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Cross-Coupling

Tosylhydrazones: New Uses for Classic Reagents in Palladium-Catalyzed Cross-Coupling and Metal-Free Reactions

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cross-coupling · diazo compounds · hydrazones · olefins · palladium

Tosylhydrazones are useful synthetic intermediates that have been used in organic chemistry for almost 60 years. The recent discovery of a palladium-catalyzed cross-coupling reaction involving a tosylhydrazone coupling partner has triggered renewed interest in these reagents. This reaction shows nearly universal generality with regard to the hydrazone and can be employed for the preparation of polysubstituted alkenes. In the course of this research, novel metal-free C–C and C–O bond-forming reactions have been discovered. Since tosylhydrazones are readily prepared from carbonyl compounds, these transformations offer new synthetic opportunities for the unconventional modification of carbonyl compounds. This Minireview discusses all of these new reactions of a classic reagent.

1. Introduction

Palladium-catalyzed cross-coupling reactions are recognized as some of the most powerful and reliable methods for the formation of C–C bonds.[1] In a broad sense, a cross-coupling reaction is the combination of an electrophile and a nucleophile in the presence of a transition-metal catalyst. Most palladium-catalyzed C–C bond-forming cross-coupling reactions fall into two categories, depending on the nature of the nucleophilic component: Heck-type reactions,[2] in which the nucleophilic component is a C–C multiple bond, and reactions in which the nucleophile is an organometallic compound (Figure 1). The second type of reaction can be classified further into reactions that employ an stoichiometric organometallic reagent as the nucleophile (e.g. Negishi, Suzuki, Stille reactions) and coupling processes in which the organometallic reagent is generated in situ, as in the Sonogashira reaction, α-arylations of carbonyl compounds and related systems,[3] and decarboxylative cross-coupling reactions.[4] From a mechanistic point of view, the two families of reactions share the first step of the catalytic cycle—the oxidative addition of the electrophile to the Pd^0 catalyst—but differ in the rest of the process: transmetalation and reductive elimination for reactions with organometallic nucleophiles, and complexation of the alkene, insertion, and β-hydride elimination in Heck reactions (Figure 1).

In the last decade, a new class of palladium-catalyzed C–C bond-forming cross-coupling has come into play that features a different type of nucleophile and also a different mechanism. In these new reactions, the nucleophilic coupling partner is a diazo compound. The characteristic steps of the catalytic cycle are the formation of a palladium–carbene complex and migratory insertion of the carbene (Figure 2). The use of tosylhydrazones as a very convenient and general source of diazo compounds has led to the development of a new palladium-catalyzed cross-coupling reaction with remarkably wide scope.

The use of tosylhydrazone salts for the generation of metal–carbene complexes in catalytic processes was introduced by Aggarwal et al.[5] and successfully exploited in a number of processes, such as olefination, epoxidation, cyclopropanation, and C–H and N–H insertion reactions. However, this chemistry[6] falls outside the scope of this Minireview.

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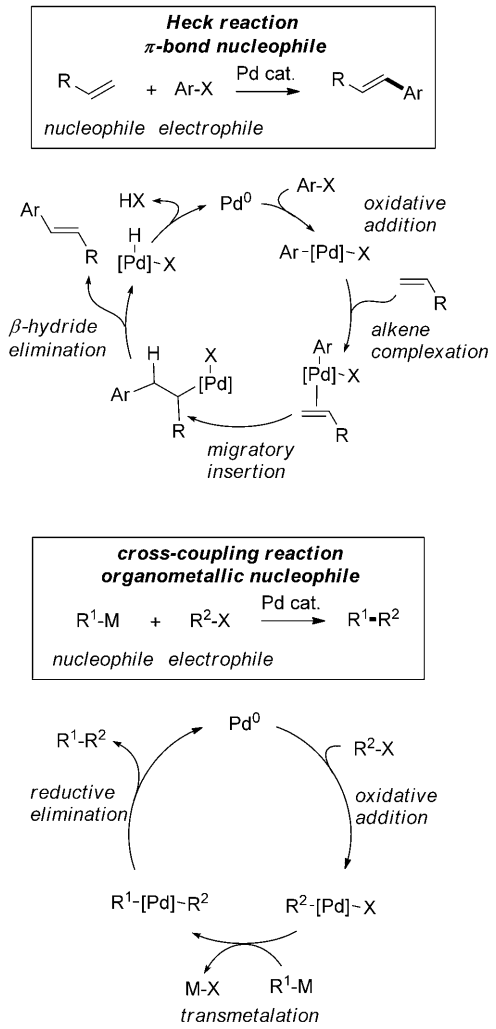

Figure 1. Palladium-catalyzed cross-coupling reactions and corresponding simplified mechanisms.

The renewed interest in tosylhydrazones has also led to the discovery of new metal-free C–C and C–O bond-forming reactions of remarkable synthetic potential. As tosylhydrazones are readily prepared from carbonyl compounds, these methodologies offer novel alternatives for the unconventional modification of carbonyl compounds. This Minireview

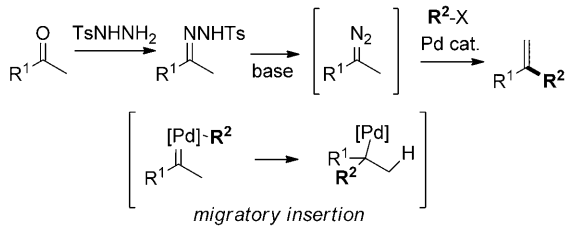

Figure 2. A new class of palladium-catalyzed cross-coupling reaction based on the use of diazo compounds or tosylhydrazones as the nucleophilic coupling partner and involving a transient palladium carbene. Ts = *p*-toluenesulfonyl.

will cover advances in this fast-evolving field in the areas of both palladium-catalyzed cross-coupling and metal-free reactions.

2. Palladium-Catalyzed Cross-Coupling Reactions of Diazo Compounds with Benzyl Halides

The first palladium-catalyzed cross-coupling involving a carbene-insertion reaction was reported in 2001 by Van Vranken and co-workers, who used trimethylsilyldiazomethane (**1**) as the carbene precursor and benzyl halides **2** as electrophiles.[7] The reaction led to styrenes **3**. A subsequent contribution by the same research group[8] expanded the reaction to ethyl diazoacetate (**4**) in a process that furnished substituted cinnamates **5** in moderate yields (Scheme 1).

The mechanism proposed for this reaction (Scheme 2) involves the following main steps: I) oxidative addition of the benzyl halide to the Pd^0 species, II) formation of the palladium–carbene complex, III) migratory insertion of the carbene, and IV) β-hydride elimination. The steps of this mechanism that differ from those of other cross-coupling reactions are the formation of the palladium–carbene complex and the migratory insertion. The generation of metal–carbene complexes from diazo compounds is well-documented.[9] Moreover, in the last decade, migratory insertion reactions have been proposed for N-heterocyclic,[10] amino-, and methoxycarbene–palladium complexes in noncatalytic processes.[11–13] However, Van Vranken and co-workers reported the first examples of the integration of these individual

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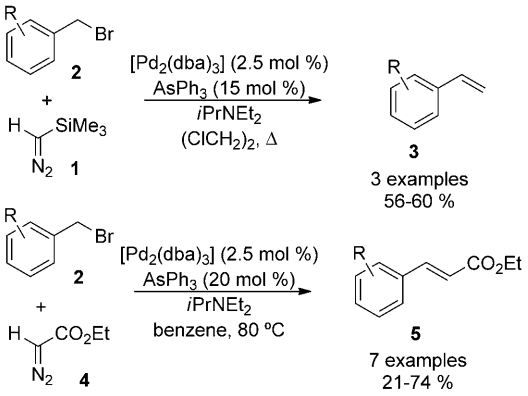
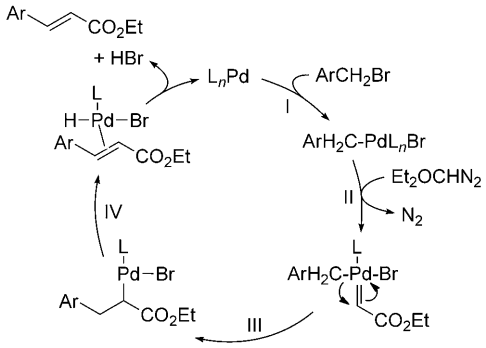
Carlos Valdés completed his PhD in chemistry in 1992 under the direction of Fernando Aznar and José Barluenga at the University of Oviedo. He then took up a Fulbright postdoctoral fellowship with Julius Rebek, Jr. at MIT, where he studied the self-assembly of "molecular tennis balls". In 1995, he returned to the University of Oviedo, where he became associate professor in 2000. His current interests include the development of transition-metal-catalyzed C–C and C–X bond-forming reactions, catalytic cascade and multicomponent processes, and environmentally friendly metal-free reactions.



