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Pd-Catalyzed Cross-Coupling Reactions with Carbonyls: Application in a Very Efficient Synthesis of 4-Aryltetrahydropyridines

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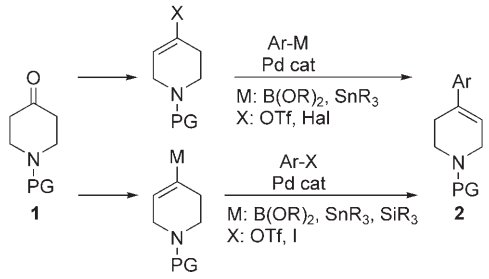
Palladium-catalyzed couplings are very powerful tools for the formation of C–C linkages.[1] A typical cross-coupling reaction involves the combination of an electrophile with a nucleophile in the presence of a metal catalyst. The classical nucleophilic components are organometallic reagents derived from, for example, magnesium,[2] boron,[3] silicon,[4] tin,[5] and zinc,[6] whereas the electrophiles are generally organic halides or sulfonates. Thus, a prerequisite for introducing an organic fragment by a cross-coupling reaction is its conversion into either the nucleophilic or the electrophilic component. In many cases, multistep, expensive, and moisture-sensitive processes are involved in these transformations.

In the recent years, important advances in the development of novel cross-coupling processes that do not require stoichiometric organometallic reagents, such as C–H activation reactions,[7] α-arylations of carbonyl compounds,[8] and decarboxylative cross-coupling reactions[9] have been disclosed.

In this context, we have recently uncovered a new Pd-catalyzed C–C bond-forming reaction that employs *N*-tosylhydrazones as nucleophilic coupling partner, eliminating the need of a stoichiometric amount of an organometallic reagent.[10] Since then, we have initiated a research program to evaluate the synthetic potential of this novel reaction. We identified 4-aryltetrahydropyridines **2** as ideal synthetic targets for our methodology. The 4-arylpiperidine scaffold is an important structure for medicinal chemistry,[11] which is present in a vast number of biologically active and therapeutically useful molecules, and is continuously employed in drug discovery programs.[12,13–18] 4-Aryltetrahydropyridines have been synthesized by different approaches starting from commercially available 4-piperidones. In the last few years, Pd-catalyzed cross-couplings have become the method of choice (Scheme 1).[14–18] Two different strategies are possible:



Scheme 1. Standard methods for the synthesis of 4-aryltetrahydropyridines **2** from 4-piperidones **1** by cross-coupling processes.

i) conversion of the ketone into the electrophilic coupling partner (alkenyl iodide, enol sulfonate), which can be coupled with an organometallic reagent such as boronic acid,[14] or an stannane,[15] ii) preparation of a vinyl organometallic reagent from the 4-piperidone,[16] followed by cross-coupling with an aryl halide.[17–19] Both approaches require several synthetic steps from the commercially available 4-piperidone and proper protection of the piperidone N–H group.

In a first run we selected the hydrazone **3a** derived from *N*-butyloxycarbonyl(*N*-Boc)-protected 4-piperidone **1a** and applied the reaction conditions previously reported towards 4-bromotoluene (Scheme 2). A very frustrating result was obtained. The tetrahydropyridine **4a**, which resulted from the thermal degradation of the tosylhydrazone, was obtained as the major product, accompanied by only 15% yield of the desired coupling product **2a** (Scheme 2). Several optimization experiments, with variation of the ligand, base, reaction conditions, and catalyst loading, were performed, but we were not able to drive the reaction to useful conversions.

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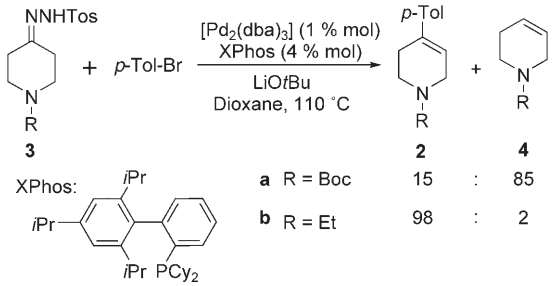


Scheme 2. Cross-coupling reaction of the tosylhydrazones **3** with *p*-bromotoluene: Influence of the *N*-protecting group.

