DOI: 10.1002/adsc.201000700

Synthesis of Dienes by Palladium-Catalyzed Couplings of Tosylhydrazones with Aryl and Alkenyl Halides

José Barluenga,[a,]* María Tomás-Gamasa,[a] Fernando Aznar,[a] and Carlos Valdés[a,]*

[a] Instituto Universitario de Química Organometálica “Enrique Moles”, Universidad de Oviedo, c/Julián Clavería 8, 33006 Oviedo, Spain
Fax: (+34)-9-8510-3446; e-mail: barluenga@uniovi.es or acvg@uniovi.es

Received: September 9, 2010; Published online: December 5, 2010

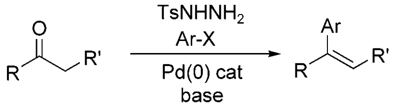
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000700.

Abstract: Two different combinations of coupling partners can be employed for the synthesis of conjugated dienes by palladium-catalyzed cross-coupling with tosylhydrazones: α,β-unsaturated ketone and aryl halide or alkenyl halide and non-conjugated tosylhydrazone. Depending on the substrate, a vinylogous hydride elimination is responsible for the formation of the final dienes.

Keywords: cross-coupling; dienes; ketones; palladium; tosylhydrazones

The discovery of new C–C bond forming reactions that work efficiently and selectively, based on easily available starting materials, is a field of constant interest in organic chemistry. Palladium-catalyzed cross-coupling reactions are among the most appealing methodologies for this purpose.[1] Their usefulness is reflected in a growing application for the synthesis of very complex organic molecules,[2] in drug discovery programs, and in industrial chemical processes.[3] Most of metal-catalyzed C–C bond forming transformations consist of the combination of an organic halide with an organometallic reagent. Nevertheless, great efforts have been devoted in the recent years towards the development of new processes for the creation of C–C linkages that do not employ stoichiometric organometallics.[4–7]

In this context, we have recently uncovered a new Pd-catalyzed coupling reaction that employs *N*-tosylhydrazones as nucleophilic partner, suppressing the stoichiometric organometallic reagent (Scheme 1).[8,9] Since then, we have initiated a research program to evaluate the synthetic potential of this novel reaction.

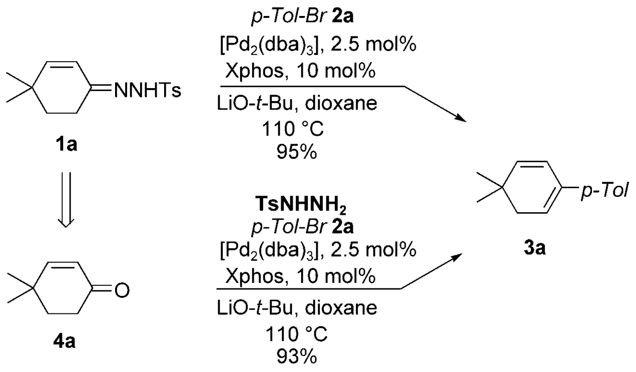


Scheme 1. Pd-catalyzed cross-coupling reactions employing carbonyls mediated by tosyl hydrazide.

Continuing the study of the scope of this C–C bond forming reaction, we turned our attention to *N*-tosylhydrazones derived from α,β-unsatured ketones. We now report that this catalytic process is an excellent method to prepare dienic structures and, in particular, homoanular cyclic dienes. Moreover, during the progress of this research, we have discovered a new reaction pathway that proceeds through a formal δ-hydride elimination. Preliminary studies of this new pathway show that it can be also employed in the preparation of conjugated dienes from tosylhydrazones and haloalkenes.

Initially we selected the cross-coupling between the hydrazone **1a** derived from 4,4-dimethyl-2-cyclohexen-1-one **4a** and *p*-bromotoluene **2a**. A screening of reaction conditions with variation of bases, ligands, and reaction temperatures was carried out. The optimal conditions found comprised [Pd$_2$(dba)$_3$] (2.5 mol%) as the metal source, Xphos (2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) as ligand, and LiO-*t*-Bu as base, in dioxane at 110 °C. Under these conditions, the diene **3a** could be obtained in very good yield (Scheme 2). By decreasing either temperature or catalyst loading, apart from an increment of the reaction time, formation of the Bamford–Stevens by-product, that occurs through a competitive uncatalyzed thermal process, took place.