Scheme 1. First examples of palladium-catalyzed cross-coupling reactions of diazo compounds.



Scheme 2. Mechanism proposed for the palladium-catalyzed cross-coupling of ethyl diazoacetate with benzyl bromides.

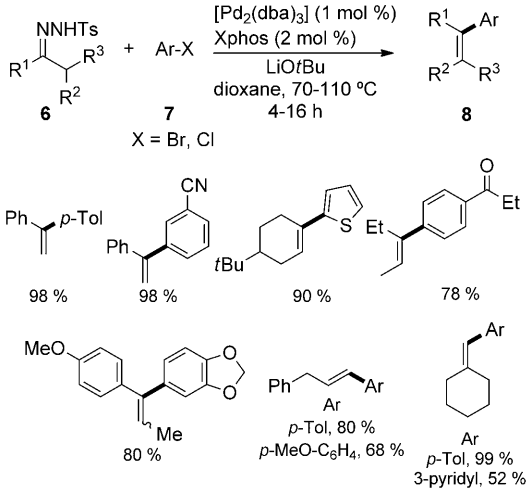
steps in a viable catalytic cycle. Nevertheless, in spite of the potential interest of this process, it was not investigated further in the following years, probably because of its limited scope.[14]

3. Palladium-Catalyzed Cross-Coupling Reactions with Tosylhydrazones

3.1. Cross-Coupling Reactions of Tosylhydrazones with Aryl Halides: Synthesis of Di- and Trisubstituted Alkenes

The starting point for the application of tosylhydrazones in new processes came in 2007, when our research group introduced these systems as coupling partners in palladium-catalyzed cross-coupling reactions.[15] Thus, the reaction between a tosylhydrazone **6** and an aryl halide **7** in the presence of LiO*t*Bu as a base and a catalytic system built from $[Pd_2(dba)_3]$ (dba = *trans*,*trans*-dibenzylideneacetone) and the ligand Xphos (2-dicyclohexylphosphanyl-2′,4′,6′-biphenyl) led to the formation of olefins **8**, usually in very high yields (Scheme 3).

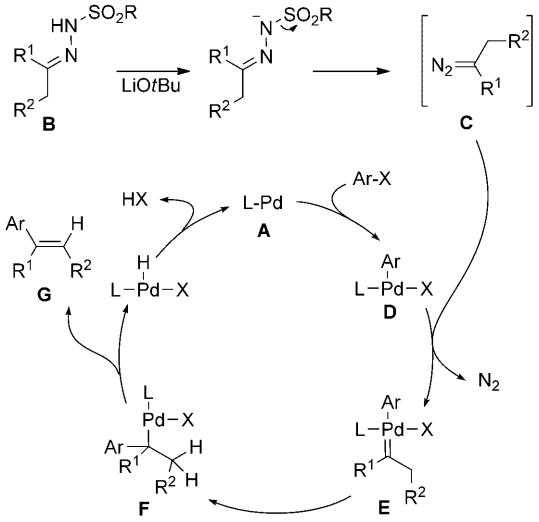
This initial report already highlights the synthetic potential of the reaction, which shows broad scope with respect to both coupling partners. The versatility in terms of the structure of the tosylhydrazone, which can be derived from



Scheme 3. Synthesis of di- and trisubstituted olefins **8** by the cross-coupling of tosylhydrazones with aryl halides. A bold bond is used to indicate the connection point between the coupling partners. This convention is used throughout the Minireview.

aryl or alkyl ketones, either acyclic or cyclic, as well as from aldehydes, is particularly interesting. Regarding the aryl halide, similar results were obtained with chlorides and bromides. The functional-group tolerance is also remarkable: the reaction can be conducted, for example, in the presence of nitrile groups and enolizable ketones. Although this reaction is very demanding in terms of the catalytic system and the reaction conditions (in particular, the use of Xphos as the ligand and LiO*t*Bu as the base was found to be crucial for the success of the reaction), we show herein that under the appropriate conditions, the coupling is very robust and highly general.

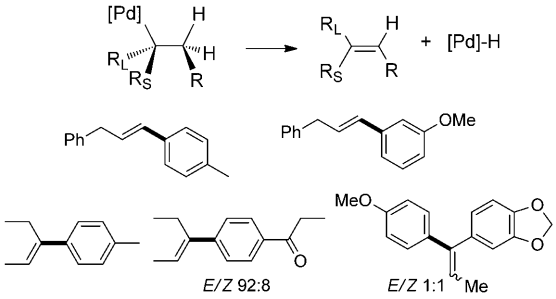
The catalytic cycle postulated for this coupling reaction (Scheme 4) is closely related to that described in Section 2 for diazo compounds (Scheme 2) and starts with the oxidative



Scheme 4. Proposed mechanism for the palladium-catalyzed cross-coupling of *N*-tosylhydrazones.

addition of the aryl halide to the Pd^0 catalyst **A** to give an aryl palladium complex **D**. Next, reaction of the diazo compound **C** (generated by the base-mediated decomposition of the tosylhydrazone **B**)[16] with **D** would produce the palladium–carbene complex **E**. The unstable aryl palladium–carbene complex **E** evolves through migratory insertion of the carbene ligand to the alkyl palladium complex **F**. Finally, β-hydride elimination would provide the arylated olefin **G** and regenerate the Pd^0 catalyst (Scheme 4).

The configuration of the final olefin is determined by the *syn* β-hydride-elimination step. Thus, in the transition state for the formation of 1,2-disubstituted and trisubstituted olefins, the bulkier R_L group would be eclipsed with the smaller substituent of the vicinal carbon atom (Scheme 5).

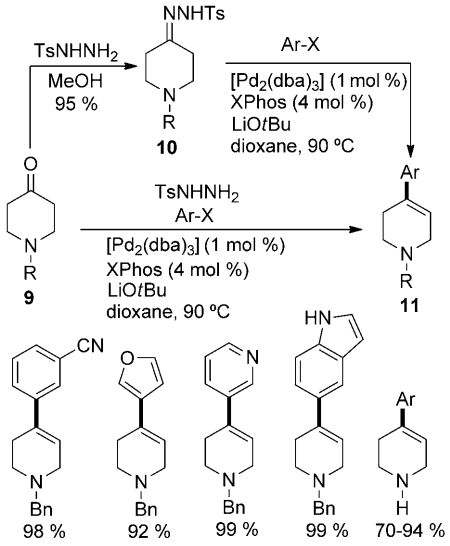


Scheme 5. A *syn* β-hydride elimination determines the configuration of the olefin products.

Indeed, hydrazones derived from nonbranched aldehydes provide *trans* olefins. Moreover, in trisubstituted olefin products, the bulkier groups on each carbon atom are also in a *trans* arrangement. Consequently, when the substituents R_S and R_L have similar sizes, a 1:1 mixture of isomers is obtained.

3.2. Direct Coupling Reactions of Carbonyl Compounds with Aryl Halides

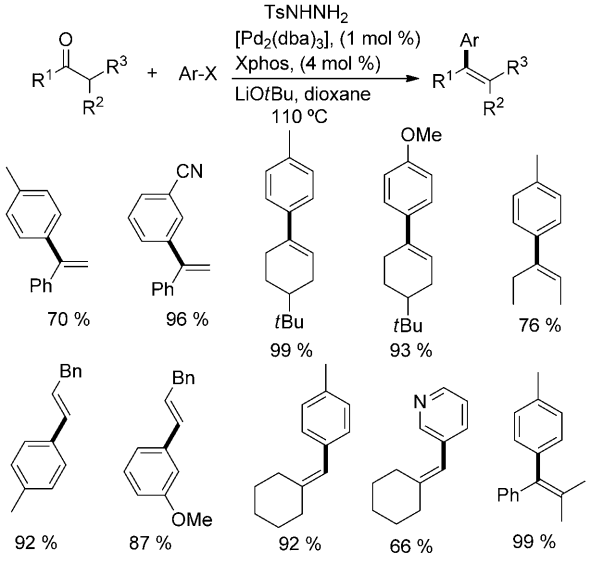
The first practical application of this methodology was the preparation from 4-piperidones of 4-aryl tetrahydropyridines. This privileged structure is present in a vast number of biologically active and therapeutically useful molecules, and is used in drug-discovery programs.[17] The required tosylhydrazones **10** were prepared by the condensation of tosylhydrazide with 4-piperidones **9**. Under appropriate reaction conditions, the coupling reaction with aryl halides then proceeded to give a set of 4-aryl tetrahydropyridines **11** in very high yields (Scheme 6). Taking into account that the tosylhydrazone substrate was readily generated from the corresponding carbonyl compound and tosylhydrazide, we went on to develop a one-step multicomponent process. Thus, treatment of the 4-piperidone **9** with tosylhydrazide, the aryl halide, and all the reagents required for the catalytic reaction led to the formation of 4-aryl tetrahydropyridines **11** in similar yields to those observed for the two-step process (Scheme 6).[18] The reaction shows remarkably wide scope



