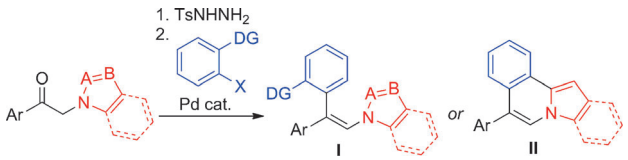

Azoles reacting in tandem: The *ortho*-stereodirecting effect is the key to the stereoselective synthesis of (*Z*)-*N*-alkenylazoles **I** through the tosylhydrazide-mediated Pd-catalyzed cross-coupling reaction of α-*N*-azoleacetophenones with *ortho*-substituted aryl halides and nonaflates (see scheme). Additionally, the preorganization of the alkene allowed for the development of an auto-tandem reaction involving an intramolecular C–H arylation leading to pyrroloisoquinolines **II**.

Domino Reactions

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Synthesis of (*Z*)-*N*-Alkenylazoles and Pyrroloisoquinolines from α-*N*-Azoleketones through Pd-Catalyzed Tosylhydrazone Cross-Couplings

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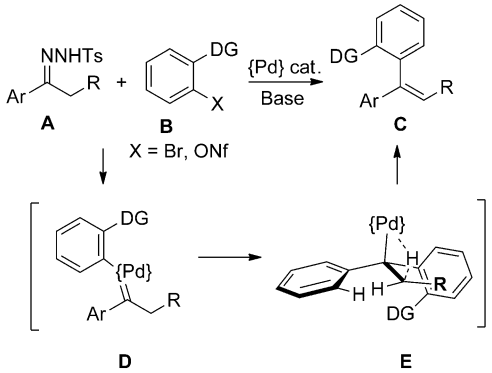
In recent years, the chemistry of tosylhydrazones has gained increasing attention as a result of the development of new metal-catalyzed and metal-free cross-coupling reactions.[1] In particular, the Pd-catalyzed cross-coupling of tosylhydrazones and organic halides represents a very efficient method to transform a carbonyl compound into the nucleophilic component of a C–C bond forming cross-coupling reaction.[2] Currently, this transformation can be regarded as a powerful method for the synthesis of polysubstituted olefins. Moreover, these reactions have been applied in the synthesis of heterocycles through one-pot and auto-tandem Pd-catalyzed cascades.[3,4]

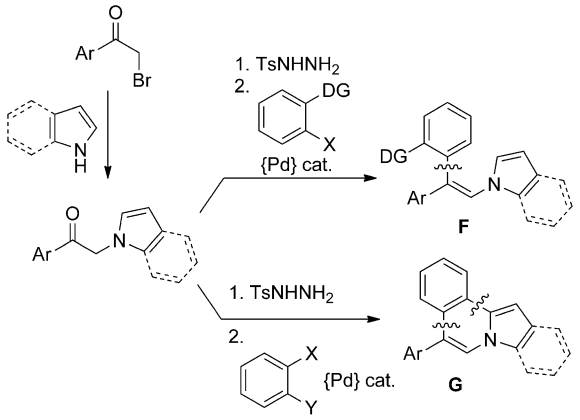
One particular feature of this Pd-catalyzed coupling reaction is the stereoselective formation of *Z*-trisubstituted olefins if *ortho*-substituted aromatic halides or sulfonates are employed (Scheme 1).[5] Thus, in the synthesis of trisubstituted 1,1-diarylolefins **C** from hydrazones derived from α-substituted acetophenones **A** and *ortho*-substituted aromatic electrophiles **B**, the substituent at C2 in **C** is placed *cis* relative to the *ortho*-substituted aryl group, and therefore, the *ortho* substituent can be regarded as a stereodirecting group.



Scheme 1. Synthesis of *Z*-trisubstituted olefins by *ortho*-directed Pd-catalyzed cross-coupling reactions (Ts = tosyl; DG = directing group).