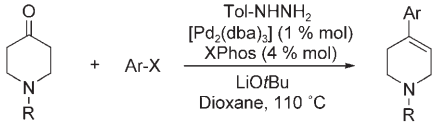
We then moved to *N*-alkyl-substituted 4-piperidones. Delightfully, when the reaction of the tosylhydrazone **3b** (R = Et) was treated with 4-bromotoluene, in the presence of $[Pd_2(dba)_3]$, XPhos, and LiO*t*Bu in dioxane at 110 °C, the desired coupling product **2b** was cleanly obtained in nearly quantitative yield. This time only traces of the tetrahydropyridine **4b**, derived from the decomposition of the tosylhydrazone, were detected (Scheme 2). After some experimentation we found that the optimal conditions for this transformation required 2% mol Pd, a 2:1 ligand/Pd ratio, and 2.3 equivalents of LiO*t*Bu.

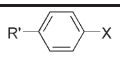
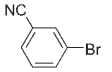
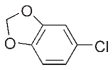
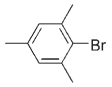
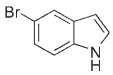
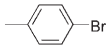
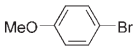
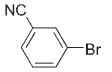
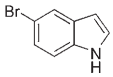
Tosylhydrazones **3** are formed by mixing in a solvent tosylhydrazine with 4-piperidones **1**. Thus, we decided to investigate whether it might be possible to carry out the coupling reaction starting directly from the piperidone **1** and the tosylhydrazine, and generating the hydrazone **3** in situ, in a multicomponent fashion. Indeed, the multicomponent process provided the coupling product **2b** in similar yield to that obtained from the preformed hydrazone **3b**. Products derived from undesired side reactions, such as ketone α-arylation[8a,b] or tosylhydrazine *N*-arylation were not observed.

These reaction conditions were applied to an array of aryl halides (Table 1). We found that the reaction is general for substituted bromo- and chlorobenzene (Table 1, entries 2, 3, 6) derivatives, bearing electron-donating (Table 1, entries 3, 6) and electron-withdrawing groups (Table 1, entry 5). Moreover, *o*-substitution is also tolerated, as seen in the coupling reaction of bromomesitylene (Table 1, entry 7). As expected, the reaction with *p*-chlorobromobenzene gives rise exclusively the 4-chlorosubstituted derivative (Table 1, entry 4). The reaction proceeds equally efficiently with aromatic heterocycles, both π-exceeding (Table 1, entries 8 and 9) or π-deficient (Table 1, entry 10). Noteworthy, 5-bromoindole was successfully coupled without protection of the N–H group (Table 1, entry 11).

Interestingly, excellent results were also obtained with N–H unprotected 4-piperidone (Table 1, entries 12–16). The possible competitive Pd-catalyzed *N*-arylation was not observed at all. These reactions are slower and in some cases required an increase in the catalyst loading to achieve complete conversion (Table 1, entries 14-16). Nevertheless, this is clearly an important advance, since it eliminates the need for a deprotecting step.

Table 1. Synthesis of 4-aryltetrahydropyridines **2** from 4-piperidones **1**.[a]



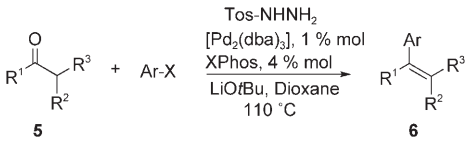
Entry	R	Ar–X	*t* [h]	Compd **2**	Yield[b,c]
					