Scheme 6. Direct synthesis of 4-aryl tetrahydropyridines **11** from 4-piperidones. Bn = benzyl.

and excellent functional-group tolerance. In particular, the coupling can be carried out with 4-piperidone itself, with a free NH group. Thus, this direct transformation of 4-piperidones into 4-aryl tetrahydropyridines is a very convenient procedure for the synthesis of these scaffolds, with advantages over other methodologies.[19]

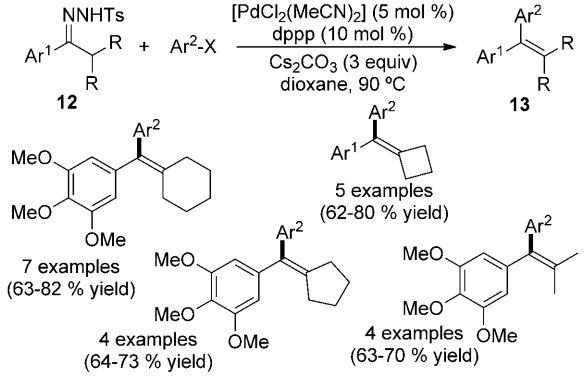
The multicomponent process can also be applied to other types of carbonyl compounds, also with excellent results. The examples in Scheme 7 show the wide scope of the reaction, which enables the use of aryl, alkyl, and cyclic ketones as well as linear and branched aldehydes to prepare di-, tri-, and even tetrasubstituted alkenes.[18,20] Thus, the reaction can be viewed as a general direct coupling of carbonyl compounds as nucleophilic coupling partners.



Scheme 7. Direct palladium-catalyzed cross-coupling of carbonyl compounds: selected examples.

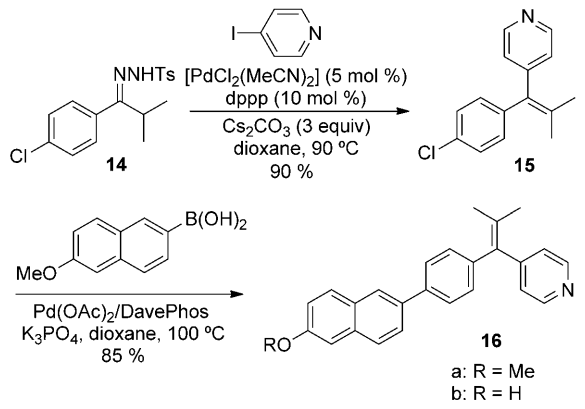
3.3. Synthesis of Tetrasubstituted Alkenes

In the search for a general method for the synthesis of tetrasubstituted alkenes, Alami and co-workers recently developed a different set of reaction conditions for the coupling of sterically hindered tosylhydrazones **12** with aryl iodides and bromides (Scheme 8). By employing a catalytic system built from $[PdCl_2(MeCN)_2]$ as the metal source and the bidentate ligand 1,3-bis(diphenylphosphanyl)propane (dppp) with the base Cs_2CO_3, they prepared an array of structurally diverse tetrasubstituted olefins **13**.[21]



Scheme 8. Synthesis of tetrasubstituted olefins by cross-coupling with sterically hindered tosylhydrazones.

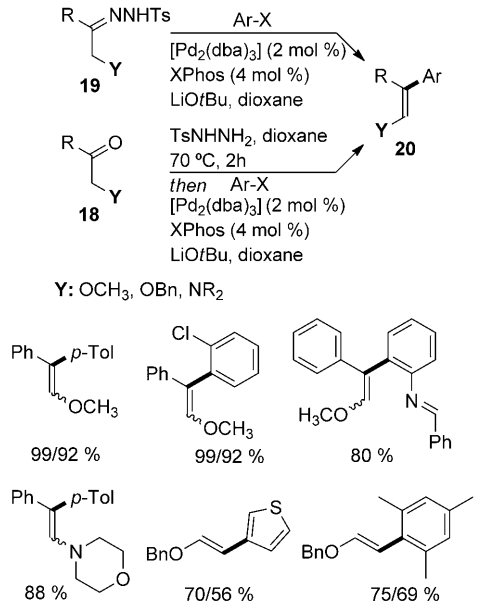
The synthetic potential of this methodology was illustrated by a very concise formal synthesis of the isopropylidene CYP17 inhibitor **16** through a two-step process consisting of the cross-coupling of hydrazone **14** with pyridyl iodide, followed by a Suzuki cross-coupling reaction (Scheme 9).



Scheme 9. Concise synthesis of a CYP17 inhibitor. DavePhos = 2-dicyclohexylphosphanyl-2′-(*N*,*N*-dimethylamino)biphenyl.

3.4. Synthesis of Functionalized Alkenes

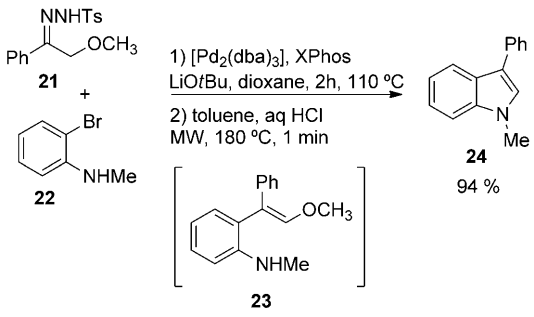
The cross-coupling reaction with tosylhydrazones can also be applied to the preparation of functionalized alkenes from the appropriate carbonyl compounds. For example, the use of α-alkoxy or α-amino carbonyl compounds **18** provided the corresponding enol ethers and enamines **20**, respectively. These reactions can either be conducted with the preformed tosylhydrazone **19** or in a one-pot process, in which the hydrazide is stirred with the carbonyl compound **18** for a period of time, and then the rest of the reagents and the catalyst are added to the reaction mixture (Scheme 10).[22]



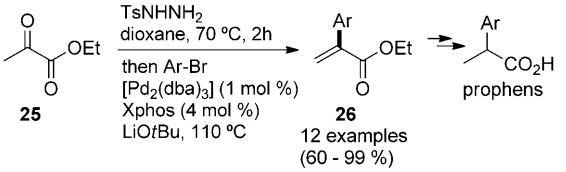
Scheme 10. Synthesis of enol ethers and enamines from α-alkoxy and α-amino carbonyl compounds: selected examples.

These reactions can be seen as the synthesis of protected carbonyl compounds that can be deprotected at the desired point in a synthetic sequence in acidic media or employed in further chemical transformations. As an example of the former approach, the palladium-catalyzed coupling of the hydrazone **21** of α-methoxyacetophenone with *o*-bromo-*N*-methylaniline (**22**) gave, after treatment with aqueous acid, the indole **24** derived from the intramolecular cyclization of the intermediate enol ether **23** (Scheme 11).

The one-pot reaction was also employed for the preparation of electrophilic olefins. Interestingly, ethyl pyruvate (**25**) could be converted into 2-aryl acrylates **26**: valuable synthetic intermediates and direct precursors of the prophen family of

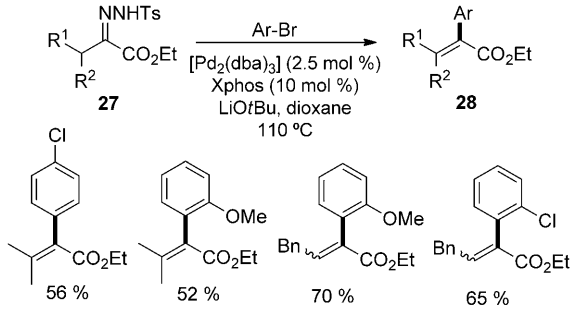


Scheme 11. Synthesis of indole **24** by a cross-coupling/heterocyclization sequence. MW = microwave irradiation.



Scheme 12. Synthesis of 2-aryl acrylates from ethyl pyruvate.

anti-inflammatory drugs (Scheme 12).[23] The ester functionality was not affected by the strongly basic alkoxide. Moreover, reactions of hydrazones **27** derived from substituted 2-oxoesters gave rise to the corresponding tri- and even tetrasubstituted functionalized alkenes **28** (Scheme 13).

