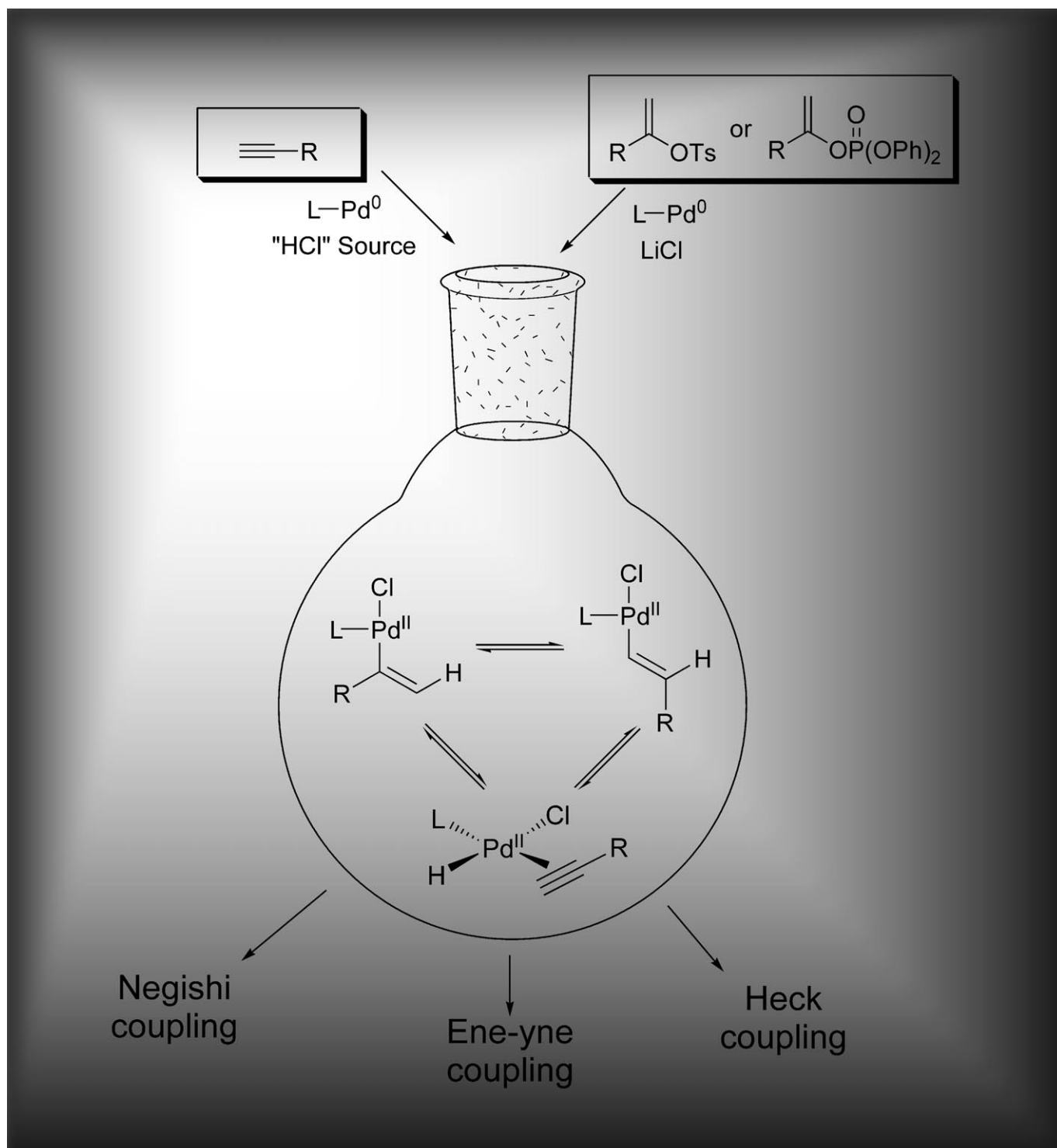# Classical Reagents: New Surprises in Palladium-Catalyzed C−C Coupling Reactions

Anders T. Lindhardt and Troels Skrydstrup*[a]

Abstract: From investigations on a relatively simple concept to identify conditions for promoting Mizoroki–Heck reactions with vinyl tosylates and phosphates, two serendipitous discoveries were made concerning new properties of palladium as a catalyst. In the first case, β-hydride eliminations well known for alkyl metal complexes were found to be equally feasible with alkenyl metal compounds. And secondly, conditions were found for promoting intermolecular ene–yne couplings via a Pd^{II}–H intermediate. This coupling reactions represents an atom economical Mizoroki–Heck type reaction.

Keywords: alkynes · hydride elimination · C—C coupling reactions · hydropalladation · palladium

Introduction

In 1968, Richard Heck published an astonishing series of seven back-to-back papers on work,[1] which paved the way for the development of one of the most exciting organic transformation over the last 35 years. This reaction allows the direct coupling of activated arenes and olefins with an unactivated alkene through palladium catalysis via a formal C—H activation, creating a σ-bond between two sp^2 carbon centers.[2] Both Mizoroki and Heck made an important contribution to this coupling independently in the early 70s reporting on the significance of added base, thereby resulting in catalytic activity with substoichiometric quantities of the transition-metal complex.[3,4] Also in the early 70s, the pioneering work of numerous brilliant chemists, including Kumada and Corriu, Negishi, Migita and Kosugi, Stille, Sonogashira, Suzuki and Miyaura, and others laid the foundation for the discovery of another valuable class of transition metal catalyzed reactions referred to as cross-couplings reactions, which bear the names of their discoverers.[5] Along side the Mizoroki–Heck (MH) coupling, these transition metal catalyzed reactions have revolutionized the synthetic strategies pursued today in both academia and industry for constructing carbon—carbon bonds in complex organic structures.[6]

Many significant developments have since then been achieved for these coupling reactions over the years improving the scope of the reactions, increasing the reactivity and chemo-, regioselectivity of the catalysts, as well as the introduction of other cross-coupling based reactions, such as the

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Hiyama reaction with readily available organosilicon reagents,[7] and the important discovery in 1995 regarding a practical approach for the assembling carbon—heteroatom bonds.[8] The importance of palladium-catalyzed coupling reactions is also reflected by the numerous reports on the application or development of such reactions in almost every issue of journals dealing with organic synthesis. A newcomer to the field of palladium catalysis would be overwhelmed by the wealth of information already published, and questions as to what else can be achieved in this field certainly must come to mind. But in spite of this, much more is still to be accomplished! As an example, numerous groups have revealed the exciting new possibilities in palladium chemistry involving applied C—H activations.[9] Many mechanistic details about the individual steps of in the catalytic cycle of the Pd-catalyzed couplings are still vague and work by Jutand, Blackmond, Espinet and others are contributing to a better understanding of the intricacies of these steps.[10]

However, discovering new chemical phenomena can depend highly on the research philosophy adapted by the individual research group. Karl Ziegler is quoted for stating,

"Keep an eye open for unexpected developments, and do not neglect new phenomena as irrelevant for the main project."[11]

In other words, following chemistry to new adventures is more likely to lead to interesting and novel discoveries than in the opposite situation where the chemist guides the chemistry to own narrow directions.

