Cross-Coupling

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Arylation of α-Chiral Ketones by Palladium-Catalyzed Cross-Coupling Reactions of Tosylhydrazones with Aryl Halides**

José Barluenga, María Escribano, Fernando Aznar, and Carlos Valdés**

The carbonyl group is probably the most versatile functional group in organic synthesis, owing to its rich and highly developed chemistry. In particular, carbonyl compounds are extraordinary sources of enantiomerically pure compounds, that can be obtained from the chiral pool from terpenes, carbohydrates, and amino acids, and also through asymmetric catalysis[1] and organocatalysis.[2] However, carbonyl compounds bearing chirality at the α carbon can be difficult to manipulate owing to their configurational instability through enolization. Moreover, the typical formation of alkenes by nucleophilic-addition/elimination sequences usually affords the more-substituted olefin,[3] with loss of the chiral information (Figure 1a), and the reactions that proceed through the formation of enolates, such as cross-coupling reactions through enol sulfonates, require tightly controlled kinetic conditions to avoid the equilibration of the chiral center (Figure 1c).[4,5] For these reasons, the development of methodologies that allow the manipulation of the carbonyl functionality with preservation of the α chirality are highly desirable.

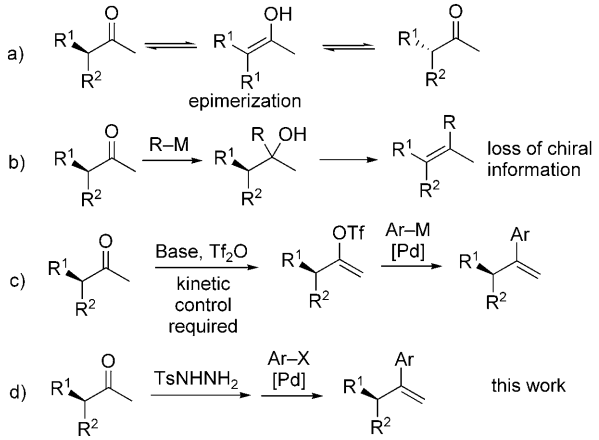

Figure 1. Problems associated with the manipulation of α-chiral ketones versus this work. Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl.

The palladium-catalyzed cross-coupling between tosylhydrazones and aryl halides, recently developed by our group,[6] constitutes an efficient method to manipulate the carbonyl functionality. The overall transformation is equivalent to a nucleophilic addition/elimination sequence. However, as we will show herein, in many cases the reaction gives the less-substituted alkene, and importantly, with no erosion of the chirality of the stereogenic center at the α position (Figure 1d); thus, we report the implementation of this new methodology for the manipulation of α-chiral ketones.

The catalytic cycle proposed for the palladium-catalyzed cross-coupling between tosylhydrazones and aryl halides is presented in Figure 2. The characteristic steps are formation of the palladium–carbene complex **VII**, migratory insertion of the aryl to give the alkylpalladium complex **VIII**,[7,8] and *syn*-β-hydride elimination, that releases the coupling product. For tosylhydrazones derived from ketones with two enolizable positions, such as **I**, two regioisomers **II** and **III** can be obtained that differ in the position of the double bond.[6a,c,8]

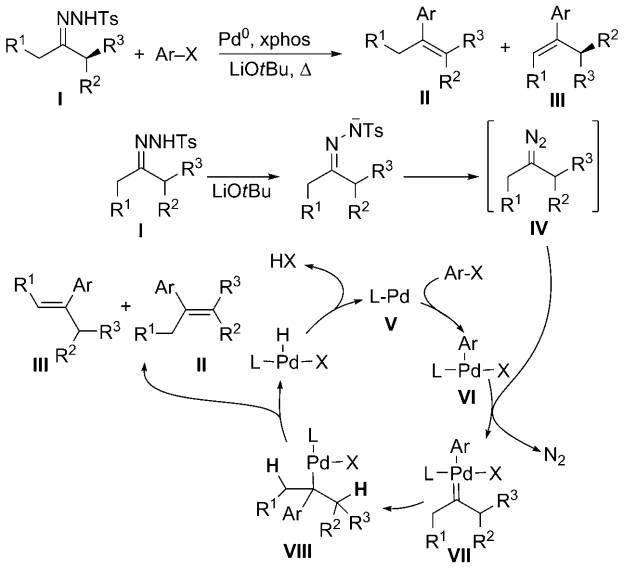

Figure 2. Cross-coupling reactions of tosylhydrazones derived from ketones with two enolizable positions and aryl halides: the regioselectivity in the formation of the double bond is determined by the *syn*-β-hydride-elimination step on alkylpalladium complex **VIII**. xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