1	Et	R′ = Me, X = Br	5	**2b**	81
2	Bn	R′ = Me, X = Cl	5	**2c**	93
3	Bn	R′ = OMe, X = Cl	6	**2d**	99
4	Bn	R′ = Cl, X = Br	8	**2e**	98
5	Bn		7	**2f**	98
6	Bn		12	**2g**	97
7	Bn		7	**2h**	92
8	Bn		5	**2i**	92
9	Et		5	**2j**	90
10	Bn		6	**2k**	99
11	Et		5	**2l**	83
12	H		19	**2m**	94
13	H		12	**2n**	90
14[d]	H		12	**2o**	93
15[d]	H		15	**2p**	70
16[d]	H		24	**2q**	76

[a] Experimental conditions: piperidone **1**, 1 mmol, $TosNHNH_2$, 1 mmol, ArX, 1 mmol, $[Pd_2(dba)_3]$, 1% mol, Xphos, 4% mol, LiO*t*Bu, 2.3 equiv dioxane, 110 °C. [b] Yield of isolated product. [c] XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [d] $[Pd_2(dba)_3]$, 2% mol and XPhos, 8% mol.

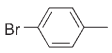
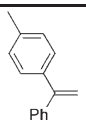
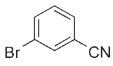
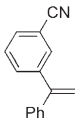
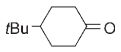
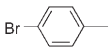
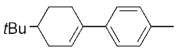
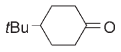
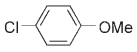
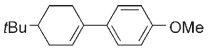
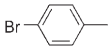
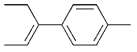
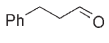
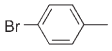
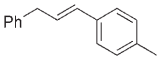
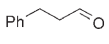
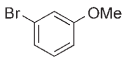
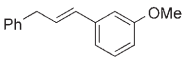
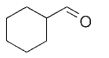
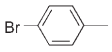
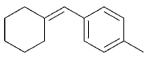
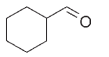
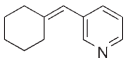
Moreover, the use of dry solvents or an inert atmosphere is not required for the coupling reaction. The same yields are obtained when the reactions are carried out in reagent grade dioxane under air as when the reactions are carried out in dry solvent under an Ar atmosphere. From a practical point of view, in this transformation *a ketone is employed as a nucleophilic cross-coupling reagent*, with no previous synthetic modification, only the addition of tosylhydrazine to the reaction medium.

These results prompted us to extend the one-pot process to other carbonyl compounds. Some preliminary examples

Table 2. Synthesis of di- and trisubstituted olefins **6** by direct cross-coupling of carbonyl compounds **5** with aryl halides.[a,c]



5 **6**

Entry	Carbonyl **5**	Ar–X	*t* [h]	Olefin **6**		Yield [%][b]
1			5		**6a**	72
2			12		**6b**	96
3			12		**6c**	98
4			12		**6d**	93
5			5		**6e**	76
6			5		**6f**	92
7			12		**6g**	87
8			6		**6h**	96
9			12		**6i**	60

[a] Experimental conditions: Carbonyl **5**, 1 mmol, $TosNHNH_2$, 1 mmol, ArX, 1 mmol, $[Pd_2(dba)_3]$, 1 % mol, XPhos, 4 % mol, LiO*t*Bu, 2.3 equiv dioxane, 110 °C. [b] Yield of isolated product. [c] XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

are presented in Table 2. In all the cases studied, the substituted olefins **6** are obtained directly from the carbonyl compounds **5** in very high yields. Like in the reaction with 4-piperidones, α-arylation products were never detected. In terms of scope and stereoselectivity, the results are comparable to those obtained previously for the reaction with preformed tosylhydrazones.[10] For instance, cyclic (Table 2, entries 3, 4) and acyclic (Table 2, entries 1, 2, 5) ketones can participate in the reaction. Moreover, very good results were obtained also with aldehydes (Table 2, entries 6–9). The reactions of 3-phenylpropanal are noteworthy (Table 2, entries 6, 7). Linear aldehydes are prone to suffer aldol condensation; however, in the presence of tosylhydrazine the only products obtained are the *trans* olefins **5** derived from the cross-coupling reaction.