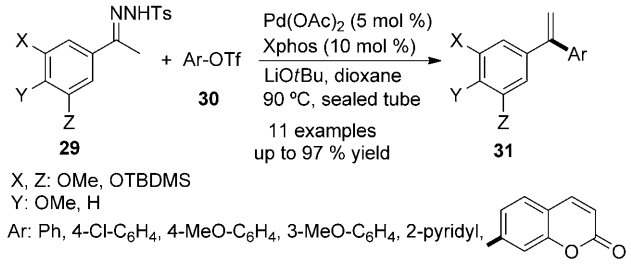


Scheme 13. Preparation of tri- and tetrasubstituted functionalized alkenes.

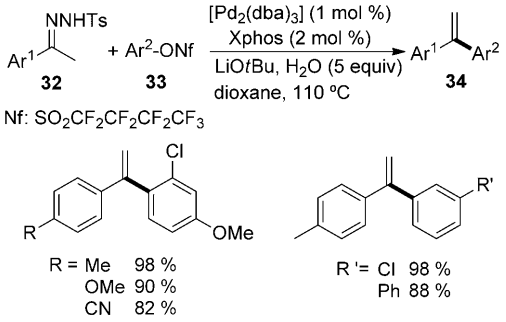
3.5. Coupling Reactions with Aryl Sulfonates

The incorporation of sulfonates instead of halides enhances the scope of cross-coupling processes, as these compounds are readily obtained from phenols, which are extremely abundant from commercial sources. In the context of the study of the synthesis of isocombretastatin analogues,[24] the Alami group optimized the cross-coupling reaction of hydrazones **29** derived from polysubstituted acetophenones with aryl triflates **30**. The catalytic conditions are very similar to the standard conditions employed in the reactions with halides, but higher catalyst loadings are required. Interestingly, a remarkable improvement in the yield was found when the reactions were carried out in a sealed tube. This methodology was used for the preparation of a variety of polyoxygenated 1,1-diaryl ethylenes **31** (Scheme 14).[25]

The use of aryl nonaflates, which are more stable than triflates but have similar reactivity,[26] enabled us to develop a very general version of the reaction. Again, subtle changes to the reaction conditions were needed for good conversion and yields to be attained. For example, coupling reactions of acetophenone derivatives **32** with aryl nonaflates **33** to give 1,1-diaryl ethylenes **34** were accelerated in the presence of water (5 equiv; Scheme 15). These reaction conditions were totally inefficient for coupling reactions with more challenging tosylhydrazones. However, the addition of LiCl (1 equiv) had a dramatic effect on the reaction. Under these modified



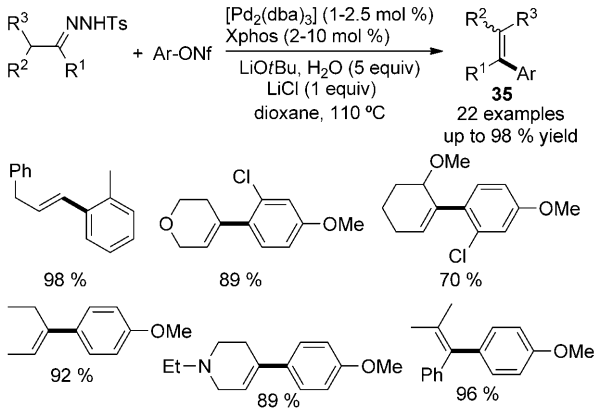
Scheme 14. Synthesis of polyoxygenated diaryl ethylenes from aryl triflates. TBDMS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.



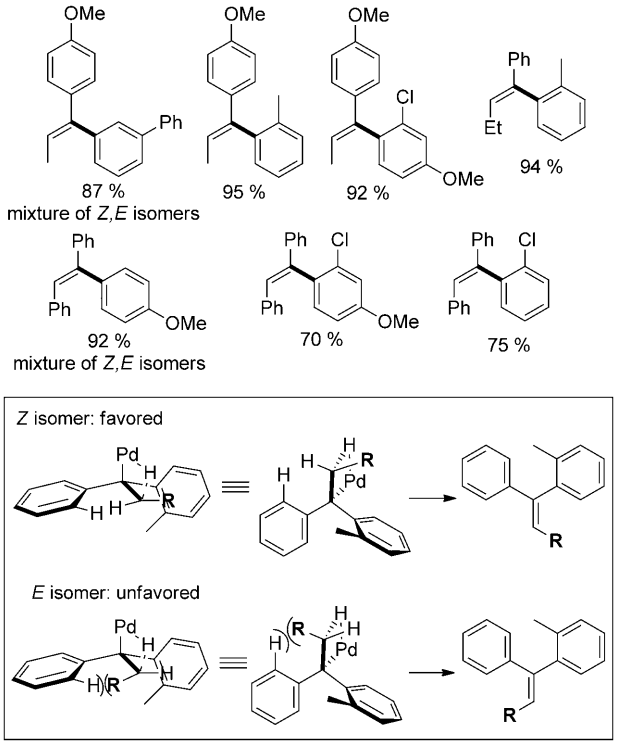
Scheme 15. Synthesis of diaryl ethylenes from aryl nonaflates.

conditions, di-, tri-, and even tetrasubstituted alkenes **35** were prepared in excellent yields (Scheme 16).[27]

The study of reactions with *ortho*-substituted nonaflates revealed quite interesting stereoselectivity in the synthesis of 1,1-diaryl trisubstituted olefins. The *ortho*-substituted aryl group is always in a *cis* relationship with the substituent on the other carbon atom of the newly formed double bond (Scheme 17). This intriguing *ortho* directing effect can be explained in terms of the orientation of the *ortho*-substituted arene in the transition state for the *syn* β-hydride elimination (Scheme 17). Molecular-modeling studies carried out with the aid of DFT computations support this mechanistic explanation.

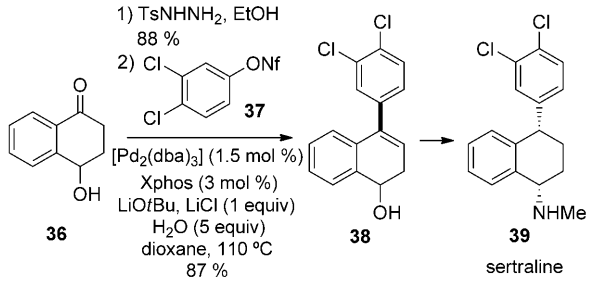


Scheme 16. General synthesis of aryl alkenes from aryl nonaflates: selected examples.



Scheme 17. Directing effect of an *ortho* substituent on the stereoselectivity of the β-hydride elimination.

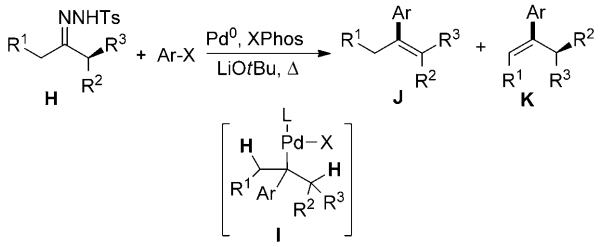
As a further illustration of the versatility of this coupling reaction, dihydronaphthalene **38**, the direct precursor of the antidepressant sertraline (**39**), was prepared from the commercially available hydroxytetralone **36** and the aryl nonaflate **37** (Scheme 18). The coupling took place in very high yield in the presence of the free OH group. Thus, this synthesis required fewer steps than existing alternatives.



Scheme 18. Expeditious formal synthesis of sertraline.

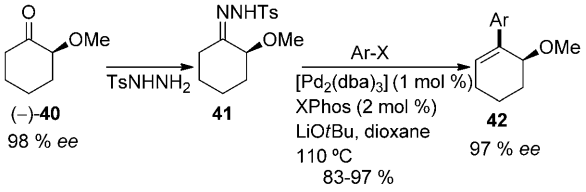
3.6. Modification of α-Chiral Carbonyl Compounds

One appealing application of the palladium-catalyzed cross-coupling of tosylhydrazones is the modification of α-chiral ketones with preservation of the configuration of the stereogenic α carbon center. If a hydrazone **H** derived from a ketone with two enolizable positions is used, a regioselective β-hydride-elimination from an alkyl palladium complex **I** would be required to give the less substituted alkene **K** (Scheme 19). The complete reaction sequence should proceed without epimerization of the stereogenic center.