[*] Prof. J. Barluenga, M. Escribano, Prof. F. Aznar, Dr. C. Valdés
Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo
c/Julián Clavería 8, 33006 Oviedo (Spain)
Fax: (+34) 985-103-446
E-mail: barluenga@uniovi.es
acvg@uniovi.es

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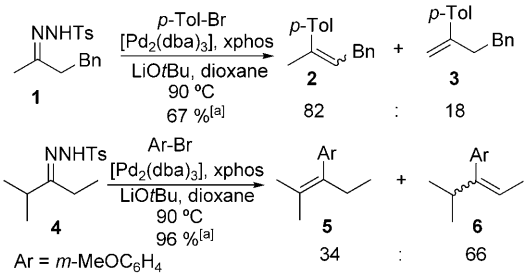
Thus, to achieve a coupling reaction with preservation of the α chirality, a regioselective β-hydride-elimination step on alkylpalladium complex **VIII** is needed, leading to the less-substituted alkene **III**.[9]

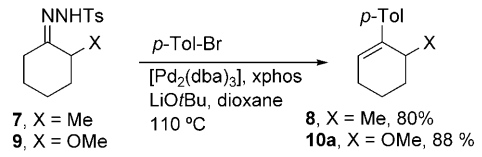
In our previous work, we observed that the selectivity in the β-hydride-elimination step depends on the type of substrate. For instance, moderate selectivity had been observed towards the more-substituted olefin **2** in methyl *n*-alkyl hydrazone **1**[6a] (Scheme 1). In contrast, in the reaction



Scheme 1. Preliminary studies on the regioselectivity of the reactions of tosylhydrazones with aryl halides. [a] Yield of the isolated mixture of isomers. Bn = benzyl, dba = *trans,trans*-dibenzylideneacetone, Tol = tolyl.

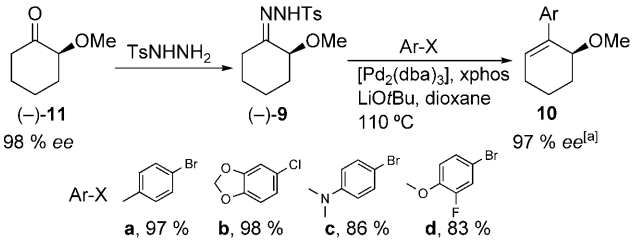
of tosylhydrazone **4**, formation of the trisubstituted olefin **6** is now favored against formation of the tetrasubstituted alkene **5**[6a] (Scheme 1).

With these preliminary results in hand, we next turned our attention to the reaction of the hydrazone **7** derived from 2-methylcyclohexanone. Interestingly, in this case, we observed total regioselectivity, thus exclusively obtaining the trisubstituted olefin **8** with high yield. A similar result was obtained when hydrazone **9**, derived from 2-methoxycyclohexanone was employed, yielding the corresponding allylic ether **10** (Scheme 2).



Scheme 2. Regioselectivity of the reactions of cyclic tosylhydrazones with aryl halides.

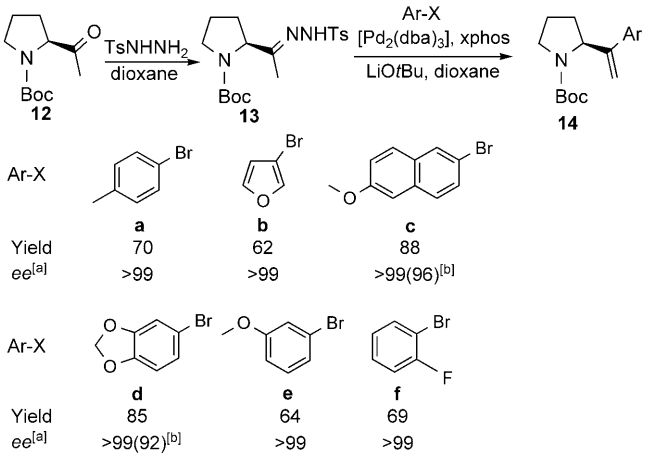
These results suggested that this methodology could be suitable for modifying cyclohexanones containing a chiral center at the α position without erosion of the chirality. Thus, we carried out coupling reactions on enantiomerically enriched hydrazone (−)-**9**, obtained from (−)-2-methoxycyclohexanone **11** (98 % *ee*).[10] To our delight, the resulting allyl ethers **10** were all obtained with very high yield and 97 % *ee*; therefore, no erosion of the chirality had occurred (Scheme 3). This important result represents a new methodology for the manipulation of chiral 2-substituted cyclohexanones,[11] and offers numerous synthetic opportunities.



