Tandem Catalysis

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Tosylhydrazide-Promoted Palladium-Catalyzed Reaction of β-Aminoketones with *o*-Dihaloarenes: Combining Organocatalysis and Transition-Metal Catalysis**

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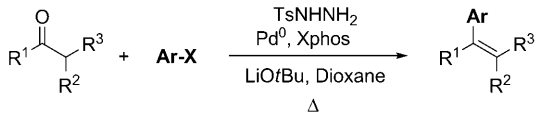
One of the main challenges of current organic synthesis is the design of practically simple and increasingly efficient organic transformations. The sequential formation of various bonds through tandem or cascade reactions constitutes one approach to achieving this goal. In these types of reactions, high molecular complexity can be built from relatively simple starting materials in a single synthetic operation.[1] Moreover, among the advantages of these processes are atom, solvent, and catalyst economy and operational simplicity, as isolation of intermediates is avoided.

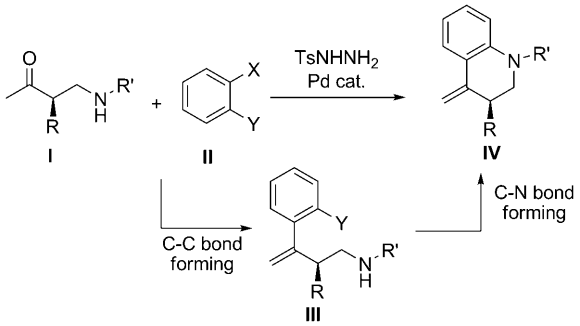
In the context of transition-metal-catalyzed reactions, processes in which a single, multifunctional metal catalyst promotes various individual reactions (auto-tandem catalysis)[2] are of great interest. By taking advantage of the wide scope, high performance, and remarkable stability of state-of-the-art Pd catalysts, a variety of Pd-catalyzed processes have been developed based on this principle.[3]

We have recently discovered a new Pd-catalyzed C–C bond-forming reaction that employs *N*-tosylhydrazones as nucleophilic component in a new type of "stoichiometric organometallic-free" cross-coupling process.[4] Moreover, the tosylhydrazone can be generated in situ from a carbonyl compound and tosylhydrazide, which implies that the carbonyl compounds can be directly employed in the cross-coupling reaction (Scheme 1).[5]



Scheme 1. Synthesis of polysubstituted alkenes by Pd-catalyzed tosylhydrazide ($TsNHNH_2$)-promoted cross-coupling reaction. Xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

Following our interest in auto-tandem Pd-catalyzed processes,[3b,c] we decided to investigate whether the new C–C bond-forming reaction with tosylhydrazones could be one of the processes promoted by a multifunctional catalyst. Following this idea, we designed a possible sequence employing hydrazones derived from β-aminoketones **I** and *o*-dihalobenzene derivatives **II** as starting materials. Thus, in the presence of the Pd catalyst two consecutive processes might occur: a C–C cross-coupling reaction (arylation) to give intermediate **III**, followed by an intramolecular C–N bond-forming reaction (amination)[6] affording substituted tetrahydroquinolines **IV** (Scheme 2). Moreover, taking into account that a variety of β-aminoketones are accessible in enantiomerically pure form through asymmetric organocatalyzed Mannich reactions,[7] our ultimate goal would be to develop a heterocyclization process that would preserve the configurationally unstable stereogenic center in the α position to the carbonyl group.[8]



Scheme 2. Proposed C–C/C–N cascade reaction.

We started our study with the model reaction between the hydrazone **2a**, derived from aminoketone **1a**, and 1-bromo-2-chlorobenzene (**3a**, Scheme 3). The initial experiments were conducted under standard conditions for the arylation reaction, but in the presence of an excess of base to also promote the intramolecular amination, which gave rise to promising results. The desired tetrahydrophenanthridine **4a** was formed together with significant amounts of cyclohexene **5**, which was generated by uncatalyzed thermal degradation of the hydrazone, and arylated cyclohexene **6**, which was formed by dehalogenation of the intermediate arylated product.