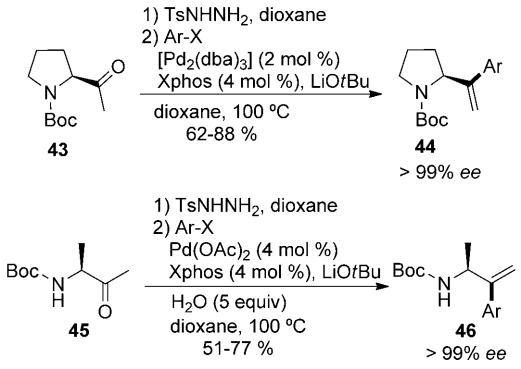
Scheme 19. Possible β-hydride-elimination pathways in the cross-coupling of hydrazones of ketones with two enolizable positions.

These conditions are met in the case of α-substituted cyclohexanones, as exemplified by the reaction of enantiomerically enriched 2-methoxycyclohexanone (**40**).[28] The synthetic sequence involving tosylhydrazone formation and cross-coupling gave rise to allylic ethers **42** without erosion of the α chirality (Scheme 20). Formation of the tetrasubstituted alkene was not observed.



Scheme 20. Synthesis of enantiomerically pure allylic ethers **42**.

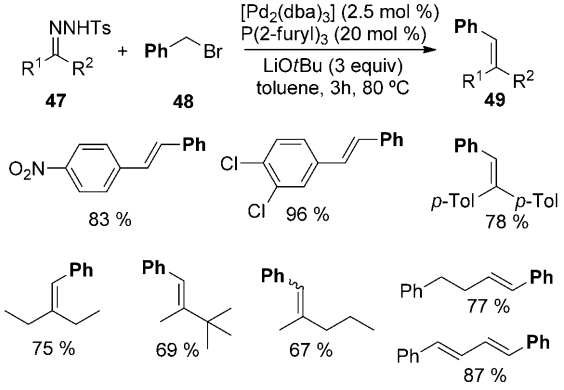
This strategy was also applied successfully to α-chiral methyl ketones **43** and **45** derived from the α-amino acids L-proline and L-alanine, respectively. Under the optimized reaction conditions, the chiral allylic amines **44** and **46** were obtained with preservation of the configuration, and again formation of the tetrasubstituted alkene was not detected (Scheme 21).



Scheme 21. Synthesis of enantiomerically pure allylic amines from methyl ketones derived from α-amino acids. Boc = *tert*-butoxycarbonyl.

3.7. Cross-Coupling Reactions of Tosylhydrazones with Benzyl Halides

In 2009, Wang and co-workers reported the palladium-catalyzed cross-coupling of benzyl halides **48** with tosylhydrazones **47** to give di- and trisubstituted olefins **49** (Scheme 22).[29] The main difference in the reaction conditions from those described above is the use of tris(2-furyl)phosphane as the ligand. Although these reactions are closely related to the seminal studies by Van Vranken and co-workers with diazo compounds (Scheme 1), the use of tosylhydrazones as the source of the diazo compound greatly expands the scope of the reaction. Indeed, hydrazones derived from aryl or alkyl aldehydes and ketones, and even an α,β-unsaturated aldehyde, could be employed as coupling partners in the reaction. The regioselectivity in the β-hydride elimination is excellent. In all cases, the alkene with the double bond conjugated with the aromatic ring was obtained exclusively.



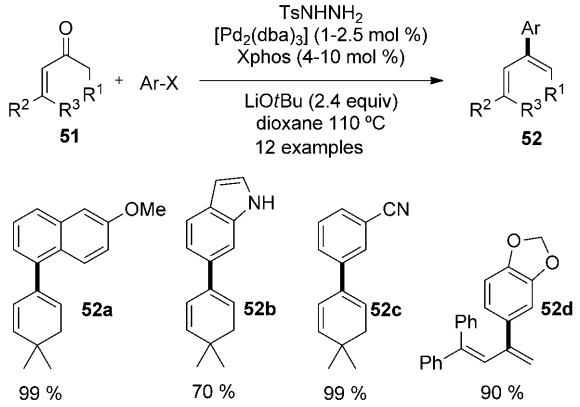
Scheme 22. Palladium-catalyzed cross-coupling reactions with benzyl halides: selected examples.

3.8. Synthesis of Conjugated Dienes by Cross-Coupling Reactions with α,β-Unsaturated Tosylhydrazones

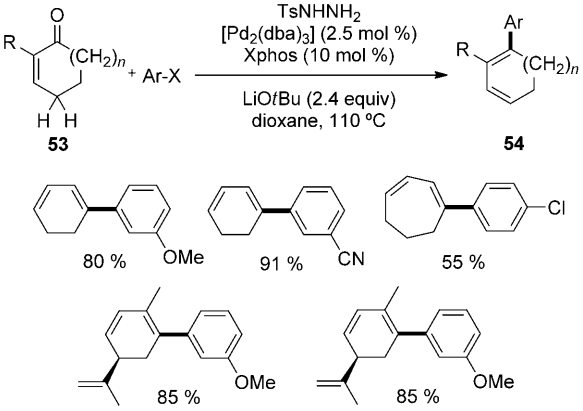
The cross-coupling of α,β-unsaturated tosylhydrazones must lead to conjugated dienes. In Scheme 22, the preparation of 1,4-diphenylbutadiene from the hydrazone of cinnamaldehyde and benzyl bromide is shown. We have studied the synthesis of conjugated dienes from aryl halides and tosylhydrazones derived from α,β-unsaturated ketones **51**. In fact, the reaction served as an excellent method for the preparation of homoannular cyclic dienes **52a–c** from cyclic enones (Scheme 23).[20]

Interestingly, the reaction of enones **53** with hydrogen atoms at the γ position gave the linear conjugated dienes **54** instead of the expected cross-conjugated dienes (Scheme 24).[20] The formation of the linear conjugated systems **54** was rationalized in terms of a formal δ-hydride elimination on the basis of the catalytic cycle depicted in Scheme 25. The initially formed σ-allyl palladium complex **M** can evolve through the π-allyl palladium complex **N** to a new σ-allyl palladium complex **O**, which can then undergo β-hydride elimination to give **54**.

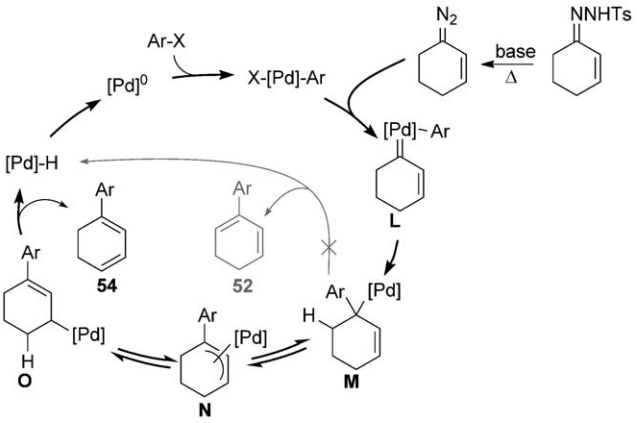
A formal δ-hydride elimination was also observed in reactions of alkenyl bromides **55** with tosylhydrazones **56** of non-enolizable carbonyl compounds. In these cases, the only



Scheme 23. Synthesis of homoannular cross-conjugated cyclic dienes.

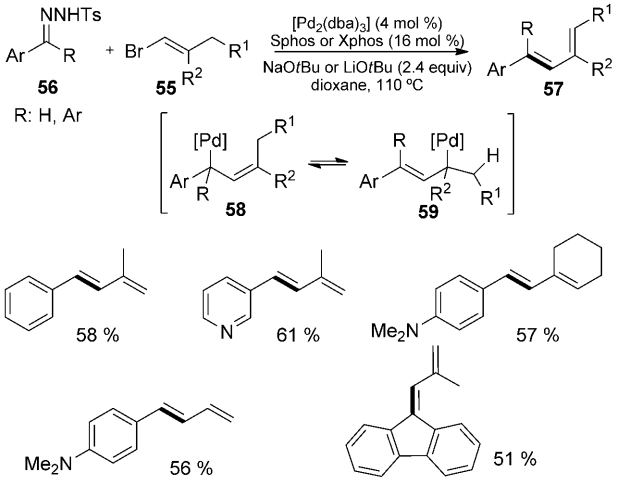


Scheme 24. Synthesis of linear conjugated dienes: selected examples.



Scheme 25. Mechanisms proposed for the formation of linear conjugated cyclohexadienes.