Our own contributions in palladium-catalyzed reactions transpired from work directed to expanding the repertoire of coupling reagents for the MH reaction. Traditionally, activated phenols and alkyl ketones in the form of aryl and alkenyl triflates or nonaflates represent worthy coupling partners with electron-deficient and electron-rich olefins.[12,13] However, stability issues of these reagents and the necessity for expensive triflating and nonaflating agents for their preparation limit the usefulness of these Heck precursors. Hence, cheaper coupling reagents that are easier to handle and stable would be more desirable. In this respect, aryl and alkenyl tosylates, mesylates and phosphates represent viable substitutes, being relatively straightforward to prepare and more convenient to handle. Furthermore, their appeal as coupling partners have already been confirmed in a variety of cross-coupling reactions such as the Kumada–Curriu, Negishi, Migita–Kosugi–Stille, Sonogashira, Suzuki–Miyaura, Buchwald–Hartwig, as well as carbonyl enolate arylations.[14] Nevertheless, for the case of nonactivated alkenyl sulfonates and phosphates and the complementary derivatives of aryl alcohols, a significant hurdle must be surmounted in the first step of the catalytic cycle, namely the oxidative addition into the C—O bond. Two approaches have been pursued to overcome this demanding step. In the first, catalysts based on palladium(0) possessing bulky electron rich phosphine ligands have been applied with great success in cross-coupling

reactions.[15] Alternatively, the use of the more reactive nickel(0) complexes can be applied.[16] Yet, at the time we commenced our work to examine these substrates for the MH reaction, there had been no previous reports in this line for this C−C bond forming reaction, which may also be explained by the dissimilarities between the MH and cross-coupling reactions. For example, catalytic systems well known to promote the cross-coupling with aryl tosylates completely fail when applied to the corresponding MH reaction.

Pursuing this line of research, we were able to successfully identify conditions, which effectively promoted the MH reaction of alkenyl tosylates and phosphates.[17] Whereas this represented an accomplishment on its own, more importantly, this work, which was originally initiated on a simple concept, led us to discover and mechanistically comprehend new properties of palladium catalysts in C−C bond forming reactions. In the first case, we have observed very effective 1,2-migrations in the MH and Negishi couplings promoted by a possible β-hydride elimination of alkenyl palladium(II) intermediates, suggesting that the boundaries for such hydride elimination processes are greater than originally assumed (Scheme 1).[14, 18] Furthermore, in our investigations of this unusual migration, an intermolecular ene–yne coupling has emerged,[19] which not only represents an atom economical version of the MH reaction, but also complements Trost's seminal work on the cycloisomerization reaction of ene–ynes.[20] The work leading to these observations and their exploitation in synthesis is outlined in this concept.
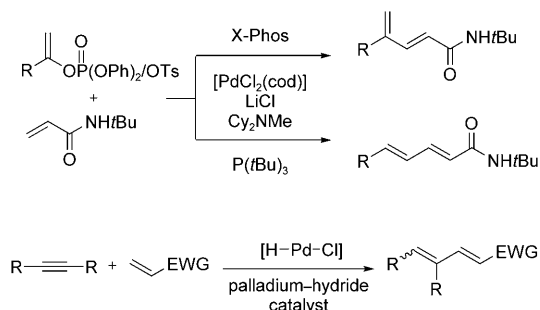

Scheme 1. Examples of MH couplings with or without 1,2-migration and Pd-catalyzed intermolecular ene–yne couplings of alkynes with olefins.

Discussion

β-Hydride elimination of alkenyl palladium(II) intermediates: β-Hydride elimination is an important elementary transformation in organometallic chemistry, where a hydride (hydrogen atom) from the β-position of the ligand is transferred to the metal center. These processes, which are more commonly observed with alkyl metal complexes, lead to the formation of a metal hydride and an olefin.[21] Although, in many instances this step represents an unproductive side reaction in transition metal catalyzed transformations, it can

also be exploited for chemical synthesis as in the Shell higher olefin process and in the MH coupling (Scheme 2).
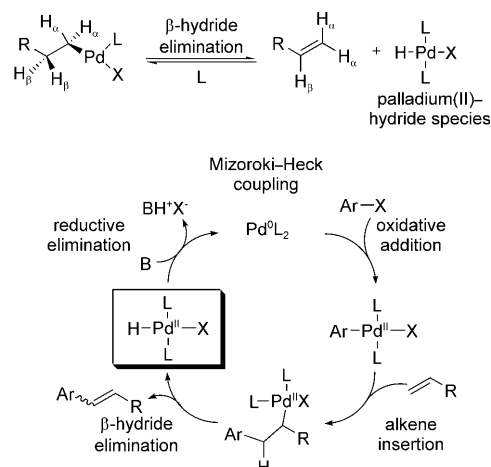
Scheme 2. β-Hydride elimination of alkyl palladium(II) species and their role in the MH coupling.

Less familiar are β-hydride eliminations involving alkenes as ligands on the metal center as illustrated in Scheme 3. In fact, general organometallic chemistry textbooks discuss only such eliminations with alkyl metal complexes, and do not describe similar eliminations to produce an alkyne or benzyne coordinated metal hydride species.
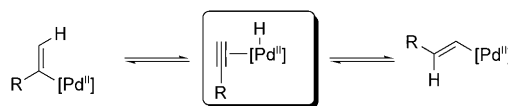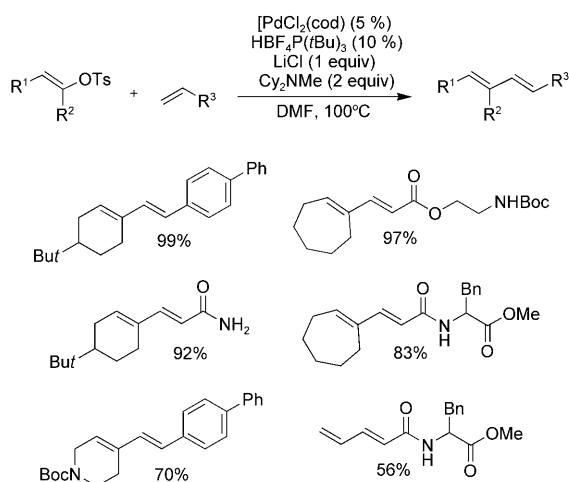

Scheme 3. β-Hydride elimination of an alkenyl palladium(II) species and re-addition of the palladium hydride intermediate.