We have previously demonstrated that the cross-coupling reaction can be carried out in a one-pot fashion directly from the carbonyl compound, by generating *in situ* the hydrazone. Having established proper reaction conditions for the coupling process, we decided to investigate whether it might be possible to apply the one-pot methodology to α,β-unsatured



Scheme 2. Pd-catalyzed cross-coupling reaction with α,β-unsaturated tosylhydrazone **1a**: preliminary results.

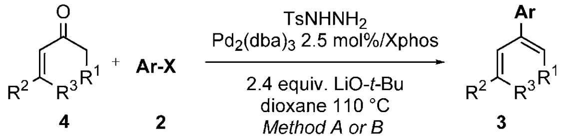
ketone **4a**. Indeed, the reaction starting directly from **4a** and tosyl hydrazide provided the diene **3a** in similar yield to that obtained from the preformed hydrazone **1a**. No undesired products from side reactions were detected (Scheme 2 and Table 1, entry 1).

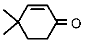
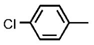
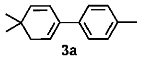
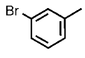
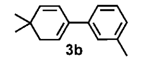
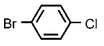
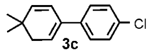
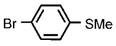
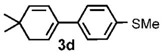
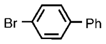
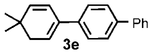
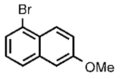
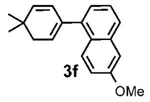
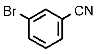
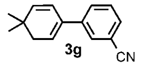
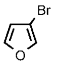
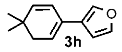
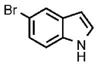
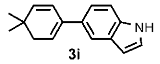
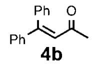
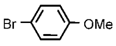
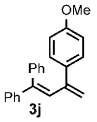
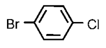
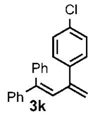
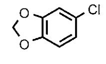
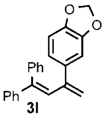
These optimized conditions were applied to a set of aryl halides **2**, giving rise to the aryl-substituted homoanular dienes **3** in very high yields in most of the cases. In general, electronic effects played a minor role and high conversions were achieved no matter if the substituents were electron-withdrawing or electron-donating. The use of the electron-rich *m*-bromotoluene, *p*-bromothioanisole, or 2-bromo-6-methoxynaphthalene gave the desired dienes in good yields (Table 1, entries 2, 4, and 6). Substituted bromobenzene derivatives, bearing electron-withdrawing groups are also tolerated (Table 1, entry 7). Both aryl chlorides as well as aryl bromides could be used (Table 1, entries 1 and 2). The reaction with *p*-chlorobromobenzene leads exclusively to the 4-chloro-substituted derivative (Table 1, entry 3). Moreover, a π-excessive heterocycle participates efficiently in the coupling (Table 1, entry 8), and 5-bromoindole was successfully coupled without protection of the N−H group (Table 1, entry 9).

The coupling reaction was also successfully accomplished with 4,4-diphenyl-3-buten-2-one **4b**, a β,β-disubstituted acyclic enone, leading to the expected acyclic dienes[10] (Table 1, entries 10–12). The best results for this system were obtained by employing a one-pot, two-steps sequence, stirring the hydrazide and the ketone at 70 °C for 2 h in dioxane, before adding the rest of the reagents (method B). Noteworthy, these reactions proceeded with significantly lower catalyst loading.

With respect to the cyclic en-one, the reaction also takes place with other cyclic systems, like 2-cyclohexen-1-one **4c** or 2-cyclohepten-1-one **4d**. However, in these cases, the linear-conjugated 1-aryldienes **5** were obtained instead of the expected cross-conjugated systems (Table 2, entries 1–3). Furthermore, the coupling

Table 1. Synthesis of dienes by cross-coupling of en-ones **4** with aryl halides **2**.[a,b]