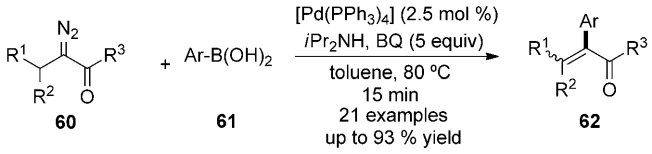
possible evolution of the allyl palladium complex **58** is a [1,3] palladatropic rearrangement to give the palladium complex **59**, followed by β-hydride elimination. Thus, conjugated dienes **57** were obtained, although only in moderate yields (Scheme 26).[20] Nevertheless, these transformations are the first examples of the use of alkenyl halides in cross-coupling reactions with tosylhydrazones.



Scheme 26. Synthesis of conjugated dienes from alkenyl halides: selected examples. The newly formed C–C bond is highlighted with a bold line. SPhos = 2-dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl.

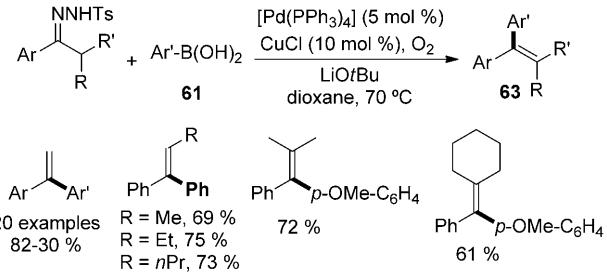
3.9. Oxidative Cross-Coupling Reactions of Tosylhydrazones with Boronic Acids

The oxidative cross-coupling of aryl boronic acids **61** with α-diazocarbonyl compounds **60**, reported by Wang and co-workers in 2008, gives rise to α-aryl α,β-unsaturated carbonyl compounds **62** (Scheme 27).[14a,30] The reaction requires the presence benzoquinone as an oxidant to regenerate the Pd^{II} catalyst.



Scheme 27. Oxidative cross-coupling of diazo compounds with aryl boronic acids. BQ = benzoquinone.

A similar transformation was later developed by the same research group, who then employed tosylhydrazones as a convenient source of the diazo substrate. As in the coupling reactions described above with aryl halides, the reaction can be applied to the preparation of di-, tri-, and tetrasubstituted alkenes **63** (Scheme 28). Under the optimized reaction conditions, LiO*t*Bu is used as the base, $[Pd(PPh_3)_4]$ as the Pd source, and a combination of CuCl (10 mol %) and O_2 as the oxidant for palladium.[31]

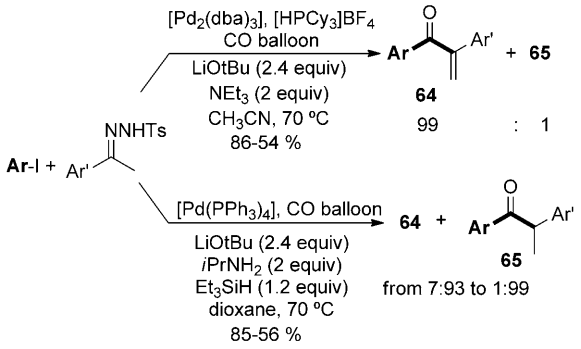


Scheme 28. Oxidative cross-coupling of tosylhydrazones with aryl boronic acids: selected examples.

4. Palladium-Catalyzed Cascade Reactions

4.1. Carbonylation/Migratory Insertion

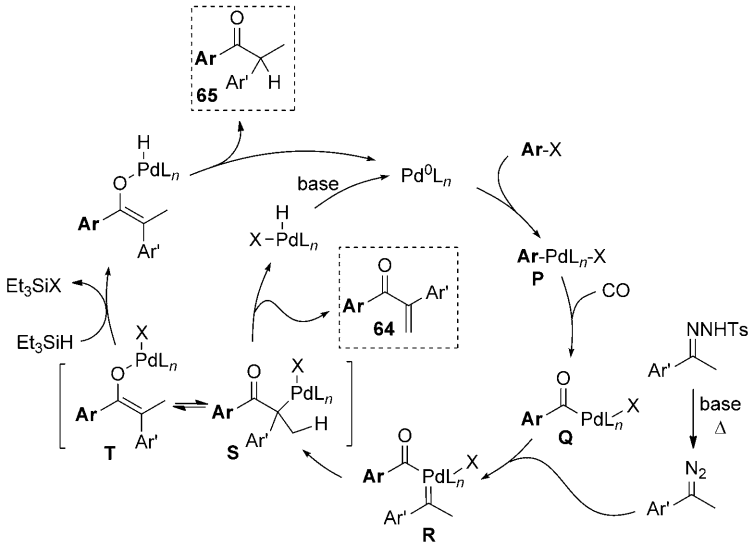
Wang and co-workers recently reported the palladium-catalyzed reaction of diazo compounds and also of tosylhydrazones with aryl halides in the presence of CO (Scheme 29).[32] The reactions with tosylhydrazones can produce two different compounds, depending on the specific conditions: the acylated alkene **64**, or if the reaction is conducted in the presence of triethylsilane as a hydride source, the ketone **65** derived from reductive acylation of the tosylhydrazone.



Scheme 29. Synthesis of aryl ketones by palladium-catalyzed reactions of aryl halides with tosylhydrazones in the presence of CO. Cy = cyclohexyl.

A mechanistic proposal that accounts for the formation of both types of ketones is presented in Scheme 30. The Pd^0 complex undergoes oxidative addition to give an aryl palladium complex **P**. A typical carbonylation then delivers an acyl palladium complex **Q**. Next, the formation of a palladium–carbene complex **R**, followed by migratory insertion, leads to the key intermediate **S**. Complex **S** can undergo β-hydride elimination to give the α,β-unsaturated ketone **64**. However, in the presence of the hydride source, the acyl palladium complex can be reduced via a palladium enolate **T** to give the saturated ketone **65**.

This elegant process shows quite limited scope at present; however, a generalization of this reaction might provide a very versatile method for the preparation of aryl ketones.

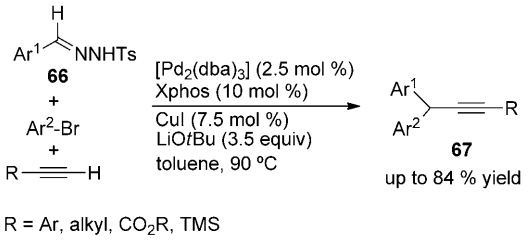


Scheme 30. Mechanistic proposal for the formation of ketones **64** and **65** through a carbonylation/migratory-insertion sequence.

4.2. Cascades Based on the Intermediate Alkyl Palladium Complex

One of the key steps of the palladium-catalyzed cross-coupling reactions discussed so far is the migratory insertion that gives rise to the alkyl palladium complex **F** (Scheme 4). This complex typically undergoes β-hydride elimination. However, when this pathway is disfavored, it should be possible to develop cascade processes, like those of domino Heck reactions.[33] Van Vranken and co-workers have exploited this concept by using diazo compounds in a series of very elegant multicomponent reactions[34] and also in intramolecular cyclizations.[35] However, a similar approach based on the use of tosylhydrazones as starting materials has not been explored in detail.

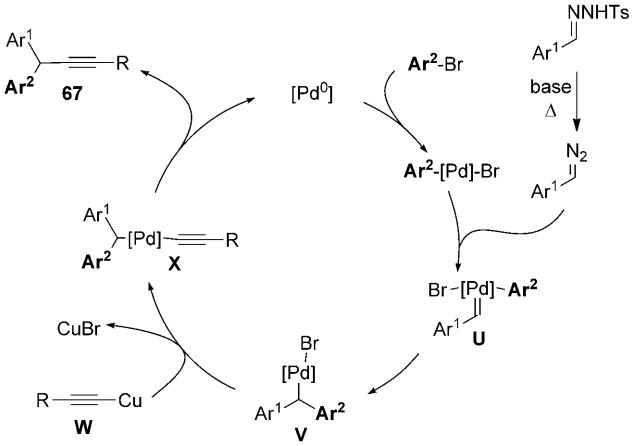
The only example of a cascade reaction of this type with tosylhydrazones was recently reported by Wang and co-workers,[36] who developed a three-component reaction that combines the tosylhydrazone cross-coupling with a Sonogashira alkynylation (Scheme 31). Thus, the reaction of the tosylhydrazone **66** of an aromatic aldehyde with an aryl halide and a terminal alkyne under the typical conditions for cross-coupling reactions with tosylhydrazones ([$Pd_2(dba)_3$], Xphos/LiO*t*Bu), but in the presence of CuI (7.5 mol%), gave rise to the product **67** of a three-component coupling.



Scheme 31. Three-component reaction of tosylhydrazones with aryl halides and terminal alkynes.

According to the mechanism proposed for this reaction (Scheme 32), after the migratory insertion, the alkyl palladium complex **V** cannot evolve through a β-hydride elimination; instead, in the presence of the copper acetylide **W**, a transmetalation to give **X** occurs, followed by reductive elimination to provide the benzhydryl acetylenic product **67**.