However, our work on the palladium-catalyzed MH and Negishi reaction suggest perhaps that such β-hydride eliminations on alkenes can indeed be quite effective leading to the corresponding alkyne metal hydride complex. This species is most likely to be a transient species as the back reaction, hydrometalation of the alkyne, is undoubtedly rapid. But nevertheless if a fast equilibrium is brought about between the β-hydride elimination and hydrometalation steps, then two isomeric σ-bound metal alkenes complexes can be generated, where the rates of the ensuing reactions will determine the regioisomeric composition of the products as in a Curtin-Hammett situation.
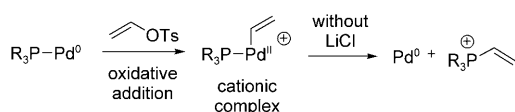
The discovery of β-hydride elimination reactions with alkenyl palladium complexes began with our work on the search for new substrates for the MH reaction as discussed in the introduction. After some experimentation, conditions were identified,[17] that effectively coupled nonactivated alkenyl tosylates to electron poor alkenes using modified conditions developed by Greg Fu's group for the coupling of

aryl bromides and chlorides to similar alkenes (Scheme 4).[22]

similar MH couplings with acrylates under phosphine free conditions with no observation of the same migration.[23]

Scheme 4. MH-couplings of nonactivated alkenyl tosylates with electron poor alkenes.

Scheme 6. Coupling of 1-tert-butyl vinyl tosylate to styrene with 1,2-migration (top). Coupling of an in situ generated 1-tert-butyl vinyl nonaflate to an acrylate without 1,2-migration (bottom).[23]

To promote these reactions, an electron-rich bulky phosphine ligand such as tri(tert-butyl)phosphine and dicyclohexylmethylamine as the base in presence of a Pd^{II} source were adapted. However, effective coupling also required the addition of one equivalent of lithium chloride to the reaction mixture, whereas other halide ions proved less effective. This observation can be accounted for by one or a combination of three explanations, where the introduction of chloride ions allows 1) the generation of a more reactive anionic Pd^0 species, which facilitates oxidative addition into the difficult C−O bond, b) the trapping of the intermediate Pd^{II} cationic species after oxidative addition to furnish the corresponding neutral complex, and c) the stabilization of the intermediate vinyl Pd^{II} cationic complex, which has been reported by Jutand et al. to undergo carbon to phosphor migration generating a vinyl phosphonium salt in the absence of chloride ions as shown in Scheme 5.[10b]

The reaction of tert-butyl vinyl tosylate with a variety of alkenes revealed this migration to be quite effective providing the linear diene in yields up to 95% and with good trans-selectivity (Scheme 7).

Scheme 7. MH couplings of tert-butyl vinyl tosylate with different electron poor alkenes.

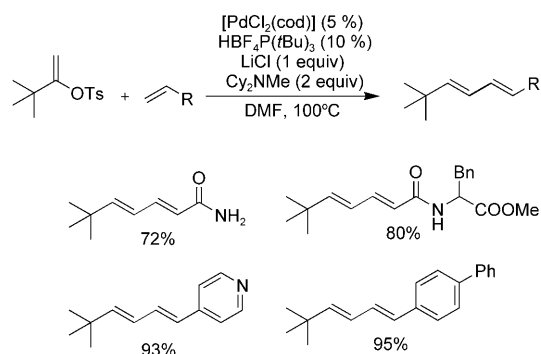Scheme 5. Formation of a vinyl phosphonium salt in the absence of chloride ions.

After screening a variety of substrates, we eventually also examined the coupling of 1-tert-butyl vinyl tosylate with styrene. To our surprise, the expected coupling product was not observed but instead the isomeric product **1** was generated from an apparent 1,2-migration of the intermediate alkenyl–Pd^{II} complex with full trans-selectivity with respect to the newly formed diene (Scheme 6). Reißig et al. have reported the use of the corresponding tert-butyl vinyl nonaflate in

Whereas, the vinyl tosylates necessitate for their formation the reaction of a preformed enolate with tosyl anhydride;[24] the corresponding and more stable vinyl phosphates can easily be prepared from the considerably less expensive phosphoryl chloride. Gratifyingly, these substrates proved their worth in the MH coupling and were also condemned to participate in the 1,2-migration when bearing the appropriate substituent in the C1 position (Scheme 8).

Further examination of the scope and limitation of this migration revealed, that the 1,2-migration in the MH coupling was confined to vinyl tosylates and phosphates bearing substituents with a quaternary carbon connected to the C1 carbon of the alkene.[18] Both alkyl and aryl substituents provided the isomerized products, although the nature and substitution pattern of these substituents was decisive on the degree of the migration, as seen with the aryl derivatives where in certain cases the migration is not complete. Where-
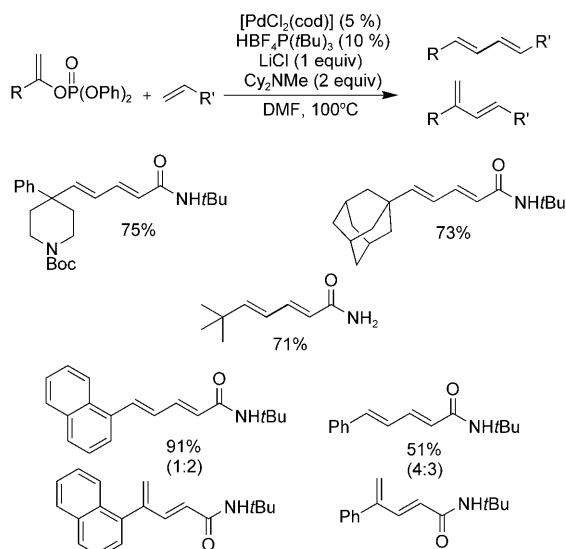
Scheme 8. MH couplings of alkenyl phosphates with 1,2-migration.

as heating was required for promoting these MH-couplings, it was interesting to observe the efficacy of the migration even at room temperature when the more reactive *tert*-butyl vinyl triflate was examined (Scheme 9).
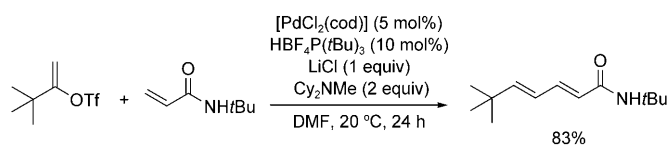
Scheme 9. Room-temperature MH coupling of *tert*-butyl vinyl triflate with 1,2-migration.