Entry	En-one **4**	Ar-X **2**	Diene **3**	Yield[%] A/B[c]
1	 **4a**		 **3a**	92 [A]
2	**4a**		 **3b**	89 [A]
3	**4a**		 **3c**	94 [A]
4	**4a**		 **3d**	95 [A]
5	**4a**		 **3e**	99 [A]
6	**4a**		 **3f**	99 [A]
7	**4a**		 **3g**	98 [A]
8	**4a**		 **3h**	95 [A]
9	**4a**		 **3i**	70 [A]
10[d]	 **4b**		 **3j**	94 [B]
11[d]	**4b**		 **3k**	88 [B]
12[d]	**4b**		 **3l**	90 [B]

---

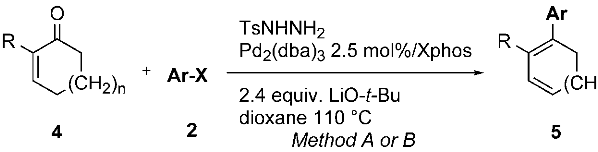
[a] Method A: ketone **4a**, 1 mmol; $TsNHNH_2$, 1.1 mmol; ArX, 1 mmol; $Pd_2(dba)_3$, 2.5 mol%; Xphos, 10 mol%; LiO-*t*-Bu, 2.4 equiv.; dioxane, 110 °C. Method B: ketone **4b**, 1 mmol; $TsNHNH_2$, 1.1 mmol; dioxane, 2 h, 70 °C; then ArX, 1 mmol; $Pd_2(dba)_3$, 2.5 mol%; Xphos, 10 mol%; LiO-*t*-Bu, 2.4 equiv., 110 °C.

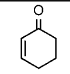
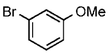
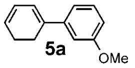
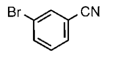
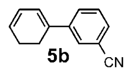
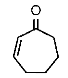
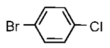
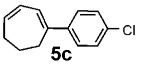
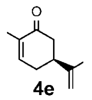
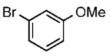
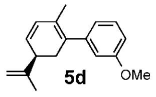
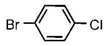
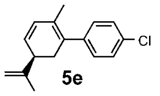
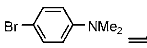
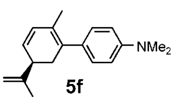
[b] Xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

[c] Yield of isolated product.

[d] $[Pd_2(dba)_3]$, 1.0–1.5 mol%, Xphos, 4–6 mol%.

Table 2. Synthesis of linear-conjugated dienes **5** by cross-coupling of en-ones **4** with aryl halides **2**.[a]



Entry	En-one **4**	Ar-X **2**	Diene **5**	Yield [%] A/B[b]
1	 **4c**			80 [A]
2	**4c**			91 [A]
3	 **4d**			55 [A]
4	 **4e**			85 (95) [B][c]
5	**4e**			51 (59) [B][c]
6	**4e**			85 (89) [B][c]

[a] Methods A and B: same conditions as in Table 1.

[b] Yield of isolated product employing method A or B.

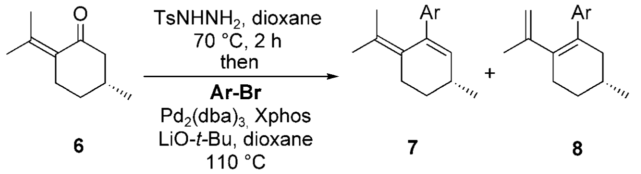
[c] The yield for the reaction starting from the previously isolated hydrazone is indicated in brackets.

reaction proceeded efficiently also with L-(−)-carvone **4e**, affording a new cyclohexadiene bearing a stereogenic center (Table 2, entries 4–6). Noteworthy, these examples led to the formation of a tetrasubstituted alkene.[11] Again, the linear-conjugated dienes were obtained for carvone derivatives. In the latter cases, better results were obtained in a two-steps process, starting from the preformed hydrazone.

In this context, we became interested in the structure of *R*-(+)-pulegone **6**, a natural α,β-unsaturated ketone which features an exocyclic propenylidene substituent. Interestingly, the coupling reaction gave rise to a mixture of two isomeric dienes, the expected diene **7** and the regioisomeric diene **8**, which differ in the position of the double bonds. In fact, under the optimized reaction conditions, diene **8**, which features linear conjugation with the aryl substituent is obtained again as major product in all the examples examined (Table 3).