In summary, we have presented an extremely efficient methodology for the preparation of 4-aryltetrahydropyridines, which are very important building blocks in medicinal chemistry, by a novel Pd-catalyzed cross-coupling reaction that employs a tosylhydrazone as the nucleophilic coupling partner, with no stoichiometric organometallic reagent added. Importantly, the tosylhydrazone can be generated in situ, which implies that 4-piperidones can be directly employed in the cross-coupling reaction, providing the tetrahydropyridines in very high yields in most cases. Moreover, N–H protection is not required, thus, enabling further diversification of the 4-arylpyperidines. For all these reasons, we believe that this reaction will be of great use in drug discovery programs. Finally, the one-pot methodology has been extended to other types of carbonyl compounds. Our preliminary results indicate that a variety of *off-the-shelf* ketones and aldehydes can be employed as nucleophilic coupling partners in a process, which does not involve stoichiometric organometallic reagents, an inert atmosphere, or dry solvents, and which generates very few residues. We are convinced that the efficiency of this transformation, in terms of yield and availability of the starting materials, may lead to it becoming the method of choice for the preparation of different types of di- and trisubstituted olefins, even at large scale. Investigations on the scope of this transformation are currently underway and will be reported in due course.

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Keywords: carbonyl compounds · cross-coupling · palladium · piperidine · polysubstituted olefins

[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] a) K. Tamao, K. Sumitani, M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374; b) R. J. P. Corriu, J. P. Masse, *J. Chem. Soc. Chem. Commun.* **1972**, 144; c) M. Kumada, *Pure Appl. Chem.* **1980**, *52*, 669.

[3] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) G. A. Molander, R. Figueroa, *Aldrichimica Acta* **2005**, *38*, 49.