These results prompted us to carry out a very exhaustive study of both steps of the cascade reaction to find the optimal

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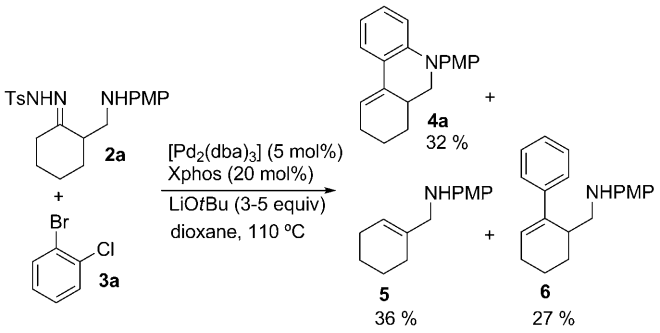
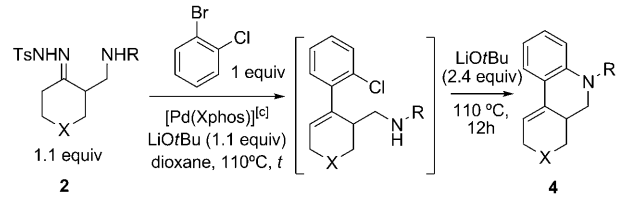


Scheme 3. Preliminary results for the C–C/C–N cascade reaction. PMP = *p*-methoxyphenyl, dba = dibenzylidene acetone.

conditions for the formation of **4a**. No improvement was found by changing either the ligand or the base. However, it was observed that the presence of an excess of base in the arylation step increased the amount of undesired cyclohexene **5**. To avoid the uncatalyzed decomposition of **2a**, a one-pot two-step sequence was devised. Moreover, it was found that the employment of a Pd^0/Xphos preformed catalyst, as recently reported by Buchwald et al.,[9] allowed a slight reduction of the catalyst loading. Thus, the best conditions found for the formation of the phenanthridine comprised two operations in a one-pot fashion: 1) treatment of the amino-hydrazone **2** and *o*-bromochlorobenzene with LiO*t*Bu (1.1 equiv) and the Pd^0/Xphos catalyst (8 mol%) in dioxane at 110 °C; and 2) once the arylation is complete (GC–MS monitoring), addition of a second portion of LiO*t*Bu (2.4 equiv). These conditions were applied to a set of cyclic β-aminohydrazones **2** leading to the corresponding tricyclic compounds **4** with moderate yields (Table 1). It must be pointed out that the time required for the arylation step before the addition of the second potion of the base had to be optimized independently for each particular reaction.

These moderately successful results prompted us to investigate microwave heating as an alternative energy source for this transformation. Again, very fine tuning of the reaction conditions was required. After extensive experimentation on the model reaction of Scheme 3, a very convenient protocol was identified for the cascade process. Thus, upon treating the mixture of hydrazone **2a** (0.27 mmol) and *o*-bromochlorobenzene (0.25 equiv) in dioxane (1.5 mL) in the presence of H_2O (10 μL), [$Pd_2(dba)_3$] (4 mol%), Xphos (16 mol%), and LiO*t*Bu (4 equiv) at 150 °C for 30 min, the phenanthridine **4a** was obtained in a 67% yield upon isolation (Table 2, entry 1, method A). Some points regarding

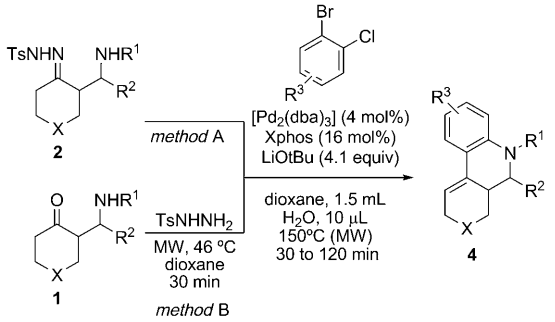
Table 1: Synthesis of phenanthridines by a one-pot reaction.[a]



Substrate	X	R	*t* [min]	Yield [%][b]
2a	CH_2	4-$MeOC_6H_4$	75	65
2b	CH_2	4-tol	75	47
2c	CH_2	Ph	150	48
2d	CH_2	4-$Me_2NC_6H_4$	120	44
2e	$(CH_2)_2$	4-$MeOC_6H_4$	120	37
2f	O	4-$MeOC_6H_4$	75	30

[a] Reaction conditions: **2**, 0.55 mmol; **3a**, 0.5 mmol; [Pd(Xphos)], 8 mol%; dioxane, 2 mL; 110 °C. [b] Yield of isolated compounds **4**. [c] The catalyst is prepared as described in Ref. [9].

Table 2: Microwave (MW)-promoted Pd-catalyzed C–C/C–N cascade reaction.[a]