The formation of the linear-conjugated dienes **5**, can be rationalized by considering the mechanism proposed for the cross-coupling reactions with tosylhydrazones (Figure 1), which involves: oxidative addition of the aryl halide to the Pd(0) catalyst, formation of Pd-carbene complex **III** by reaction of the diazo compound **II** (generated from the tosylhydrazone) with the arylpalladium complex **I**, and migratory insertion of the aryl group to the carbenic carbon to form η^1-allylpalladium intermediate **IV**. At this point, β-hydride elimination on complex **IV** would release the olefin **3** and a Pd-hydride complex. This pathway operates in the case of hydrazones derived from 4,4-dimethylcyclohexenone **4a** (Table 1), but does not explain the formation of linear dienes from 4-unsubstituted enones **4c**, **4d** and **4e** (Table 2). For these systems, the formation of the linear diene **5** can be rationalized through a β-hydride elimination on complex **VI**,[12] upon metallatropic rearrangement through the η^3-allylpalladium complex **V**.[13] Moreover, a simi-

Table 3. Synthesis of chiral dienes by cross-coupling of *R*-(+)-pulegone **6** with aryl halides.[a]



Entry	Ar	Ratio **7**:**8**	Yield [%][b]
1	*p*-Tol	20:80	70
2	*p*-MeO-C_6H_4	10:90	71
3	p-Me_2N-C_6H_4	33:66	71
4	*p*-biphenyl	10:90	64

[a] *Experimental conditions:* pulegone **6**, 1 mmol; $TsNHNH_2$, 1.1 mmol; ArX, 1 mmol; $Pd_2(dba)_3$, 2.5 mol%; Xphos, 10 mol%; LiO-*t*-Bu, 2.4 equiv.; dioxane, 110 °C.

[b] Isolated yield of the mixture of isomers.

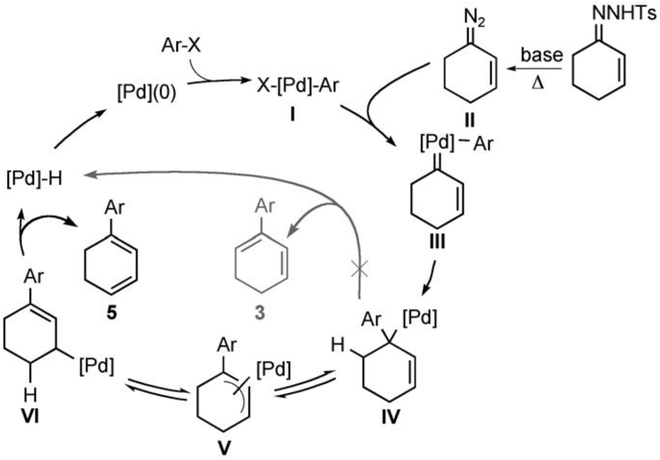


Figure 1. Mechanisms proposed for the formation of cyclohexadienes **3** and **5**.

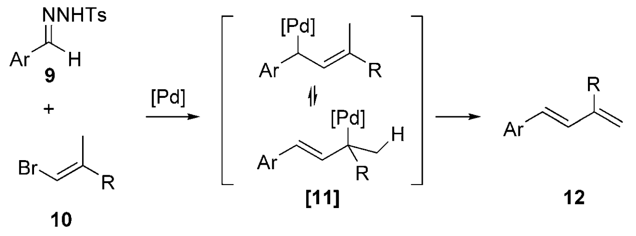


Figure 2. Reaction of 1-bromoalkenes **10** and aromatic tosylhydrazones **9**

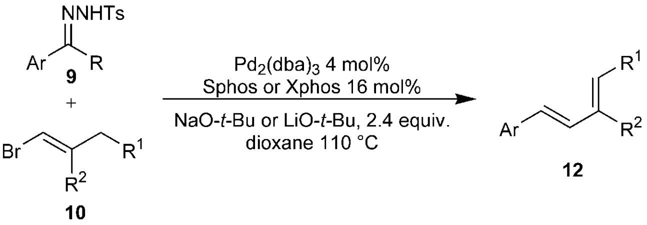
lar mechanism could be also proposed for the formation of linear dienes **8** from pulegone.