[4] a) T. Hiyama, Y. Hatanaka, *Pure Appl. Chem.* **1994**, *66*, 1471; b) For a review see: S. E. Denmark, M. H. Ober, *Aldrichimica Acta* **2003**, *36*, 75.
[5] J. K. Stille, *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
[6] a) O. King, N. Okukado, E. Negishi, *J. Chem. Soc. Chem. Commun.* **1977**, 683; b) for a recent review see: E. Negishi, Q. Hu, Z. Huang, M. Qian, G. Wang, *Aldrichimica Acta* **2005**, *38*, 71.
[7] a) For a recent account see: K. Godula, D. Sames, *Science* **2006**, *312*, 67. for some relevant recent contributions: b) S. Proch, R. Kempe, *Angew. Chem.* **2007**, *119*, 3196; *Angew. Chem. Int. Ed.* **2007**, *46*, 3135; c) K. L. Hull; M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904; M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11 904; d) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404; e) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172; f) G. L. Turner, J. A. Morris, M. F. Greaney, *Angew. Chem.* **2007**, *119*, 8142; *Angew. Chem. Int. Ed.* **2007**, *46*, 7996.
[8] Arylation of ketones: 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; arylation of esters: c) T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177; d) W. A. Moradi, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7996; arylation of amides: e) T. Hama, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 4976; arylation of aldehydes: f) Y. Terao, Y. Fukuoka, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2002**, *43*, 101; g) R. M. Martín; S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 7374; *Angew. Chem. Int. Ed.* **2007**, *46*, 7236.
[9] a) L. J. Goossen, G. Deng, L. M. Levy, *Science* **2006**, *313*, 662; b) L. J. Goossen, N. Rodríguez, B. Melzer, C. Linder, G. Deng,, L. M. Levy, *J. Am. Chem. Soc.* **2007**, *129*, 4824; c) P. Forgione, M.-C. Brochu, M. St-Onge, K. H. Thesen, M. D. Bailey, F. Bilodeau, *J. Am. Chem. Soc.* **2006**, *128*, 11350; d) O. Baudoin, *Angew. Chem.* **2007**, *119*, 1395; *Angew. Chem. Int. Ed.* **2007**, *46*, 1373; e) J.-M. Becht, C. Catala, C. Le Drian, A. Wagner, *Org. Lett.* **2007**, *9*, 1781.
[10] J. Barluenga, P. Moriel, C. Valdés, F. Aznar, *Angew. Chem.* **2007**, *119*, 5683.; *Angew. Chem. Int. Ed.* **2007**, *46*, 5587.
[11] a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfield, *J. Med. Chem.* **1988**, *31*, 2235; b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893.
[12] A simple Scifinder Scholar search of the *4-arylpiperidine* concept between 1997 and 2007 gave over 50 entries of patents that referred to the synthesis and/or clinical applications of molecules containing this moiety.
[13] a) M. V. Patel, T. Kolasa, K. Mortell, M. A. Matulenko, A. A. Hakeem, J. J. Rohde, S. L. Nelson, M. D. Cowart, M. Nakane, L. N. Miller, M. E. Uchic, M. A. Terranova, O. F. El-Kouhen, D. L. Donnelly-Roberts, M. T. Namovic, P. R. Hollingsworth, R. Chang, B. R. Martino, J. M. Wetter, K. C. Marsh, R. Martin, J. F. Darbyshire, G. Gintant, G. C. Hsieh, R. B. Moreland, J. P. Sullivan, J. D. Brioni, A. O. Stewart, *J. Med. Chem.* **2006**, *49*, 7450; b) L. J. Hampson, C. Arden, L. Agius, M. Ganotidis, M. N. Kosmopoulou, C. Tiraidis, Y. Elemes, C. Sakarellos, D. D. Leonidas, N. G. Oikonomakos, *Bioorg. Med. Chem.* **2006**, *14*, 7835; c) C. R. Hopkins, M. Czekaj, S. S. Kaye, Z. Gao, J. Pribish, H. Pauls, G. Liang, K. Sides, D. Cramer, J. Cairns, Y. Luo, H.-K. Lim, R. Vaz, S. Rebello, S. Maignan, A. Dupuy, M. Mathieue, J. Levell, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2734; d) S. A. Filla, B. M. Mathes, K. W. Johnson, L. A. Phebus, M. L. Cohen, D. L. Nelson, J. M. Zgombick, J. A. Erickson, K. W. Schenck, D. B. Wainscott, T. A. Branchek, J. M. Schaus, *J. Med. Chem.* **2003**, *46*, 3060; e) S. Sakamuri, I. J. Enyedy, A. P. Kozikowsky, W. A. Zaman, K. M. Johnson, S. Wang, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 495; f) J. C. Barrow, P. G. Nantermet, H. G. Selnick, K. L. Glass, K. E. Rittle, K. F. Gilbert, T. G. Steele, C. F. Homnick, R. M. Freidinger, R. W. Ransom, P. Kling, D. Reiss, T. P. Broten, T. W. Schorn, R. S. L. Chang, S. S. O'Malley, T. V. Olah, J. D. Ellis, A. Barrish, K. Kassahun, P. Leppert, D. Nagarathnam, C. Forray, *J. Med. Chem.* **2000**, *43*, 2703.