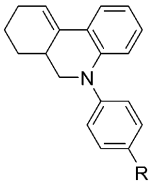
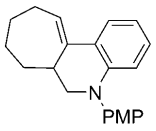
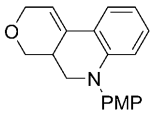
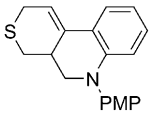
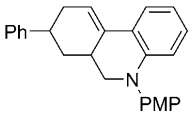
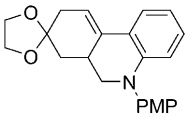
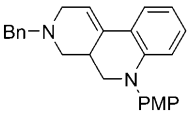
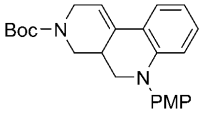
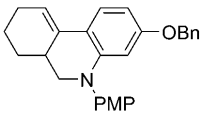
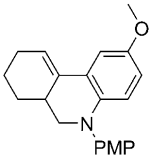
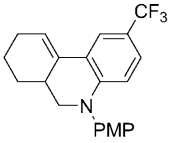
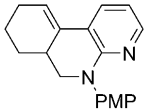
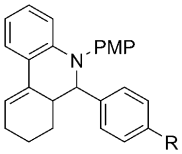
Entry	Product		Yield [%][b]
1		**4a** (R = MeO)	67 (70)
2		**4b** (R = Me)	76 (73)
3		**4c** (R = H)	60
4		**4d** (R = Me_2N)	76 (75)
5		**4e**	52
6		**4f**	72 (61)
7		**4g**	41
8		**4h**	55
9		**4i**	77
10		**4j**	41
11		**4k**	30

Table 2: (Continued)

Entry	Product		Yield [%][b]
12		**4l**	90 (60)
13		**4m**	41
14		**4n**	71 (40)
15		**4o**	35 (20)
16		**4p** (R = H)	77 (40)
17		**4q** (R = Me)	55

[a] Method A: hydrazone **2**, 0.27 mmol, 1.1 equiv; bromochloroarene, 0.25 mmol, 1 equiv; method B: Mannich adduct **1**, 0.27 mmol, 1.1 equiv; tosylhydrazide, 0.27 mmol, bromochloroarene, 0.25 mmol, 1 equiv. [b] Yield of isolated product for method A; the yield for method B is indicated in parentheses. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

the optimized reaction conditions are worth noting. 1) The concentration of the reagents and the amount of H_2O added are crucial for the success of the reaction. A variation in the amount of water added (500, 100, 60, 40, and 5 μL) leads to an increase in the elimination product **5**. 2) The use of the preactivated Pd^0/Xphos catalyst is no longer necessary, and in fact is detrimental to the yield of the reaction. 3) The total reaction times are remarkably reduced. 4) The LiO*t*Bu is added in one portion at the beginning of the reaction. This is an important advantage when compared with the conventionally heated one-pot reaction. Therefore, the microwave-heated process can be considered a real cascade reaction.

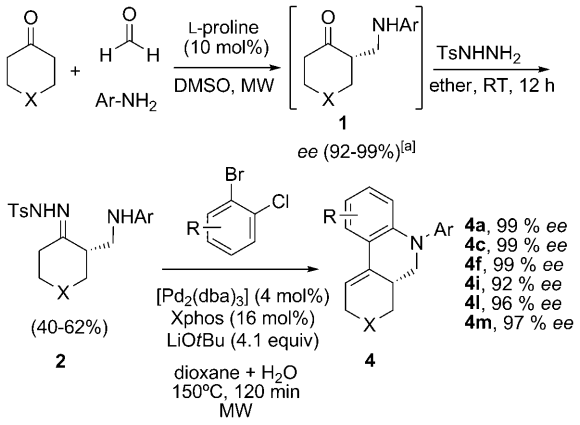
These reaction conditions (Table 2, method A) were applied to an expanded set of systems by variation of the substituents of the amine (**4a–d**), the cyclic ketone skeleton (**4e–k**), and the *ortho*-dihalogenated aromatic system (**4l–o**).

Regarding the substitution at the nitrogen atom, the cascade reaction proceeds efficiently with neutral or electron-rich aromatic substituents (Table 2, entries 1, 2, and 4); however, with electron-withdrawing substitution, the cyclization reaction failed and the intermediate arylation product was obtained (not shown in Table 2). The reaction can be applied to diverse 1-bromo-2-chlorobenzene derivatives bearing electron-donating groups (Table 2, entries 12 and 13), electron-withdrawing groups (Table 2, entry 14), and even with an aromatic heterocycle (Table 2, entry 15). The reaction proceeds efficiently with hydrazones derived from different types of cyclic ketones, including 4-substituted cyclohexanones, cycloheptanone, and heterocyclic derivatives of 4-piperidone, dihydro-2*H*-pyran-4-one, and dihydro-2*H*-thiopyran-4-one. Finally, the reaction could also be carried out with β-branched systems (**4p**, **4q**).[10] Of note, the diastereomeric ratio was not altered in the reaction.[11]

Furthermore, we investigated whether it might be possible to carry out the coupling reaction starting directly from the ketone **1**, and generate the hydrazone **2** in situ, in a multicomponent fashion under microwave conditions. To our delight, after a new optimization process, a microwave-promoted sequence hydrazone formation (30 min, 46 °C) and Pd-catalyzed auto-tandem reaction (2 h, 150 °C) allowed the preparation of the tricyclic systems **4** directly from the Mannich adducts **1** in yields comparable to those of the two-step process (Table 2, method B).