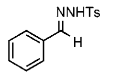
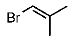
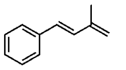
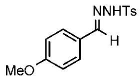
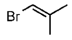
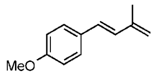
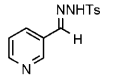
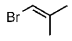
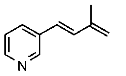
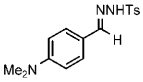
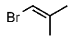
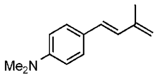
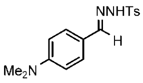
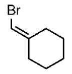
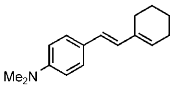
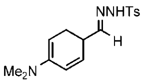
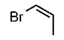
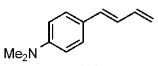
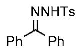
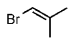
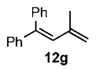
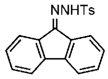
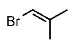
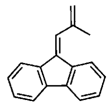
Taking into account this mechanistic model, we decided to investigate other combinations of coupling partners that could also participate through hydride elimination involving a π-allylpalladium intermediate. We selected the reaction of hydrazones **9** derived from aryl aldehydes and alkenyl halides **10**. As shown in Figure 2, the only possible evolution of the allylpalladium intermediate [**11**] would be the hydride elimination through the palladatropic rearrangement/β-hydride elimination sequence to produce diene **12**.

After some optimization work, the reactions proceeded as planned with moderate yields for 1-bromo-2-methylpropene, (Table 4, entries 1–4), (bromomethylene)cyclohexane (Table 4, entry 5) and 1-bromopropene (Table 4, entry 6). Noteworthy, in all cases, the *trans* isomer was obtained as a single stereoisomer. Moreover, the reaction proceeded also with the hydrazones derived from the non-enolizable ketones benzophenone and fluorenone (Table 4, entries 7 and 8). For these reactions to take place, depending on the particular substrates, it is necessary to employ the proper ligand Xphos or Sphos, as well as the adequate base NaO-*t*-Bu or LiO-*t*-Bu, leading again to the expected dienes through the vinylogous hydride elimination pathway.[14]

In summary, we have described a new methodology for the preparation of aryl-substituted conjugated dienes by the coupling reaction of tosylhydrazones derived from α,β-unsaturated ketones. The reaction is particularly effective for the preparation of homoanular dienes. Moreover, in the course of this research, a variation of the reaction that involves a hydride elimination involving a π-allylpalladium intermediate has been discovered. Preliminary studies indicate that this new transformation may represent an efficient way to carry out the synthesis of linear conjugated dienes from readily available starting materials. Further applications of this methodology as well as detailed mechanistic studies are ongoing and will be reported in due course.

Table 4. Synthesis of linear dienes **12** by cross-coupling of aryl tosylhydrazones and bromoalkenes.[a,b]



Entry	Hydrazone **9**	Bromide **10**	Diene **12**	Yield [%][c]
1			 **12a**	58
2			 **12b**	47
3[d]			 **12c**	61
4[d]			 **12d**	55
5[e]			 **12e**	57
6[d]			 **12f**	56
7[e]			 **12g**	40
8[e]			 **12h**	51

[a] *Experimental conditions:* hydrazone **9**, 1 mmol; bromoalkene **10**, 2 mmol; $Pd_2(dba)_3$, 4 mol%; Sphos 16 mol%; NaO-*t*-Bu, 2.4 equiv.; dioxane, 110 °C.

[b] Sphos = 2-dicyclohexylphosphino-2′,6′-dimethoxylbiphenyl.

[c] Isolated yield.

[d] The reaction is carried out in the presence of 5 equivalents of water.

[e] *Experimental conditions:* hydrazone **9**, 1 mmol; bromoalkene **10**, 2 mmol; $Pd_2(dba)_3$, 4 mol%; Xphos 16 mol%; LiO-*t*-Bu, 2.4 equiv.; dioxane, 110 °C.