Scheme 3. Synthesis of enantiomerically pure allyl ethers **10**. Reaction conditions: (−)-**9** (0.55 mmol), Ar–X, (0.5 mmol), [$Pd_2(dba)_3$] (1 mol %), xphos (2 mol %), LiO*t*Bu (1.4 mmol), dioxane (2 mL), 110 °C, 4 h. [a] Determined by HPLC on a chiral stationary phase.

Encouraged by these results, we decided to examine other types of α-chiral ketones. As the regioselectivity of the β-hydride elimination is necessary to preserve the chiral center, we decided to concentrate on methyl ketones. We thought that the *syn*-β-hydride elimination of one of the hydrogen atoms of the methyl group should be favored, thus leading to the formation of the terminal disubstituted double bond.

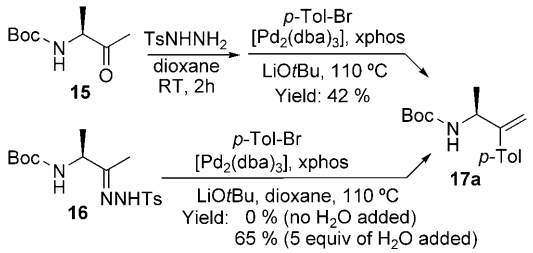
Methyl ketone **12**, which was easily obtained in enantiomerically pure form from L-proline,[12] was selected as model to check this hypothesis. To avoid unnecessary steps, the reactions were carried out directly from the ketone—without isolation of the intermediate hydrazone—in a one-pot process. As expected, in every case the disubstituted terminal olefin **14** was the only coupling product observed. No tetrasubstituted alkene was detected in the reaction mixture. In most of the cases, the protected allylamines **14** were obtained in 99 % *ee*, as determined by HPLC. Again the integrity of stereogenic center was preserved (Scheme 4). However, in some examples, in the one-pot reaction, a slight decrease in the enantiomeric excess was observed (**14c** and



Scheme 4. Synthesis of enantiomerically pure disubstituted alkenes **14** from coupling reactions with proline derivatives **13.** Reaction conditions: **13** (0.55 mmol), Ar–X, (0.5 mmol), [$Pd_2(dba)_3$] (2 mol %), xphos (4 mol %), LiO*t*Bu (1.4 mmol), dioxane (2 mL), 110 °C, 12 h. [a] Determined by HPLC on a chiral stationary phase. [b] The *ee* value for the one-pot process is indicated in brackets only for the cases in which erosion of chirality was observed. Boc = *tert*-butoxycarbonyl.

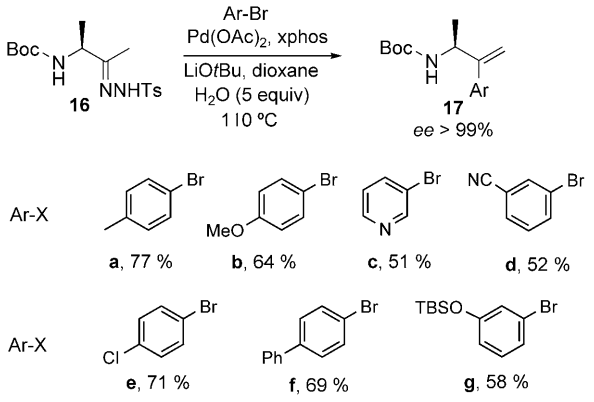
14d). Nevertheless, these allyl amines could be prepared in 99% *ee* from the previously isolated hydrazone **13** under the standard conditions (Scheme 4).

The reaction was also attempted with ketone **15**, derived from L-alanine, as a representative of natural amino acid derivatives. However, this transformation turned out to be more challenging and required some additional experimental work. In a first attempt, we performed the coupling reaction under the standard reaction conditions from hydrazone **16**, but no coupling product was detected (Scheme 5). Surprisingly, when the same reaction was conducted in a one-pot procedure directly from ketone **15**, with pre-formation of the hydrazone in situ, the expected coupling product **17a** was isolated in 42% yield (Scheme 5).



Scheme 5. Coupling reaction with alanine derivatives **15** and **16**: influence of the presence of H_2O.