The *Z* stereoselectivity can be explained by the mechanism proposed for the coupling process.[2a] Thus, after formation of Pd–carbene **D**, migratory insertion gives alkylpalladium complex **E**. Next, *syn*-β-hydride elimination provides the final olefin. The last step defines the stereochemistry of the final product. With the aid of DFT computations, it has been determined that, to avoid steric interactions, the optimal arrangement for the transition state of the *syn*-β-hydride elimination places the R substituent on the same side of the incipient double bond as the *ortho*-substituted arene.[5a]

The stereoselective synthesis of trisubstituted olefins is a highly interesting and challenging task that usually requires stepwise processes to introduce the different substituents in a sequential manner.[6] Unlike most methodologies, in the *ortho*-directed cross-coupling reaction with tosylhydrazones, no previous stereochemical restrictions are required for the stereoselective synthesis of the alkenes. Therefore, we envisioned that this methodology might be useful for the preparation of functionalized trisubstituted olefins not easily available through conventional methods. In particular, we focused on 1,1-diaryl-2-*N*-azoleethylenes **F** (Scheme 2), a



Scheme 2. Stereoselective synthesis of *N*-alkenylazoles and auto-tandem C–C/C–C reactions reported in this paper.

particularly appealing class of alkenes that might find interesting applications in medicinal chemistry,[7] agrochemistry,[8] and materials science.[9] The synthesis of *N*-alkenylazoles has generally been accomplished by reaction of the corresponding N–H-free azoles with alkynes[10] or carbonyl com-

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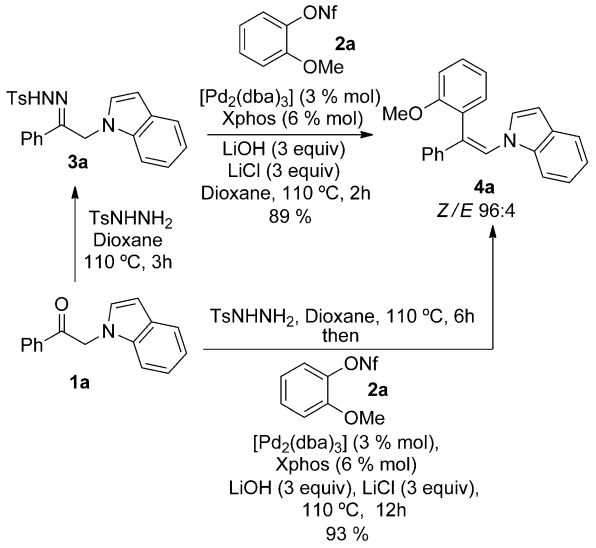
pounds,[11] under harsh conditions and without stereochemical control, or by Pd-catalyzed cross-couplings with vinyl bromides or triflates.[12] Furthermore, the introduction of a potentially reactive *ortho*-stereodirecting group might allow for additional transformations to occur in a cascade. In particular, and continuing with our interest in auto-tandem-catalyzed processes,[13,14] we wanted to explore the combination of tosylhydrazone cross-coupling with an intramolecular C–H arylation reaction that might lead to complex pyrroloisoquinoline derivatives **G** in a simple manner (Scheme 2). Herein, we wish to report our initial progress towards these goals.

In a preliminary experiment, we studied the coupling reaction between tosylhydrazone **3a**, obtained from α-*N*-indoleacetophenone **1a**, with *ortho*-methoxybenzene nonaflate (**2a**; Scheme 3). After some experimentation, we found that,



Scheme 3. Cross-coupling between tosylhydrazone **3a** and nonaflate **2a** and the one-pot reaction from **1a**.

under reaction conditions similar to those previously reported for the coupling of other classes of tosylhydrazone with aryl nonaflates,[4,5a] the trisubstituted alkene **4a** could be obtained in high yield. As expected, the *Z* isomer was obtained as the major isomer in very high stereoselectivity. Moreover, the reaction could be carried out directly from carbonyl compound **1a**, without isolation of tosylhydrazone **3a**. Thus, (*Z*)-*N*-alkenyl azole **4a** was obtained in high yield and very high stereoselectivity by stirring a solution of ketone **1a** (1.5 equiv) and tosylhydrazide (1.65 equiv) in dioxane at 110 °C for 6 h and then adding nonaflate **2a** (1 equiv) and all components for the coupling reaction ([$Pd_2(dba)_3$] (3 % mol) as metal source, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos; 6 % mol) as ligand, LiOH as base (3 equiv), and LiCl (3 equiv) and stirring for a further 12 h at 110 °C.