Experimental Section

Reaction of Cyclic En-ones with Aryl Halides: Method A (Table 1, entries 1–9; Table 2, entries 1–3)

A carousel reaction tube under a nitrogen atmosphere was charged with 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (23.8 mg, 0.05 mmol, 10 mol%), tris(dibenzylideneacetone)dipalladium(0) (11.4 mg, 0.013 mmol, 2.5 mol%), lithium *tert*-butoxide (96.0 mg, 2.4 equiv.), the cyclic en-one **4** (0.55 mmol), *p*-toluenesulfonyl hydrazide (0.64 mmol) and dioxane (2 mL). After 1 min, the aryl halide **2** (0.5 mmol) was added. The system was heated at 110 °C with stirring and reflux. The reaction was monitored by GC-MS. When the reaction was completed, the crude reaction mixture was allowed to reach room temperature, taken up in dry pentane, hexanes or dichloromethane (15 mL), and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel or desactivated silica gel.

Reaction of En-ones with Aryl Halides: Method B (Table 1, entries 10–12; Table 2, entries 4–6; Table 3)

A carousel reaction tube under a nitrogen atmosphere was charged with the ketone (0.55 mmol), *p*-toluenesulfonyl hydrazide (0.64 mmol) and dioxane (1 mL), and heated at 70 °C with stirring for two hours. The reaction mixture was allowed to reach room temperature. Then, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (4–10 mol%), tris(dibenzylideneacetone)dipalladium(0) (1.0–2.5 mol%) (see Tables for ligand and catalyst loadings), and lithium *tert*-butoxide (96.0 mg, 2.4 equiv.) were added. After 1 min, the aryl halide **2** (0.5 mmol) and 1 mL of dioxane were added. The system was heated at 110 °C with stirring and reflux. The reaction was monitored by GC-MS. When the reaction was completed, the crude reaction mixture was allowed to reach room temperature, taken up in dry pentane, hexanes or dichloromethane (15 mL), and filtered through celite. The solvents were evaporated under reduced pressure; the residue was purified by flash chromatography on silica gel.

Cross-Coupling of *N*-Tosylhydrazones 9 with Alkenyl Halides 10 (Table 4)

A carousel reaction tube under a nitrogen atmosphere was charged with 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (38.1 mg, 0.08 mmol, 16 mol%) or dicyclohexylphosphino-2′, 6′-dimethoxybiphenyl (Sphos) (32.9 mg, 0.08 mmol, 16 mol%) (see Table 4), tris(dibenzylideneacetone)dipalladium(0) (18.3 mg, 0.02 mmol, 4 mol%), lithium *tert*-butoxide (96.0 mg, 2.4 equiv.) or sodium *tert*-butoxide (115.2 mg, 2.4 equiv.), the tosylhydrazone **9** (0.5 mmol) and dioxane (2 mL). After 1 min, the alkenyl halide **10** (1 mmol) was added, followed by the addition of 5 equiv. of water (45 μL) when necessary. The system was heated at 110 °C with stirring and reflux. The reaction was monitored by GC-MS. When the reaction was completed, the crude reaction mixture was allowed to reach room temperature, taken up in dry pentane, hexanes or dichloromethane (15 mL), and filtered through celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel.

Acknowledgements

This work was supported financially by DGI of Spain (CTQ2007-61048/BQU) and Consejería de Educación y Ciencia of Principado de Asturias (IB08–088). An FPU predoctoral fellowship to M. T.-G. is gratefully acknowledged.

References

[1] a) *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E. Negishi), Wiley, Hoboken, NJ, **2002**; b) *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; c) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **2004**.

[2] K. C. Nicolau, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.

[3] a) D. S. Johnson, J. J. Li, *The art of drug synthesis*, Wiley Inter-Science, **2007**; b) R. D. Larsen, *Organometallics in Process Chemistry*, Springer, Heidelberg, Berlin, **2004**; c) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027.

[4] Metal-catalyzed C−H arylations: a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; b) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013; c) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173.

[5] Carbonyl α-arylations: a) J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360; b) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473; c) R. M. Martín, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 7374; *Angew. Chem. Int. Ed.* **2007**, *46*, 7236; d) G. D. Vo, J. F. Hartwig, *Angew. Chem.* **2008**, *120*, 2157; *Angew. Chem. Int. Ed.* **2008**, *47*, 2127, and references cited therein.

[6] Decarboxylative couplings: L. J. Goossen, N. Rodríguez, B. Melzer, C. Linder, G. Deng, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824.