A mechanistic understanding of these migrations was brought to light through DFT calculations performed by the group of Norrby at the Technical University of Denmark.[17] The hypothesis that a β-hydride elimination pathway of the intermediate alkenyl palladium(II) species followed Pd–alkyne dissociation/association and then hydropalladation was examined in this study. As with β-hydride elimination involving an alkyl metal complex, a vacant site on the metal center is imperative. This criterion is most likely fulfilled under our reaction conditions, as a trigonally coordinated T-shaped Pd^{II} complex is the most likely species after the oxidative addition step, due to the sterical bulk of the monodentate phosphine ligand employed.[25] Calculations performed at the B3LYP/LACVP* level concluded that the highest barrier for isomerization between the two isomeric palladium–alkenyl intermediates is only 62 kJ mol^{-1}, suggesting migration proceeds rapidly under the reaction conditions employed (Scheme 10).[17]

Furthermore, our calculations suggested that the product outcome for this substrate is determined at the more energetically demanding carbopalladation step as in a Curtin–Hammett situation. Partial support for this mechanism was
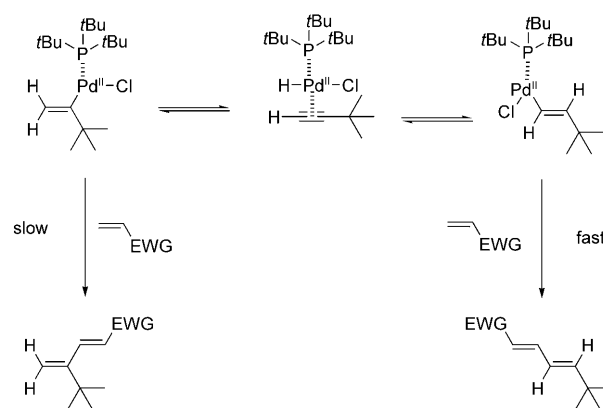
Scheme 10. Mechanistic proposal for the 1,2-migration.

acquired from the deuterium labeling experiment with the vinyl tosylate **2** (Scheme 11). Greater than 95% deuterium incorporation was obtained in the diene product with a *trans*-relationship between the two deuterium atoms. Finally, it is interesting to note, that C1 substituents at the alkene bearing α-hydrogens were not suitable for these MH reactions, which is explained by an alternative and more favorable β-hydride elimination pathway involving the alkyl substituent side chain.
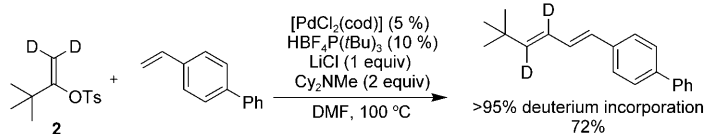

Scheme 11. 1,2-Migration with deuterium labeling.

With conditions in hand for promoting the 1,2-migration, we then undertook studies in attempts to identify alternative reaction conditions, which suppress the migration and afford the normal MH products.[18] Our initial attempts were focused at blocking the empty coordination site on the Pd–metal center employing an electron-rich bidentate phosphine, but after extensive experimentation a catalyst system composed of [PdCl$_2$(cod)], the dialkylbiarylphosphine, X-Phos,[26] in the presence of 10 equivalents of LiCl proved to be the most active and general (Scheme 12). This catalyst composition proved effective in the MH reaction for all alkenyl phosphates tested with or without C1- or C2-alkyl substituents bearing α-hydrogens. Although, X-Phos is in general considered as a bulky electron rich monodentate ligand, the sterically encumbering diaryl moiety could simply block the vacant site of the possible trigonally coordinated metal center.

Whereas 1,3-, 1,4-, and 1,6-migrations are more commonly observed in Pd-catalyzed reactions,[27] examples of 1,2-migration are extremely rare. Hartwig and co-workers observed a single case of this migration in the Kumada–Corriu
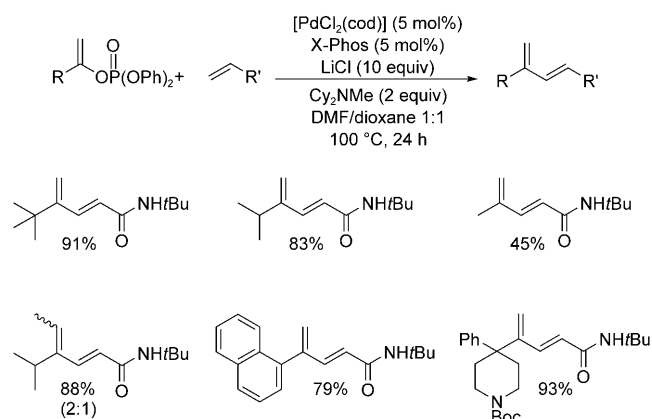
Scheme 12. MH-couplings of alkenyl phosphates without 1,2-migration.

coupling of the vinyl tosylate **3** with phenyl magnesium bromide in the presence of a palladium catalyst with the bidentate Josiphos ligand, (R,S)-Cy$_2$PF-PtBu$_2$ (Scheme 13).[24]
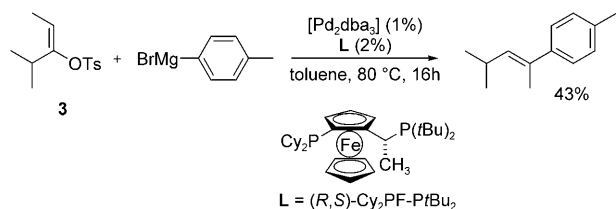
Scheme 13. Kumada–Corriu coupling with 1,2-migration.

Here too, a β-hydride mechanism was briefly discussed as a possible explanation for this observation. Nevertheless, if this mechanism is operating for this single case, then it is remarkable that *trans*-metalation followed by reductive elimination to provide the final olefin, is faster than β-hydride elimination with one of the three hydrogens of the methyl group! Although speculative, perhaps the *trans*-metalation takes place before the oxidative addition step such that reductive elimination is fast after isomerization. The ligand structure and reactions conditions appear also to have an important influence on the efficiency of this elimination pathway as no migration was observed in the analogous product from 1-phenyl vinyl tosylate in contrast to our observations in the MH couplings.