The Mannich adducts **1**, which are the starting materials for the cascade reaction, can be synthesized in enantiomerically enriched form by L-proline α-aminomethylation of ketones either by classical heating[12] or by microwave activation.[13] However, these adducts are configurationally unstable, and usually have to be isolated after reduction of the carbonyl compound. Since the arylation of tosylhydrazones derived from α-chiral ketones proceeds with preservation of the α chirality,[8] we decided to pursue a combined organocatalysis/Pd catalysis sequence to prepare the enantiomerically enriched phenanthridines **4**.

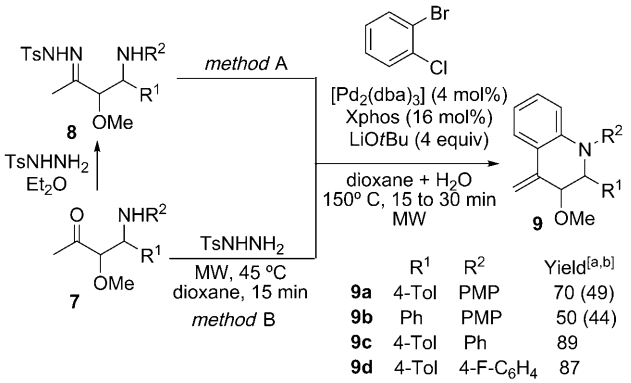
It was soon discovered that dimethyl sulfoxide (DMSO), the solvent required to achieve the enantioselective Mannich reaction, was not appropriate for the formation of the hydrazone. Nevertheless, the hydrazones could be obtained in fairly good yields upon aqueous workup and extraction with ether, by direct treatment of the ethereal organic layer with tosylhydrazide.[14] When the methodology mentioned above for the Pd-catalyzed cascade reaction was applied to the enantiomerically enriched hydrazones, the tetrahydrophenanthridines **4** were obtained with high enantiomeric excess (*ee*; Scheme 4). Very importantly, in spite of the known configurational instability of the stereogenic center of the



Scheme 4. Synthesis of enantiomerically enriched tetrahydrophenanthridines **4** through an organocatalyzed/Pd-catalyzed C–C/C–N sequence. [a] Compounds **1** are not isolated and the ethereal extracts are directly treated with tosylhydrazide.

Mannich adducts,[14] no decrease in enantioselectivity was observed during the whole sequence consisting of formation of the hydrazone and the Pd-catalyzed reaction.

This reaction was also extended to Mannich adducts **7**[7b] derived from acyclic ketones to afford tetrahydroquinoline derivatives **9** (Scheme 5). As in the cases discussed before, the



Scheme 5. Synthesis of quinoline derivatives **9**. [a] Yield of isolated product for the mixture of diastereoisomers. [b] Yields for method B are indicated in parentheses.

tosylhydrazone derivatives **8** were successfully isolated from the reaction using ether as solvent, and then subjected to the Pd catalysis conditions to afford the isoquinoline derivatives **9** in good yields. Interestingly, the formation of derivatives **9** takes place more easily than the formation of the tetrahydrophenanthridines **4**: the reactions require shorter times to reach complete conversion, and tolerate the presence of electron-withdrawing substituents on the nitrogen atom (**9d**). Moreover, the integrity of the stereogenic centers is again retained, as the quinoline derivatives **9** are obtained in the reaction crude in the same diastereomeric ratio as the starting hydrazones **8**.[15]

In summary, we have developed a new Pd-catalyzed process which consists in the cross-coupling of the tosylhydrazone of a Mannich adduct with a 1,2-dihalogenated aromatic system, followed by an intramolecular C–N bond-forming reaction. Notably, the same Pd catalyst promotes both independent steps. Moreover, this is the first example in which the Pd-catalyzed cross-coupling reaction with tosylhydrazones is included in an auto-tandem catalysis process, which opens the door to the development of other appealing cascade transformations. Finally, we have shown that the combination of organocatalysis and the Pd-catalyzed cross-coupling reaction of tosylhydrazones allows the ready transformation of enantiomerically enriched Mannich adducts, which are otherwise configurationally unstable.

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[11] Although the Mannich reaction gives rise to a mixture of two diastereomers, they could be separated at the tosylhydrazone stage, and thus the Pd-catalyzed cascade reaction was carried out with a single diastereoisomer.
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[14] In our hands, attempts to isolate the Mannich adducts prior to formation of the hydrazone led to partial epimerization.
[15] The Mannich reaction leads to a mixture of diastereoisomers that could not be separated, and therefore were employed as a mixture in the Pd-catalyzed cascade reaction.