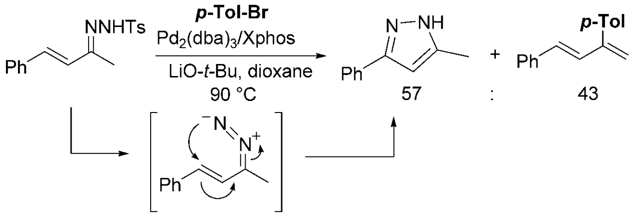
[7] Carbonyl acylation: J. Ruan, O. Saidi, J. A. Iggo, J. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 10510.

[8] a) J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 5683; *Angew. Chem. Int. Ed.* **2007**, *46*, 5587; b) J. Barluenga, M. Tomás-Gamasa, P. Moriel, F. Aznar, C. Valdés, *Chem. Eur. J.* **2008**, *14*, 4792; c) J. Barluenga, M. Escribano, P. Moriel, F. Aznar, C. Valdés. *Chem. Eur. J.* **2009**, *15*, 13291.

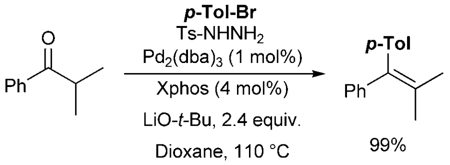
[9] For related Pd-catalyzed processes based on diazo compounds, see: a) K. L. Greenman, D. S. Carter, D. L. Van Vranken, *Tetrahedron* **2001**, *57*, 5219; b) K. L. Greenman, D. L. Van Vranken, *Tetrahedron* **2005**, *61*, 6438; c) S. K. J. Devine, D. L. Van Vranken, *Org. Lett.* **2007**, *9*, 2047; d) S. K. J. Devine, D. L. Van Vranken, *Org. Lett.* **2008**, *10*, 1909; e) S. Chen, J. Wang, *Chem. Commun.* **2008**, 4198; f) C. Peng, Y. Wang, J. Wang, *J. Am. Chem. Soc.* **2008**, *130*, 1566; g) W.-Y. Yu, Y.-T. Tsoi, Z. Zhou, A. S. C. Chan, *Org. Lett.* **2009**, *11*, 469; h) R. Kudirka, S. K. J. Devine, C. S. Adams, D. L. Van Vranken, *Angew. Chem.* **2009**, *121*, 3731; *Angew. Chem. Int. Ed.* **2009**, *48*, 3677; i) X. Xiao, J. Ma, Y. Yang, Y, Zhang, J. Wang, *Org. Lett.* **2009**, *11*, 4732.

[10] The coupling reaction with hydrazones derived from less substituted acyclic α,β-unsaturated ketones, such as

benzylideneacetone, gives rise, under optimized reaction conditions, to a 57: 43 mixture of the expected diene and the pyrazole that is formed by decomposition of the tosylhydrazone followed by electrocyclic ring closure.



[11] The Pd-catalyzed synthesis of tetrasubstituted olefins by the reaction of tosylhydrazones with aryl halides has been recently published under slightly different reaction conditions: E. Brachet, A. Hamze, J.-F. Peyrat, J.-D. Brion, M. Alami, *Org. Lett.* **2010**, *12*, 4042. Nevertheless, we have observed that our protocol can be also employed for the preparation of simple tetrasubstituted alkenes.



[12] DFT computations show that the TS of the β-hydride elimination from **VI**, that leads to the linear dienes **5** is 13 kcal mol^{-1} (ΔG) more stable than the TS of the β-hydride elimination from **IV**, that leads to the cross-conjugated diene. A very large energy difference may justify the exclusive formation of the linear dienes (see Supporting Information for details).

[13] For some leading references regarding hydride eliminations on π-allylpalladium complexes see: a) I. Shimizu, in: *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E. Negishi), Wiley, Hoboken, NJ, **2002**, p 1981; b) H. Matsushita, E. Negishi, *J. Org. Chem.* **1982**, *47*, 4161; c) J. M. Takacs, E. C. Lawson, F. Clement, *J. Am. Chem. Soc.* **1997**, *119*, 5956.

[14] The reaction with the hydrazone of 3-phenylpropanal led to a 10: 1 mixture of the dienes derived from β-hydride elimination and the vinylogous hydride elimination, respectively.