These 1,2-migrations are not only confined to the MH and the Kumada–Corriu coupling reactions. We have recently reported similar observations for the Negishi coupling of alkenyl phosphates and tosylates with aryl and alkyl zinc reagents.[14] Several surprises also came about in this study. Initial work was concentrated on the exploitation of a Ni-catalyzed Suzuki–Miyaura coupling for the preparation of 1,1-diaryl and 1-alkyl-1-aryl olefins from C1-aryl and C1-alkyl vinyl phosphates. While this reaction performed admirably in many cases, increased steric bulk at the C1 position of the alkenyl phosphates or at the *ortho*-position of the aryl

boronic acids led to drastic reductions in the coupling yields (Scheme 14).
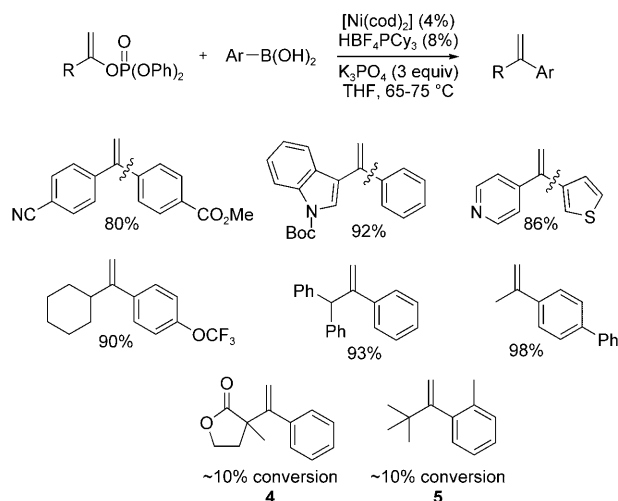
Scheme 14. Suzuki–Miyaura couplings of alkenyl phosphates with boronic acids.

As an alternative solution, we resorted to examining zinc reagents under the hypothesis that transmetalation is faster with such reagents than with the corresponding boronic acids and hence steric effects would be less imperative. Of the five ferrocene diphosphine ligands tested, two proved to demonstrate synthetic use. The palladium catalyst with DPPF as the ligand provided good coupling yields even in the synthesis of highly encumbered products as **4** and **5** (Scheme 15). It was vital to run the reactions with chloride as the counterion of the organozinc reagents as the corresponding bromide provided no turnover unless added LiCl was present. Noteworthy is the observation that the use of DPPF in the MH reactions with the same alkenyl phosphates did not even promote the first step, oxidative addition, of the catalytic cycle!
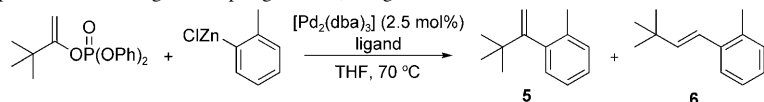
The other ferrocene-based diphosphines included four representatives of the commercially available Josiphos ligands.[28] Only the two ligands possessing the di-*tert*-butyl-
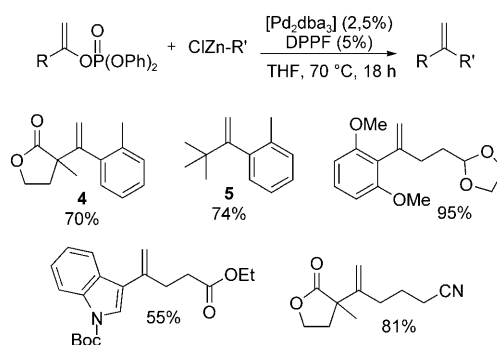
Scheme 15. Negishi couplings of alkenyl phosphates with organozinc reagents.

phosphine moiety exhibited good reactivity (Table 1). However, where catalysts generated with (R,S)-Cy₂PF-PtBu₂ provided a mixture of the normal and migrated coupling products (entry 3), the use of (R,S)-PPF-PtBu₂ led to almost complete isomerization (entry 5). This observation deviates from those observed by Hartwig and co-workers, where the former ligand was reported to promote full migration in the Kumada–Corriu reaction.[24] Additionally, it is interesting to note the poor regioselectivity observed for this reaction when tri-tert-butylphosphine was tested (entry 4), where the normal Negishi product was obtained as the major regioisomer, in contrast to complete migration in the MH coupling.

Table 1. Optimization of Negishi couplings with 1,2-migration.

| Entry	Ligand (%)	Conversion [%][b] (Yield [%])	Ratio 5/6
1	(R,S)-PPF-PCy₂ (5)	0	–
2	(R,S)-Cy₂PF-PCy₂ (5)	0	–
3	(R,S)-Cy₂PF-PtBu₂ (5)	100	43:57
4	P(tBu)₃ (10%)	n.d.[c]	72:28
5	(R,S)-PPF-PtBu₂ (5)	100	1:99

[a] Reactions were run in sealed sample vials. [b] Conversions measured by ¹H NMR spectroscopy. [c] Not determined.
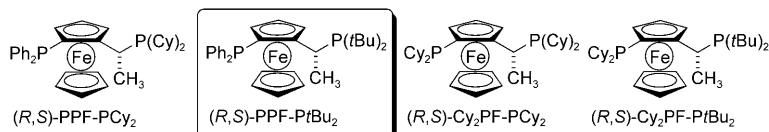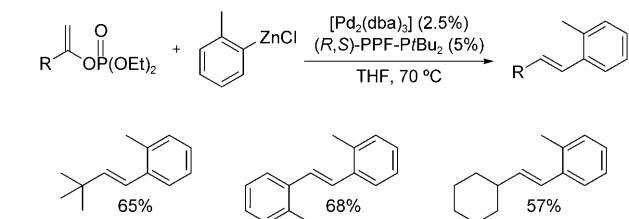

Cleaner reactions were noted when the alkenyl diphenyl phosphates were replaced by either the tosylates or diethyl phosphates. Nevertheless, due to stability issues of certain vinyl tosylates particularly those bearing a C1-aryl substituent, further studies were continued with the dialkyl phosphates. These substrates also performed well with the examples illustrated in Scheme 16 with aryl zinc reagents, though under the criteria that the chloride counter ion is present. Again, subtle changes in the reaction conditions have a marked influence on the product outcome and yield. For example, 1-ispropyl-2-methylvinyl phosphate does not react under these Negishi conditions with (R,S)-PPF-PtBu₂. Also noteworthy are the observations that alkyl zinc reagents

only lead to the formation of coupling products without 1,2-migration.