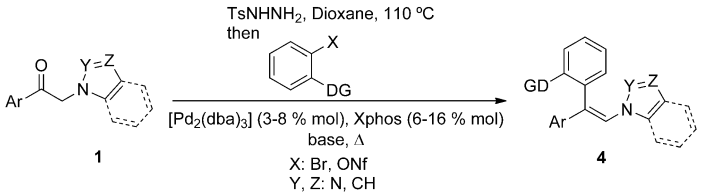
These reaction conditions were applied to a set of *ortho*-substituted aryl nonaflates (**2**) and α-*N*-azoleacetophenones (**1**) to provide the corresponding *N*-alkenylazoles (**4**) with high yields and *Z* stereoselectivities (Table 1, entries 1–9). The reaction has been tested with a variety of azoles, including indoles, pyrroles, and imidazoles. With regard to the directing *ortho* substituent, alkyl, alkoxy, and chlorine substituents were able to drive the reaction to form the *Z* isomer, although a drop in selectivity was observed for an *ortho*-cyano substituent (Table 1, entry 6). The reaction in the presence of a chlorine substituent is noteworthy (Table 1, entry 2) because it may enable further modification of the stereodirecting substituent. As expected, further diversity can be incorporated by the use of acetophenones with substituents on the aryl group (Table 1, entries 7 and 9).

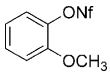
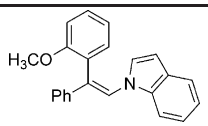
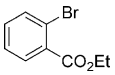
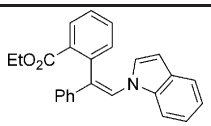
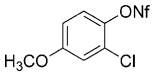
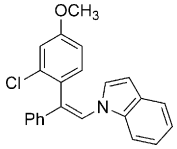
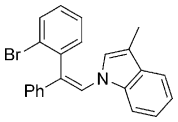
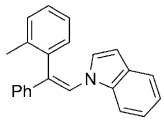
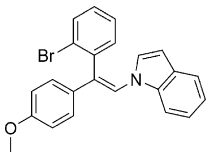
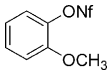
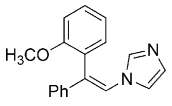
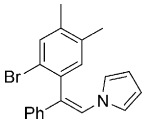
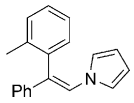
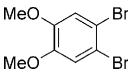
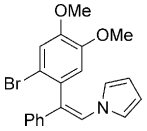
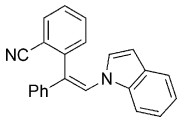
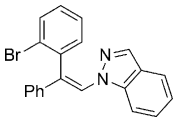
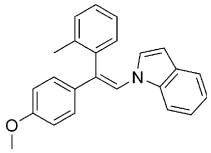
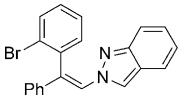
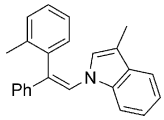
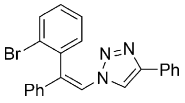
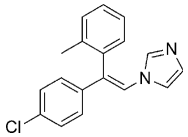
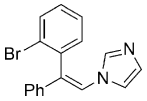
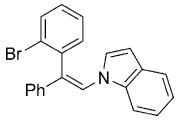
The cross-coupling reaction was then studied with aryl bromides **5** instead of nonaflates (**2**). After some experimentation, we found that for these systems the coupling product could be obtained by employing the same {Pd}/Xphos catalytic system, but with LiO*t*Bu as the base and without an additional additive. In this manner, and again in a one-pot process from the carbonyl compounds, *N*-alkenylazoles **4** were obtained in very high *Z* stereoselectivities and good yields in most cases. It is noteworthy that both *ortho*-chloro and *ortho*-bromo substituents are compatible with the coupling reaction, allowing for further modifications of the directing group. To test the functional group tolerance of the reaction, the coupling process was conducted with ethyl *ortho*-bromobenzoate, leading to the corresponding alkene in good yield and stereoselectivity (Table 1, entry 12). Again, the reaction is compatible with a variety of azoles, including indoles, pyrroles, imidazoles, indazoles, and triazoles (Table 1, entries 10–21). Notably, the use of 2-bromo-3-chlorothiophene as a coupling partner also led to the corresponding trisubstituted alkene (Table 1, entry 22), widening the scope of the method to include heterocyclic derivatives.