[14] a) M. G. Bursavich, C. W. West, D. H. Rich, *Org. Lett.* **2001**, *3*, 2317; b) W. L. Cody, D. D. Holsworth, N. A. Powell, M. Jalaie, E. Zhang, W. Wang, B. Samas, J. Bryant, R. Ostroski, M. J. Ryan, J. J. Edmunds, *Bioorg. Med. Chem.* **2005**, *13*, 59.
[15] a) J. Levell, P. Astles, P. Eastwood, J. Cairns, O. Houille, S. Aldous, G. Merriman, B. Whiteley, J. Pribish, M. Czekaj, G. Liang, S. Maignan, J.-P. Guilloteau, A. Dupuy, J. Davidson, T. Harrison, A. Morley, S. Watson, G. Fenton, C. McCarthy, J. Romano, R. Mathew, D. Engers, M. Gardyan, K. Sides, J. Kwong, J. Tsay, S. Rebello, L. Shen, J. Wang, Y. Luo, O. Giardino, H.-K. Lim, K. Smith, H. Pauls, *Bioorg. Med. Chem.* **2005**, *13*, 2859; b) J. S. Lee, Y. S. Cho, M. H. Chang, H. Y. Koh, B. Y. Chungb, A. N. Pae, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4117.
[16] a) C. A. Quesnelle, P. Gill, S. Roy, M. Dodier, A. Marinier, A. Martel, L. B. Snyder, S. V. D′Andrea, J. J. Bronson, M. Frosco, D. Beaulieu, G. A. Warr, K. L. DenBleyker, T. M. Stickle, H. Yang, S. E. Chaniewski, C. A. Ferraro, D. Taylor, J. W. Russell, K. S. Santone, J. Clarke, R. L. Drain, J. O. Knipe, K. Mosure, J. F. Barrett, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2728; b) A. Darwish, J. M. Chong, *J. Org. Chem.* **2007**, *72*, 1507.
[17] Suzuki coupling: a) P. L. Eastwood, *Tetrahedron Lett.* **2000**, *41*, 3705; b) G. N. Boice, C. G. Savarin, J. A. Murry, K. Conrad, L. Matty, Edw G. Corley, H. Smitrovich, D. Hughes, *Tetrahedron* **2004**, *60*, 11367; c) N. Díaz, M. Benvenga, P. Emmerson, R. Favors, M. Mangold, J. McKinzie, N. Patel, S. Peters, S. Quimby, H. Shannon, M. Siegel, M. Statnick, E. Thomas, J. Woodland, P. Surface, C. Mitch, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3844; d) Y. Jiang, C.-A. Chen, K. Lu, I. Daniewska, J. DeLeon, R. Kong, C. Forray, B. Li, L. G. Hegde, T. D. Wolinsky, D. A. Craig, J. M. Wetzel, K. Andersen, M. R. Marzabadi, *J. Med. Chem.* **2007**, *50*, 3870.
[18] Stille coupling: a) J. S. Kiely, E. Laborde, L. E. Lesheski, R. A. Bucsh, *J. Heterocycl. Chem.* **1991**, *28*, 1581; b) Q. Tan, E. T. Birzin, W. Chan, Y. T. Yang, L.-Y. Pai, E. C. Hayes, C. A. DaSilva, F. DiNinno, S. P. Rohrer, J. M. Schaeffer, M. L. Hammond, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3747; c) D. Kim, L. Wang, J. J. Hale, C. L. Lynch, R. J. Budhu, M. MacCoss, S. G. Mills, L. Malkowitz, S. L. Gould, J. A. DeMartino, M. S. Springer, D. Hazuda, M. Miller, J. Kessler, R. C. Hrin, G. Carver, A. Carella, K. Henry, J. Lineberger, W. A. Schleif, E. A. Emini, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129; d) K. Yoshida, K. Nakayama, N. Kuru, S. Kobayashi, M. Ohtsuka, M. Takemura, K. Hoshino, H. Kanda, J. Z. Zhang, V. J. Lee, W. J. Watkins, *Bioorg. Med. Chem.* **2006**, *14*, 1993.
[19] C. Morrill, N. S. Mani, *Org. Lett.* **2007**, *9*, 1505.
[20] We speculate that the dramatically different behavior between *N*-Boc and *N*-alkyl tosylhydrazones, might be due to the particular steric requirements imposed by the Boc group. According to our mechanistic proposal (see ref. [10]), the last step of the catalytic cycle is a β-hydrogen elimination, requiring a *syn* arrangement of the Pd and the hydrogen atom, which might be difficult in the *N*-Boc-substituted system. Therefore, the thermal uncatalyzed tosylhydrazone decomposition to give tetrahydropyridine **3** becomes the main reaction pathway.

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