Although a full understanding of the driving force and intricacies behind this 1,2-migration necessitates further investigations, there are still some characteristic traits that can be drawn about the catalytic system required for promoting isomerization in the MH, Negishi and Kumada–Corriu couplings. Firstly, steric effects involving the C1 substituents of the alkene appear to be important. And secondly, a catalyst generated with bulky phosphine ligands bearing for example tert-butyl groups appear to be mandatory for encouraging the migration. This was clearly illustrated from our observations in the Negishi couplings, where the simple exchange of the tert-butyl to cyclohexyl groups in the Josiphos ligands completely abolished the reactivity. Nevertheless, Josiphos is normally classified as a bidentate ligand, which would not provide an empty site on the metal center for β-hydride elimination. However, because of the different electronic and sterical nature of the two phosphorus atoms on this class of ligands, these diphosphines can possibly switch between two different binding states, displaying either bi- or monodentate character depending on the re-
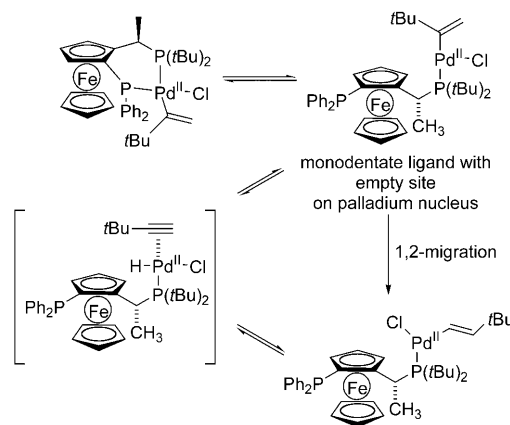
Scheme 17. Josiphos-type ligand acting both as a bidentate and monodentate ligand affording 1,2-migration.

action conditions used (Scheme 17). Further studies are now underway to confirm this hypothesis.

An atom-efficient Mizoroki–Heck reaction: The development of atom-efficient reactions is of ever increasing interest not only for minimizing waste production in fine chemi-

Scheme 16. Negishi couplings of alkenyl phosphates with 1,2-migration.

cals manufacturing but certainly also for reducing environmental issues involved in the treatment of wastes. Hence much effort is being made to the discovery and implementation of new catalytic processes, which display good atom economy.[29]

The palladium-catalyzed enyne cycloisomerizations, first reported about 20 years ago by Trost and co-workers, represent an excellent example of an atom economical transformation for the preparation of 1,3- or 1,4-dienes.[20,30] An impressive display of applications to complex natural and non-natural products have since then been reported exploiting this reaction as a key intramolecular C–C bond forming reaction. The catalytic system, which primarily is composed of [Pd₂(dba)₂] and a triaryl phosphine ligand in the presence of acetic acid, was proposed by Trost to proceed via a palladium(II) hydride intermediate involving hydropalladation of the alkyne, cyclization and subsequent β-hydride elimination to regenerate the Pd–H complex and the diene product. In spite of the numerous papers dealing with cycloisomerizations, the intermolecular version of this Pd-catalyzed reaction is not known. Whereas cationic Ru^{II} complexes can initiate the coupling of alkynes with olefins, the majority of the products are branched 1,4-dienes as illustrated in the upper example of Scheme 18.[31] Only one paper reported by Wata-
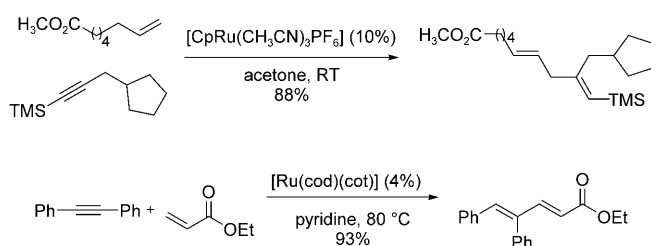
Scheme 18. Examples of Ru-catalyzed intermolecular ene–yne couplings.

nabe et al. deals with the Ru-catalyzed coupling of alkynes to acrylates generating linear 1,3-dienes.[32] In this communication, a 5-membered metallocycle via a [2+2+1] cycloaddition step was invoked to explain the product outcome, rather than hydrometalation.

Our work in this area originated from mechanistic studies on the 1,2-migrations observed in the MH couplings. As an alkyne coordinated palladium(II) complex was hypothesized to be the intermediate of the migration, we speculated whether the addition of another alkyne would allow crossover under the reaction conditions and subsequently be incorporated into the final MH product. Sure enough, the addition of diphenyl acetylene to the coupling of *tert*-butyl vinyl phosphate and an acrylamide at 100 °C in DMF furnished the diene **6** in a 90 % yield (Scheme 19).[19] Continued work on this reaction, revealed that neither the base, nor the vinyl phosphate or the lithium chloride were necessary for promoting this ene–yne coupling. On the other hand, after extensive screening, the structure of the phosphine
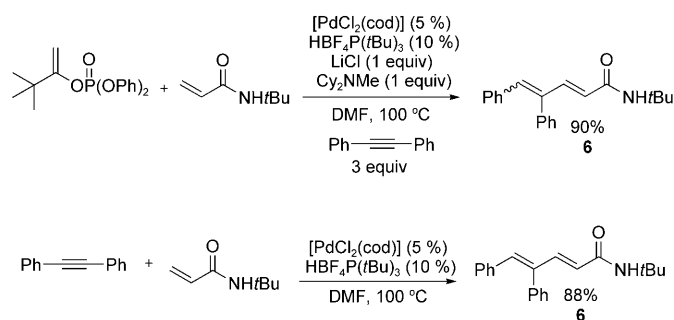
Scheme 19. Pd-catalyzed intermolecular ene–yne coupling between diphenyl acetylene and an acrylamide.

ligand proved to be essential for catalyst reactivity. Only catalysts generated with monodentate bulky alkyl phosphines such as tri(*tert*-butyl) and diadamantyl(*n*-butyl)phosphine were capable of promoting the codimerization of the acetylene with the alkene. It is noteworthy that the reaction conditions earlier developed by Trost for the enyne cycloisomerization were ineffective for promoting this transformation.

Other disubstituted alkynes could also be exploited for this coupling, but nevertheless they were limited to those bearing substituents lacking α-protons (Scheme 20). Terminal alkynes proved less effective for C–C bond formation where the acetylene competes with the alkene in the coupling step as seen by the formation of oligomeric by-products derived only from the starting alkyne. On the other hand, the typical olefinic accepters encountered in the MH reactions including acrylates, acrylamides, styrenes and allylic derivatives proved worthy for this coupling.
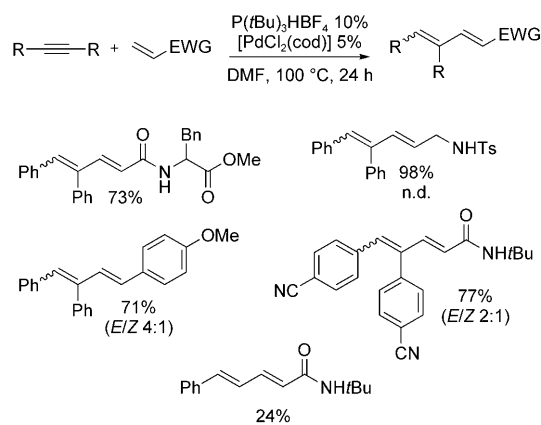
Scheme 20. Ene–yne couplings of mono- and disubstituted alkynes with electron deficient alkenes.