As a result of the *Z* stereoselectivity of the coupling reaction, the systems that feature a halogen substituent as the directing group are properly preorganized to participate in a Pd-catalyzed intramolecular cyclization through a C–H arylation reaction of the heterocyclic nucleus[15,16] (Scheme 2). Thus, we set out to investigate this transformation in order to develop a new auto-tandem-catalyzed process. It is worth noting that auto-tandem Pd-catalyzed reactions involving tosylhydrazones have previously been included in C–C/C–N cascades,[3,17] but not in the more challenging C–C/C–C auto-tandem processes.[18] Furthermore, this cascade process would lead to pyrrolo[2,1-*a*]isoquinoline derivatives, a heterocyclic fragment that is present in a number of natural products with biological activity.

Our initial experiments were conducted with **4b**, the indole derivative featuring a chlorine atom in the *ortho* position. However, this molecule turned out to be extremely unreactive, and the starting material was recovered unaltered when treated under several different reaction conditions typical for C–H arylation reactions.[16] Therefore, we turned our attention to the more reactive bromo-substituted deriva-

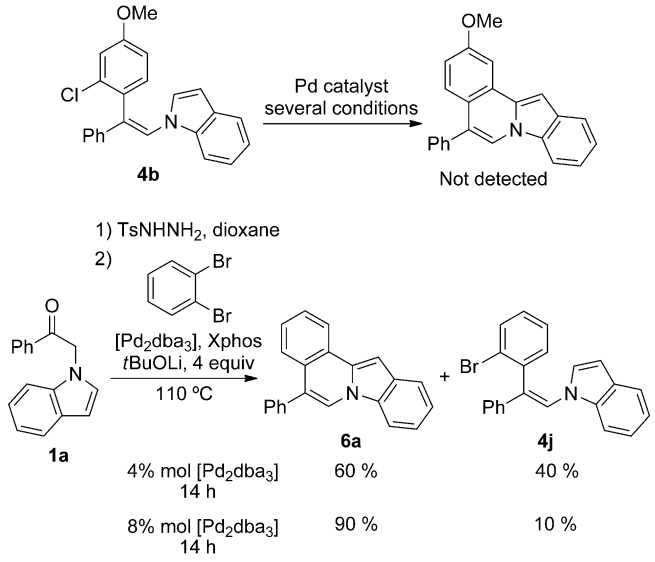
Table 1. Stereoselective synthesis of (*Z*)-*N*-alkenylazoles.[a]



Entry	Electrophile **2**, **5**	Alkene **4**		*Z*/*E*	Yield [%][b]	Entry	Electrophile **2**, **5**	Alkene **4**		*Z*/*E*	Yield [%][b]
1			**4a**	96:4	93	12			**4l**	84:16	76
2			**4b**	85:15	98	13			**4m**	91:9	67
3			**4c**	85:15	82	14			**4n**	95:5	51
4[c]			**4d**	94:6	84	15			**4o**	98:2	65
5			**4e**	90:10	97	16			**4p**	98:2	79
6			**4f**	70:30	70	17			**4q**	100:0	87
7			**4g**	88:12	82	18			**4r**	100:0	95
8			**4h**	85:15	76	19			**4s**	80:20	55
9[c]			**4i**	100:0	57	20[d]			**4t**	100:0	46
10			**4j**	98:2	74	21[d]			**4u**	100:0	58
11			**4k**	96:4	85	22			**4v**	100:0	55

[a] See the Supporting Information for experimental details. [b] Yields after column chromatography. [c] Carried out from the preformed tosylhydrazone. [d] Carried out from the preformed tosylhydrazone under microwave heating at 150 °C.

tives. In this case, preliminary experiments starting from carbonyl **1a**, tosylhydrazide, and 1,2-dibromobenzene, under reaction conditions similar to those employed in Table 1, but with an excess of the base, led to the formation of substantial amounts of cyclization product **6a**, together with coupling product **4j**, and therefore showed the feasibility of the C–C/C–C auto-tandem process (Scheme 4).