This process involves the creation of two C–C bonds at the same carbon atom in a single reaction and therefore invites the development of new reactions based on this principle.

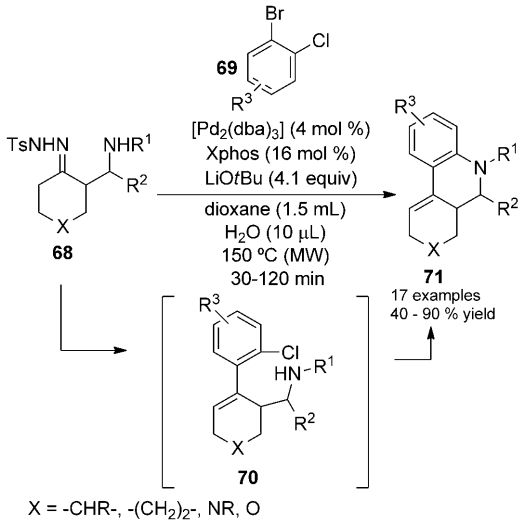


Scheme 32. Mechanism proposed for the three-component reaction. TMS = trimethylsilyl.

4.3. Autotandem Catalytic Processes

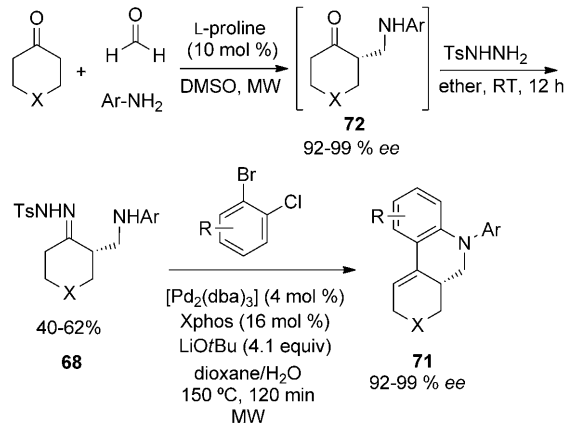
The term "autotandem" catalysis refers to metal-catalyzed cascade reactions in which a single catalytic system promotes two or more independent reactions.[37] There are currently many examples of palladium-catalyzed processes based on this principle.[38] In this context, our research group has recently developed palladium-catalyzed autotandem

processes involving the tosylhydrazone cross-coupling reaction.[39] Thus, under appropriate reaction conditions, the cross-coupling of tosylhydrazones **68** derived from β-aminoketones with *o*-bromochlorobenzene derivatives **69** afforded condensed quinoline derivatives **71** in a process that involves C–C bond formation to produce intermediate **70**, followed by intramolecular arylation of the amine. The two individual steps are promoted by the same Pd catalyst (Scheme 33).



Scheme 33. Palladium-catalyzed autotandem C–C/C–N coupling.

The starting β-aminoketones **72** can be synthesized in enantiomerically enriched form through an L-proline-organocatalyzed Mannich reaction.[40] Although the Mannich adducts are configurationally very unstable, it has been possible to devise a sequential protocol that enables the preparation of quinoline derivatives **71** with the high *ee* values of the β-aminoketones derived from the organocatalyzed reaction (Scheme 34). In this way, organocatalysis has been combined with Pd catalysis for the synthesis of useful heterocyclic structures in enantiomerically enriched form. Moreover,



Scheme 34. Synthesis of enantiomerically enriched quinoline derivatives **71** by a combination of organocatalysis and a palladium-catalyzed autotandem C–C/C–N coupling reaction. DMSO = dimethyl sulfoxide.

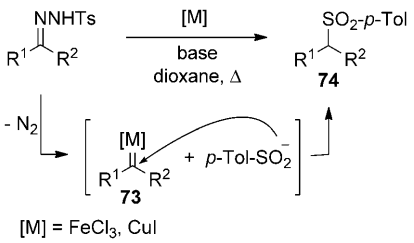
these results invite the development of further palladium-catalyzed cascades triggered by the tosylhydrazone cross-coupling reaction.

5. Metal-Free Reactions with Tosylhydrazones

The studies described above together demonstrate that in the presence of a Pd catalyst, tosylhydrazones can be used as a general source of diazo compounds from carbonyl compounds without any limitation in the structure of the carbonyl precursor. We have also discovered that the same strategy can be applied in the absence of a metal catalyst. Thus, some unprecedented transformations of carbonyl compounds have been developed.

5.1. Reductive Cross-Coupling Reactions of Tosylhydrazones with Boronic Acids

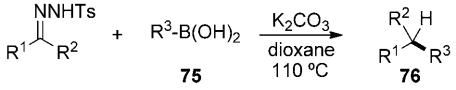
While studying cross-coupling reactions of tosylhydrazones with aryl halides in the presence of different metal catalysts, we[41] and others[42,43] observed the formation of a sulfone **74**. The formation of this product can be explained by the nucleophilic attack of the sulfinate anion on the metal–carbene complex **73** (Scheme 35).



Scheme 35. Metal-promoted decomposition of tosylhydrazones to sulfones **74**.

These observations prompted us to study a similar type of process, but in the presence of external nucleophiles. The use of boronic acids led to the discovery of a novel reductive coupling of carbonyl compounds. Moreover, the presence of a metal catalyst was not necessary. Thus, when the tosylhydrazone, a boronic acid **75**, and the base K_2CO_3 were mixed, the reductive coupling occurred to give products **76** in high yield (Scheme 36).[44]

The scope of the reaction is truly remarkable (Figure 3). It can be carried out with hydrazones derived from either aldehydes or ketones and with aryl or alkyl boronic acids. The reaction is particularly efficient for the preparation of diaryl



Scheme 36. Reductive coupling of tosylhydrazones with boronic acids.

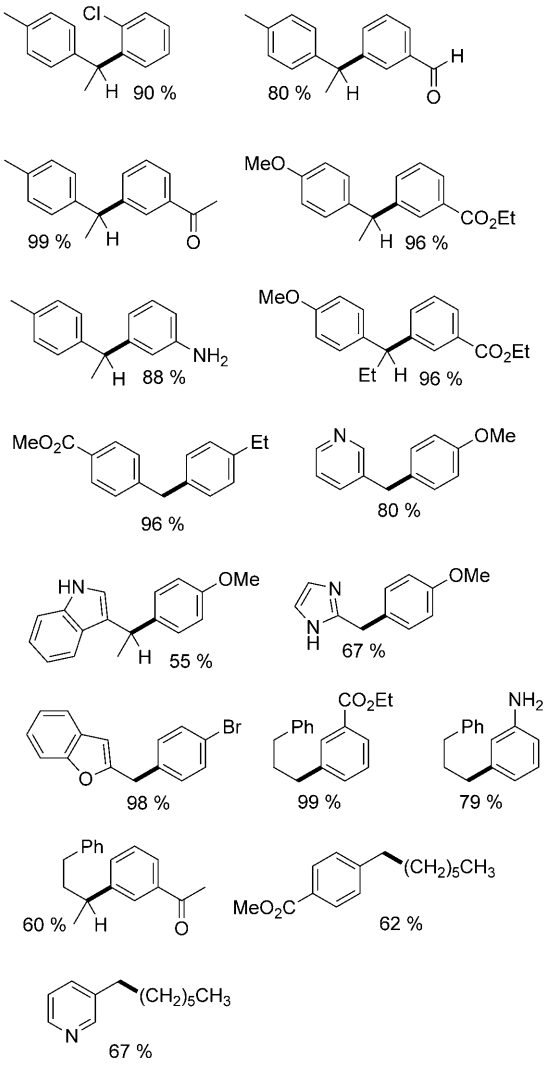
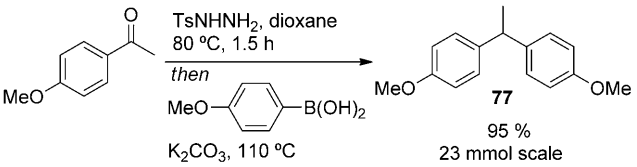


Figure 3. Reductive coupling of tosylhydrazones with boronic acids: selected examples of products.