We speculated whether a palladium(II) hydride intermediate was being generated under the reaction conditions, which subsequently participates in hydropalladation of the starting alkyne.[33] The alkenyl Pd^{II} species formed could then follow a similar sequence of events as proposed for the
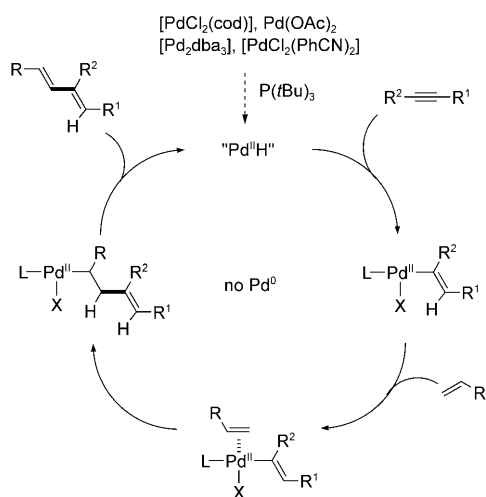
Scheme 21. A possible mechanism for the direct ene–yne coupling.

catalytic cycle of the MH leading to the diene product and the starting Pd^{II}–H complex, as depicted in Scheme 21. The presence of base does not influence the outcome of the reaction, suggesting that hydropalladation of the alkyne is faster than base promoted reduction to Pd^0. Moreover, if this catalytic cycle is operating, then the metal center does not need to fluctuate between different oxidative states, remaining as Pd^{II}. The role of the bulky monodentate phosphine ligands may be related to the nature of the Pd^{II} complexes involved in the catalytic cycle. Such ligands generate T-shaped trigonally coordinated Pd^{II} complexes rather than the more commonly observed tetracoordinated square planar species.[25] Possibly, the good binding properties of the alkyne to the metal center,[34] competes effectively with the diene product followed immediately by the hydropalladation step. Hence, the life time of the Pd^{II}-H species is very short.

To test the possible intervention of a Pd^{II}–H intermediate, we prepared the $[\{(tBu)_3P\}_2PdHCl]$ according to a procedure reported by the group of Fu.[22a] Interestingly, 5 mol% of this complex catalyzed efficiently the coupling of diphenylacetylene with acrylamide in THF even at 20°C furnishing an 87% coupling yield (Scheme 22). However, the instability of
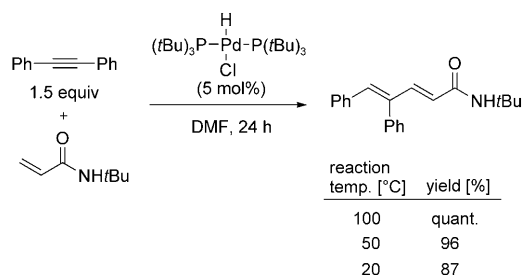
Scheme 22. Ene–yne couplings with a palladium hydride added as the catalytic species.

this hydride metal species limited its usefulness requiring synthesis in a glovebox prior to the coupling reactions.

An alternative and more practical approach to this coupling would be to generate the hydride species in situ. After some screening of possible additives, which would promote the in situ preparation of the active catalyst, we found that alkyl acid chlorides possessing a β-hydrogen added in substoichiometric amounts to a solution of $[Pd(dba)_2]$ and $(tBu)_3P$ efficiently catalyzed the coupling of a variety of al-
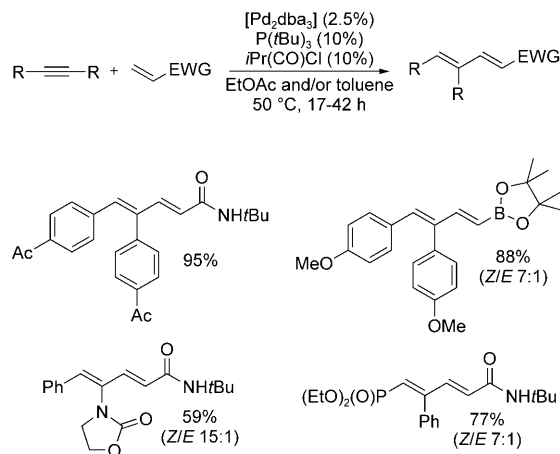
Scheme 23. Ene–yne coupling utilizing the second-generation catalytic system with improved functional group tolerance.

kynes to alkenes in a Mizoroki–Heck type manner (Scheme 23). Although, a reaction temperature of 50°C was required, importantly, the reaction could be run in many cases in a variety of solvents such as THF, EtOAc and toluene. These conditions dramatically improved coupling yields and allowed reactions of substrates not possible employing the earlier conditions in DMF at 100°C. Furthermore the range of substrates could also be increased as seen in the coupling of heteroatom substituted alkynes. And finally, mono substituted alkynes such as phenyl- and *tert*-butylacetylene also proved possible with yields attaining 60%, although further work is required to improve the efficiency of coupling for these substrates.

^{31}P NMR experiments confirmed the hypothesis of a Pd–H intermediate, as a solution of $[Pd(dba)_2]$ and $(tBu)_3P$ in THF with added isobutyric chloride led to a ^{31}P NMR signal corresponding to that of $[\{(tBu)_3P\}_2PdHCl]$.[35] Further work is now underway to identify conditions for improving the scope of the reaction with monosubstituted alkynes, as well as with substituents other than aryl or *tert*-alkyl groups.

Conclusion

Starting from investigations on a relatively simple concept to find conditions for promoting Mizoroki–Heck reactions with vinyl tosylates and phosphates, we successfully made two serendipitous discoveries concerning the properties of

palladium as a catalyst. In the first case, we hope with this concept to have convinced the reader, that β-hydride eliminations well known from alkyl metal complexes also can be achieved efficiently with alkenyl metal compounds. The coupling products from the 1,2-migrations observed in the Mizoroki–Heck and Negishi reactions themselves useful products, as without migration they would represent coupling products from vinyl tosylates/phosphates prepared from the corresponding aldyhdes, which is not always an easy task, compared to ketones. The intricacies of these β-hydride eliminations and migrations are not completely delineated and more ligand and substrate screening is required to provide the complete picture of this interesting phenomena.

Finally, work initiated in these migrations have allowed us to also develop an efficient intermolecular ene–yne coupling, which represents an atom economical Mizoroki–Heck reaction. The reaction can be catalyzed by in situ generation of a Pd[II]-hydride species which appears to be insensitive to the solvent. Additional work is though required to improve the scope of the reaction in order to place this version along side the very successful enyne cycloisomerization reactions developed by Trost.

[1] R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5518; R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5526; R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5531; R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5535; R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5538; R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5542; R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5546.