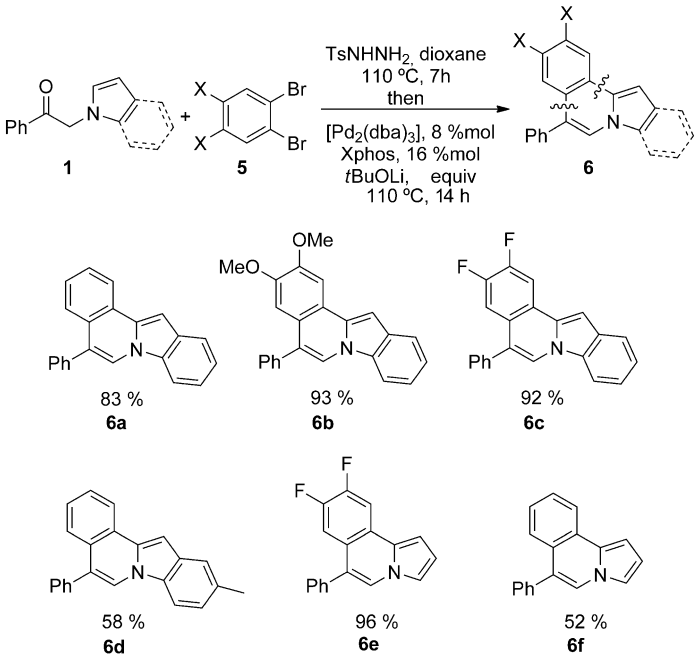
Scheme 4. Preliminary experiments on the Pd-catalyzed C–C/C–C auto-tandem process.

Encouraged by these observations, optimization of the auto-tandem-catalyzed process was conducted. After a set of experiments, it was found that to achieve the C–C/C–C cascade process with high conversion it was necessary to increase the catalyst loading and reaction time. Under the optimized reaction conditions, indoloisoquinoline **6a** was isolated in high yield.

This methodology could be applied to the synthesis of a set of polyheterocyclic compounds featuring the pyrroloisoquinoline scaffold (Scheme 5). The sequence was carried out in a one-pot fashion in all cases, leading directly to the polycyclic structures **6** from the carbonyl compounds. The auto-tandem reaction was conducted with *N*-indole and *N*-pyrrole α-substituted acetophenones, leading to the corresponding indolo- and pyrrolo[2,1-*a*]isoquinoline derivatives, respectively, in yields ranging from excellent to moderate.[19,20,21]

It is worth noting that the pyrrolo[2,1-*a*]isoquinoline substructure is present in lamellarins, a class of marine natural products with useful biological properties such as antitumor and anti-HIV activities.[22] Taking into consideration that the starting ketones **1** are readily prepared from the corresponding N–H azoles and bromoketones, this methodology may represent a highly modular approach for the preparation of this class of heterocycles.

In conclusion, we have presented a new method for the stereoselective synthesis of (*Z*)-*N*-alkenylazoles, taking advantage of the *ortho*-stereodirecting effect in the cross-coupling reaction. The process is quite general, allowing for the participation of any azole ring, and opening the door to the preparation of unprecedented molecules featuring these privileged heterocyclic structures. Moreover, the preorganization of the trisubstituted alkene products has permitted the development of a novel C–C/C–C auto-tandem process, giving rise to new compounds featuring the biologically relevant pyrrolo[2,1-*a*]isoquinoline substructure.



Scheme 5. Indolo- and pyrrolo[2,1-*a*]isoquinolines **6** prepared through the Pd-catalyzed tosylhydrazone coupling/C–H arylation auto-tandem process.

Acknowledgements

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Keywords: auto-tandem catalysis · azoles · cross-coupling · domino reactions · palladium · tosylhydrazones

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