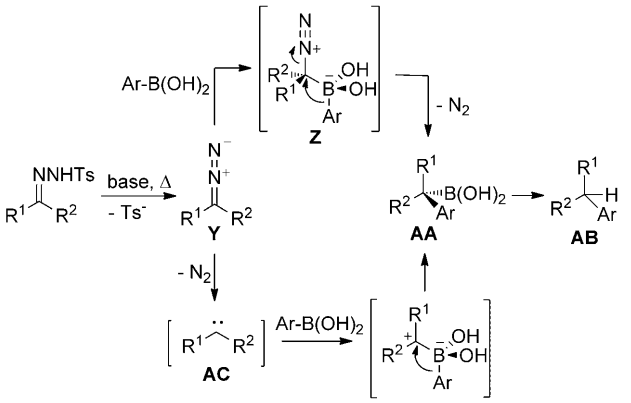
methanes. Moreover, it tolerates the presence of most functional groups, including those that are incompatible with other organometallic compounds. For example, substrates containing an ester or other carbonyl group, or a free azole or amine NH group can be used. Reactions with alkenyl boronic acids also proceeded efficiently, but gave rise to a mixture of isomers with respect to the position of the double bond and are therefore less useful from a synthetic point of view at this point of development.

Like the preceding palladium-catalyzed processes, the reaction can be conducted in a one-pot fashion directly from the carbonyl compound and on a relatively large scale, as exemplified by the synthesis of 1,1-bis(4-methoxyphenyl)-ethane (**77**; Scheme 37). This one-step reductive coupling of a carbonyl compound is an unprecedented transformation. The experimental procedure is extremely simple: the two reagents are simply mixed with tosylhydrazide and K_2CO_3, without the need for dry solvents or an inert atmosphere.

The mechanism proposed for this reaction (Scheme 38) is similar to those accepted for the classic Hooz[45] and Brown[46]



Scheme 37. Direct reductive coupling of a carbonyl compound with a boronic acid.

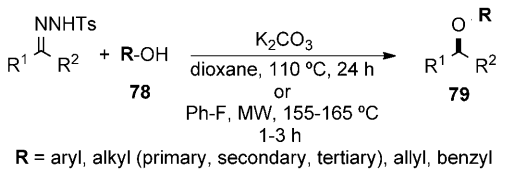


Scheme 38. Mechanism proposed for the reductive coupling.

reactions of stabilized diazo compounds with alkyl boranes and the reaction with boroxines described recently by Wang and co-workers.[47] The diazo compound **Y** generated from the tosylhydrazone reacts with the boronic acid to produce a boronate intermediate **Z**. Migration of the Ar group, with concomitant loss of N_2, gives a new alkyl boronic acid **AA**, which undergoes protodeboronation to give the final product **AB**. A similar mechanism involving the formation of a carbene **AC** from the diazo compound could also operate.

5.2. Reductive Etherification of Tosylhydrazones with Phenols and Alcohols

The catalytic insertion of metal–carbene complexes into X–H bonds (C–H, N–H, O–H) are very well known reactions with enormous synthetic potential. Their insertion into O–H bonds was studied on the basis of metal-free reductive coupling reactions with boronic acids. These investigations led to a very simple protocol for the conversion of tosylhydrazones into ethers **79** by treatment with the corresponding alcohols or phenols **78** (Scheme 39).[48,49] The overall reaction is a reductive etherification of a carbonyl compound.



Scheme 39. Reductive etherification of tosylhydrazones.

Again, the reactions take place simply upon the heating of a solution of both reactants in the presence of K_2CO_3. They can be conducted under conventional thermal conditions or by heating through microwave irradiation. The transformation is very general with regard to both reaction partners (Figure 4). Tosylhydrazones derived from a variety of aldehydes and ketones undergo the reaction. Regarding the alcohol substrate, optimum results were obtained with phenols, but all types of alcohols can be used. In particular, the reaction with phenols could be viewed, in many cases, as an environmentally friendly alternative to the Mitsunobu reaction for the synthesis of aryl ethers—a structural moiety present in a large number of biologically relevant molecules.

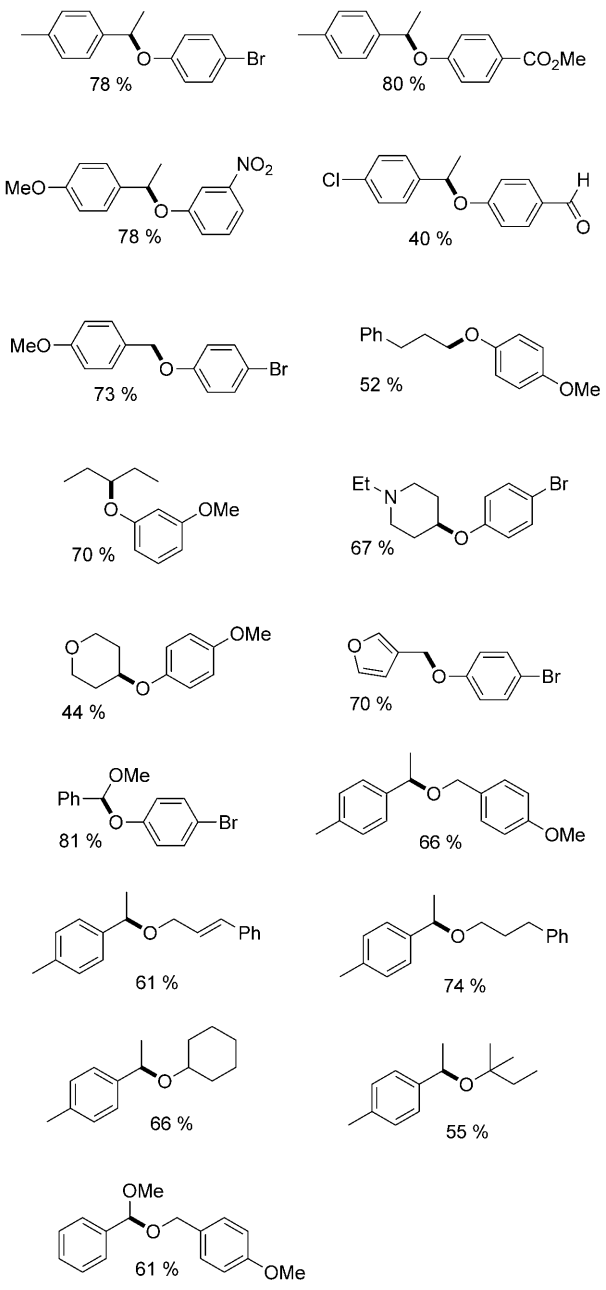


Figure 4. Scope of the reductive etherification of tosylhydrazones: selected examples of products.

6. Conclusions and Outlook

The use of sulfonylhydrazones in organic chemistry spans almost 60 years, since the seminal contribution of Bamford and Stevens,[16] and it has been well established that these reagents can be employed as a source of diazo compounds from carbonyl compounds. Nevertheless, the recent advances presented herein indicate that their synthetic potential had remained underexploited. Under appropriate reaction conditions, a variety of new transformations of diazo compounds can be conducted with tosylhydrazones, with nearly no structural limitations with regard to the hydrazone. The palladium-catalyzed reaction of tosylhydrazones with organic halides or pseudohalides is a valuable addition to the repertoire of palladium-catalyzed cross-coupling reactions. Conceptually, it is a new class of cross-coupling reaction with a distinct mechanism that does not involve the participation of a stoichiometric organometallic species. From a synthetic point of view, it is an original and very efficient method for the modification of carbonyl compounds. Some variations of the basic reaction have already appeared, such as oxidative cross-coupling reactions and various types of cascade reactions. Nevertheless, we consider that this field is still in its infancy, and there is ample room for further development, such as the incorporation of different types of electrophiles, the development of more-sophisticated cascades, the incorporation of this reaction in C–H-functionalization sequences, and the application of these methodologies in the synthesis of natural products. The metal-free C–C and C–O bond-forming reactions are unprecedented transformations that enable quite complex modifications of carbonyl compounds in an extraordinarily simple manner. These new methodologies based on tosylhydrazones will undoubtedly find application in many synthetic processes, and we believe that they will also stimulate the discovery of other novel transformations with sulfonylhydrazones.

7. Addendum (22 June 2011)

Since the submission of the revised version of this Minireview, remarkable advances have appeared in the literature that indicate the synthetic potential of this fast-evolving field. The Pd-catalyzed arylation has been applied in the synthesis of 4-arylchromenes and related heterocycles.[50] The research group of Wang has developed a copper(I)-catalyzed coupling reaction between *N*-tosylhydrazones and terminal alkynes,[51] and applied this method to the synthesis of benzofurans and indoles.[52] Tosylhydrazones have been employed for the Cu-catalyzed direct C–H benzylation and allylation of 1,3-azoles.[53] The research group of Wang has also reported a very attractive approach to ketenes by Pd-catalyzed carbonylation of diazocompounds or *N*-tosylhydrazones.[54] The method described for the reductive etherification has been applied for the preparation of thioethers.[55]

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