 6.31 (dq, 1H, 16.0, 6.8 Hz), 1.73 (dd, 3H, J = 6.8, 1.6 Hz). ^{13}C NMR (100 MHz, C_6D_6): δ 148.8, 147.9, 139.1, 135.6, 127.4, 126.9, 126.0, 125.8, 120.9,

(40) A 1/1 mixture of $Pd(dba)_2$ and isobutyryl chloride does not provide an active catalyst in control experiments, suggesting that the catalytically active species carries at least one phosphine ligand.

(41) Fujihara, T.; Katafuchi, Y.; Iwai, T.; Terao, J.; Tsjui, Y. *J. Am. Chem. Soc.* **2010**, *132*, 2094.

(42) Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.

(43) Bahloul, A.; Sebban, A.; Dardari, Z.; Boudouma, M.; Kitane, S.; Belghiti, T.; Joly, J.-P. *J. Heterocycl. Chem.* **2003**, *40*, 243.

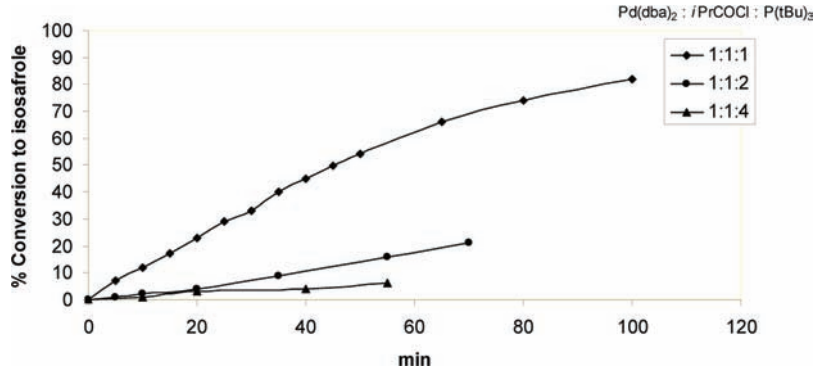


Figure 5. Influence of additional equivalents of P(*t*Bu)$_3$ on the conversion of safrole to isosafrole (**15**).

120.4, 117.5, 18.9. HRMS (*m*/*z*): $C_{12}H_{11}NO$ [M + Na^+], 208.0738; found, 208.0730.

(*E*)-*tert*-Butyl Pent-3-enyl(tosyl)carbamate (34) (Scheme 4).[10] General Procedure for the One-Carbon Migration. *tert*-Butyl pent-4-enyl(tosyl)carbamate (**33**) (135.0 mg, 0.4 mmol) dissolved in toluene (1.0 mL), $Pd(dba)_2$ from a 0.01 mg μL^{-1} stock solution in toluene (230.4 μL, 4.0 μmol), P(*t*Bu)$_3$ from a 0.02 mg μL^{-1} stock solution in toluene (40.5 μL, 4.0 μmol), and isobutyryl chloride from a 0.01 mg μL^{-1} stock solution in toluene (42.8 μL, 4.0 μmol) were reacted for 24 h at 80 °C. The crude reaction was concentrated in vacuo and purified by flash chromatography on silica gel using pentane/Et_2O (7:3) as eluent. This afforded 135.0 mg of *tert*-butyl pent-3-enyl(tosyl)carbamate (**34**) (99% yield, *E*/*Z* > 95:5) as a white solid. Mp: 67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, 2H, J = 8.2 Hz), 7.27 (d, 2H, J = 8.2 Hz), 5.52 (dqt, 1H, J = 15.3, 6.3, 1.2 Hz), 5.38 (dqt, 1H, J = 15.3, 6.9, 1.4 Hz), 3.83−3.80 (m, 2H), 2.43−2.37 (m, 2H), 2.41 (s, 3H), 1.64 (dd, 3H, J = 6.3, 1.4 Hz), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 144.1, 137.6, 129.2, 128.1, 127.9, 126.9, 84.0, 46.9, 33.5, 27.9, 21.6, 18.0. GCMS for $C_{17}H_{25}NO_4S$ (*m*/*z* (relative intensity)): 239 (0.5), 184 (84, $CH_3(CH)_2(CH_2)_2NBoc^•$), 155 (100, Ts$^•$), 91 (70), 65 (12).

Acknowledgment. We are deeply appreciative of generous financial support from the Danish National Research Foundation, The Danish Natural Science Research Council, the Carlsberg Foundation, and the University of Aarhus. We gratefully appreciate the donation of ligands and catalysts from Solvias. We also thank Henrik H. Jensen, Martin J. Pedersen, and Jonas Krag for supplying us with the glucosamine derivatives.

Supporting Information Available: Text, figures, and tables giving experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds and a CIF file giving crystallographic data for compound **76**. This material is available free of charge via the Internet at http://pubs.acs.org.

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