The only difference between the two experiments was the presence of 1 equivalent of water in the second reaction, released in the formation of hydrazone **16** from tosylhydrazide and the ketone **15**. For this reason, we carried out a study of the influence of different amounts of water, which revealed that the coupling reaction could be best accomplished in the presence of 5 equivalents of water. Under these conditions, the allyl amine **17a** was obtained in an acceptable 65% yield (Scheme 5).[13] Further experimentation revealed that the use of $Pd(OAc)_2$ instead of $[Pd_2(dba)_3]$ provided higher yields. Employing this methodology, a variety of chiral *N*-Boc-protected allyl amines **17** were prepared from tosylhydrazone **16** (Scheme 6). In all cases, the reactions took place with total retention of configuration of the stereogenic center.



Scheme 6. Synthesis of chiral *N*-Boc-protected allyl amines **17** from the coupling reactions of tosylhydrazone **16** with aryl halides. Reaction conditions: **16** (0.55 mmol), Ar–Br, (0.5 mmol), $Pd(OAc)_2$ (4 mol%), xphos (8 mol%), LiO*t*Bu (1.4 mmol), dioxane (2 mL), 110°C, 4 h.

It is worth noting that the coupling reactions to produce chiral alkenes discussed herein are very general with regard to the aryl halide. In the synthesis of compounds **10**, **14**, and **17** we successfully employed electron-rich and electron-poor benzene derivatives as well as heteroaromatic halides. Moreover, these reactions can be carried out in the presence of free NH groups, as shown with tosylhydrazone **16**.

The high regioselectivity observed in the reactions of hydrazones derived from methyl ketones can be explained by considering the *syn* arrangement required for the β-hydride elimination on alkylpalladium complex **VIII**. As presented in Figure 3, the conformation required for the formation of the tetrasubstituted double bond (**VIII-a**), is clearly disfavored, because the bulky groups of both carbon atoms C1 and C2 have to adopt an eclipsed conformation. However, in the conformation required for the formation of the disubstituted double bond (**VIII-b**), the bulky groups attached at C1 are eclipsed with hydrogen atoms of the methyl group, and therefore, this situation is clearly favored.

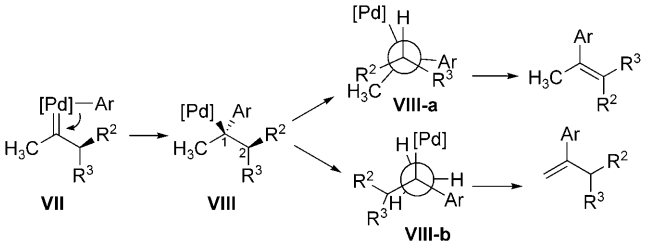


Figure 3. Different possibilities for the *syn*-β-hydride-elimination step on systems derived from methyl ketones.

Regarding the reactions with hydrazones derived from 2-substituted cyclohexanones (Scheme 2 and Scheme 3), the higher regioselectivity observed when compared with similar acyclic system **4** (Scheme 1) must be due to the restrictions imposed by the cyclic structure. We propose that the migratory insertion occurs on the less-hindered face of the ring to give intermediate **X** (Figure 4), leaving the methyl group and the palladium moiety in a *cis* arrangement. Then, only *syn*-β-hydride elimination can occur to give the trisubstituted olefin (Figure 4). Formation of the tetrasubstituted olefin, not observed, could only occur from the diastereomeric intermediate **XI**.[14]

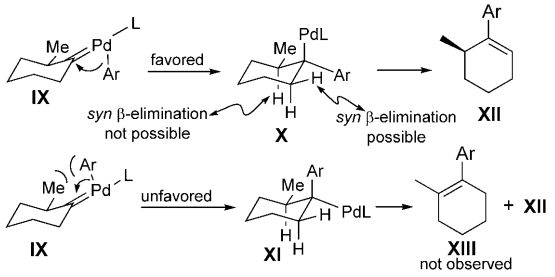


Figure 4. Rationale for the high regioselectivity observed in the coupling reaction of tosylhydrazones derived from 2-substituted cyclohexanones.

In summary, we have shown that the palladium-catalyzed cross-coupling between tosylhydrazones and aryl halides is a powerful methodology for the manipulation of chiral ketones with total preservation the stereochemistry of the α carbon. As a proof of concept, we have synthesized aryl-substituted chiral cyclohexenes from α-chiral cyclohexanones, and chiral allylamines from methyl ketones that were easily obtained from α-amino acids. Taking into consideration the wide availability, but also the configurational instability, of α-chiral ketones, this catalytic process may represent a very useful transformation in organic synthesis. Our current work in this area includes the extension of this methodology to other types of chiral carbonyl compounds, the use of alkenyl halides in the synthesis of dienes, and applications in natural products synthesis.

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