[2] For some recent reviews on the Heck reaction, see a) R. F. Heck, *Synlett* **2006**, 2855; b) N. T. S. Phan, M. Van Der Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609; c) F. Alonso, I. P. Beletskaya, M. Yus, *Tetrahedron* **2005**, *61*, 11771.

[3] T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

[4] a) R. F. Heck, J. P. Nolley Jr. , *J. Org. Chem.* 1972, 37, 2320; b) H. A. Dieck, R. F. Heck, *J. Am. Chem. Soc.* **1974**, *96*, 1133.

[5] a) A. de Meijere, F. Diederich, Metal-catalyzed Cross-Coupling Reactions, 2nd ed., Wiley-VCH, Weinheim, **2004**; b) J. Tsuji, *Palladium Reagents and Catalysts, New Perspectives For the 21st Century*, Wiley, West Sussex, **2004**; c) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley-Interscience, New York, **2002**.

[6] J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651.

[7] a) Y. Hatanaka, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 918.

[8] a) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem.* **1995**, *107*, 1456; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348; b) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609.

[9] For a few recent reviews on the subject, see a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; b) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173; c) L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichimica Acta* **2007**, *40*, 35. K. Godula, D. Sames, *Science* **2006**, *312*, 67.

[10] For representative examples, see a) C. Amatore, B. Godin, A. Jutand, F. Lemaitre, *Organometallics* **2007**, *26*, 1757; b) A. Jutand, *Appl. Organomet. Chem.* **2004**, *18*, 574; c) C. Amatore, B. Godin, A. Jutand, F. Lemaitre, *Chem. Eur. J.* **2007**, *13*, 2002; d) J. S. Mathew, M. Klussmann, H. Iwamura, F. Valera, A. Futran, E. A. C. Emanuelsson, D. G. Blackmond, *J. Org. Chem.* **2006**, *71*, 4711; e) A. C. Ferretti, J. S. Mathew, D. G. Blackmond, *Ind. Eng. Chem. Res.* **2007**, *46*, 8584; f) J. A. Casares, P. Espinet, B. Fuentes, G. Salas, *J. Am. Chem. Soc.* **2007**, *129*, 3508.

[11] A. Yamamoto, *J. Organomet. Chem.* **2002**, *653*, 5, and references therein.

[12] For some representative examples of the use of triflates in Heck reactions, see a) A. L. Hansen, T. Skrydstrup, *J. Org. Chem.* **2005**, *70*, 5997; b) J. Mo, L. Xu, J. Xiao, *J. Am. Chem. Soc.* **2005**, *127*, 751; c) K. S. A. Vallin, Q. Zhang, M. Larhed, D. P. Curran, A. Hallberg, *J. Org. Chem.* **2003**, *68*, 6639; d) P. Nilsson, M. Larhed, A. Hallberg, *J. Am. Chem. Soc.* **2001**, *123*, 8217, and references therein.

[13] For examples of the use of nonaflates in the Heck reaction, see a) J. Högermeier, H.-U. Reißig, I. Brüdgam, H. Hartl, *Adv. Synth. Catal.* **2004**, *346*, 1868; b) I. M. Lyapkalo, M. Webel, H.-U. Reißig, *Eur. J. Org. Chem.* **2002**, 3646; c) I. M. Lyapkalo, M. Webel, H.-U. Reißig, *Eur. J. Org. Chem.* **2001**, 4189, and references therein.

[14] See A. L. Hansen, J.-P. Ebran, T. Gøgsig, T. Skrydstrup, *J. Org. Chem.* **2007**, *72*, 6464, and references therein.

[15] For references on the development and application of bulky electron rich phosphines for cross-coupling reactions notably through the work of Fu, Buchwald, Hartwig and Beller, see A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431.

[16] S. Ma, H. Wang, K. Gao, F. Zhao, *J. Mol. Catal. A* **2006**, *248*, 17, and references therein.

[17] A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby, T. Skrydstrup, *Angew. Chem.* **2006**, *118*, 3427; *Angew. Chem. Int. Ed.* **2006**, *45*, 3349.

[18] J.-P. Ebran, A. L. Hansen, T. Gøgsig, T. Skrydstrup, *J. Am. Chem. Soc.* **2007**, *129*, 6931.

[19] A. T. Lindhardt (né) Hansen, M. L. H. Mantel, T. Skrydstrup, *Angew. Chem.* **2008**, *120*, 2708; *Angew. Chem. Int. Ed.* **2008**, *47*, 2668.

[20] For an account on this work, see B. M. Trost, *Chem. Eur. J.* **1998**, *4*, 2405.

[21] a) R. H. Crabtree, The Organometallic Chemistry of Transition Metals, Wiley, **1988**; b) J. P. Collman, J. S. Hegedus, J. R. Norton, R. G. Finke, Principles and Applications of Organotransition Metal Chemistry, University Science Books, Mill Valley, CA, **1987**.

[22] a) I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 13178; b) A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989; c) M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295; d) A. F. Littke, G. C. Fu, *J. Org. Chem.* **1999**, *64*, 10.

[23] I. M. Lyapkalo, M. Webel, H.-U. Reissig, *Eur. J. Org. Chem.* **2001**, 4189.

[24] M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364.

[25] J. P. Stambuli, C. D. Incarvito, M. Bühl, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 1184.

[26] a) K. Billingsley, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 3358; b) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685, and references therein.

[27] A. J. Mota, A. Dedieu, *Organometallics* **2006**, *25*, 3130.

[28] The Josiphos type ligands are commercially available from Strem.

[29] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259; c) B. M. Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

[30] a) B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1988**, *110*, 1636; b) B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34; c) B. M. Trost, M. Yanai, K. Hoogsteen, *J. Am. Chem. Soc.* **1993**, *115*, 5294; d) B. M. Trost, V. K. Chang, *Synthesis* **1993**, 824; e) B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan, D. T. Macpherson, *J. Am. Chem. Soc.* **1994**, *116*, 4255; f) B. M. Trost, M. J. Krische, *Synlett* **1998**, 1; g) B. M. Trost, F. D. Tosate, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067.

[31] For a review, see B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067.

[32] T. Mitsudo, S-.W. Zhang, M. Nagao, Y. Watanabe, *J. Chem. Soc. Chem. Commun.* **1991**, 598.

[33] For a review on palladium hydride complexes, see V. V. Grushin, *Chem. Rev.* **1996**, *96*, 2011.

[34] a) M. Alhquist, G. Fabrizi, S. Cacchi, P-O. Norrby, *J. Am. Chem. Soc.* **2006**, *128*, 12 785; b) M. Alhquist, G. Fabrizi, S. Cacchi, P-O. Norrby, *Chem. Commun.* **2005**, 4196.

[35] A. T. Lindhardt, T. Skrydstrup, unpublished results.

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