Isocyanides' Latest Trick:

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Summary

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Palladium-Catalyzed Imidoylative Cross-Coupling Reactions

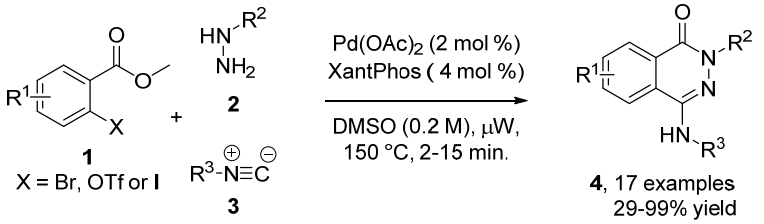
Chemical synthesis is an advanced science capable of synthesizing most of the complex compounds found in nature by a linear total synthesis. The main challenge for the future therefore lies in producing these complex molecules in a more efficient and economical manner, which will enable the use of more sophisticated compounds in industry and academia. In this respect especially step economy is an important factor, since accessibility highly depends on the amount of steps required to reach the desired compounds. In addition, reducing the number of synthetic steps towards valuable fine chemicals also reduces the amount of solvents and energy required and thus helps save the environment. Cascade reactions are important tools to meet these challenges synthetic chemists are currently facing. Cascade reactions are sequences of transformations where the product of the first step serves as the substrate for the second step, whose product is again the substrate for the next step and so on. This process is repeated until a product stable under the reaction conditions is formed. The intrinsic advantage of such cascade reactions is the step economy, since multiple bond formations are combined in one pot.

Palladium is a versatile transition metal showing useful reactivity with various functional groups. Consequently, the various Pd-catalyzed cross-couplings nowadays are essential tools for the construction of carbon-carbon bonds. The significance of palladium catalysis and the cross-couplings in particular has recently been illustrated by the Nobel Prize for Chemistry in 2010, which was awarded to Heck, Negishi and Suzuki for the development of their Pd-catalyzed cross-coupling reactions.

The chemistry of palladium is generally quite well understood and versatile, which means there is a huge potential for Pd-catalyzed cascade reactions. Chemists have exploited this potential and many interesting Pd-catalyzed cascade reactions have been reported (**Chapter 1**). We became interested in using isocyanides as C_1

building blocks in palladium catalysis and have developed several new transformations based on the insertion of isocyanides between two coupling fragments. In the timeframe of our studies this topic has received increasing attention and many other groups have started using isocyanides in palladium catalysis (**Chapter 2**).

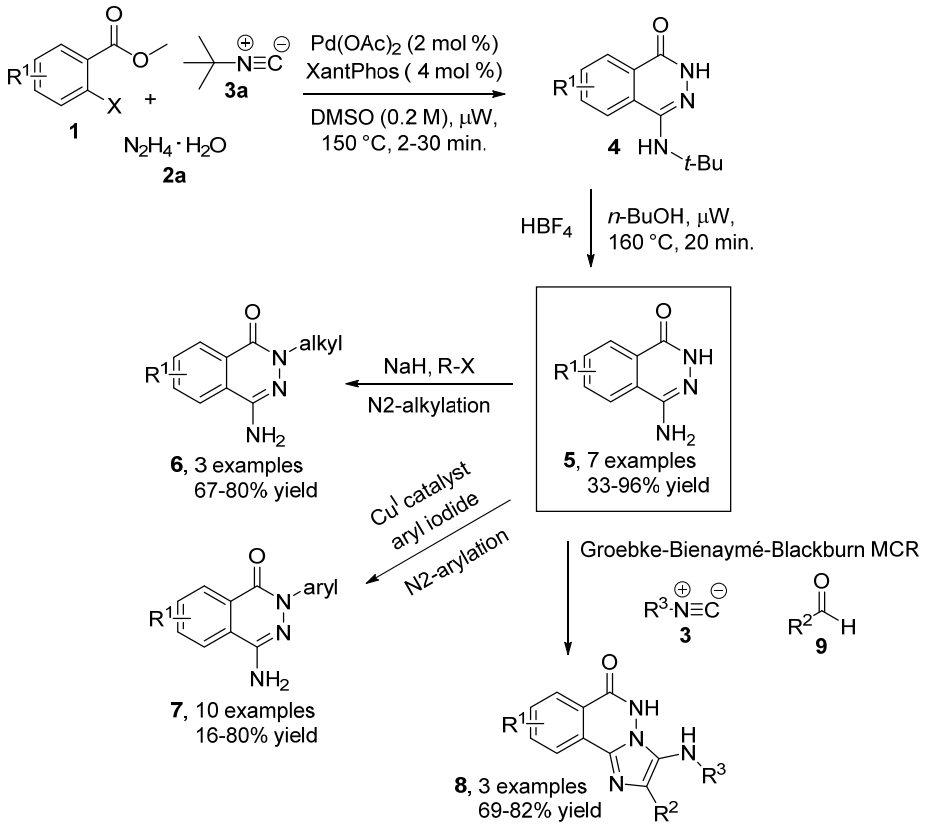
The most common type of reaction in this field involves amidination of aryl halides by imidoylative cross-coupling with amines, but in 2011 only a few examples had been reported. We envisioned a useful application of this chemistry in the synthesis of heterocycles by combining the amidination event with a cyclization step in a cascade fashion. **Chapter 3** describes how we realized this concept by using hydrazines, which are difficult coupling patterns, as amine inputs in amidination reactions of 2-(pseudo)halobenzoates (Scheme 1). The cyclization event occurs in a cascade fashion by lactamization and furnishes 4-aminophthalazin-1(2*H*)-ones (APOs, **4**) in a single reaction step in just five minutes. APOs are valuable in medicinal chemistry where they are studied, *e.g.*, for their potential in the treatment of cancer. The classical synthesis of APOs is a lengthy three to five step sequence. Our approach is not only faster it also allows, for the first time, non-symmetric substitution of the phenyl ring ($R^1 \neq H$). The traditional chemistry used to obtain APOs unavoidably leads to regioisomers, severely hampering the yield and simplicity of the synthesis. Our method should therefore prove highly useful in the future by allowing more efficient and diverse structure-activity relationship (SAR) studies.



Scheme 1. Pd-catalyzed imidoylative cascade towards APOs.

There are limitations to our cascade synthesis of APOs, as is the case in most synthetic strategies. Although the benzoate (**1**) can be varied extensively, only tertiary aliphatic isocyanides (**3**) can be used and monosubstituted hydrazines (**2**) are poorly available and could not be varied to the desired degree. We were able to overcome these limitations by developing a semi one-pot removal of the *tert*-butyl group derived from the isocyanide (**Chapter 4**, Scheme 2). This sequence requires a solvent switch, but no purification is necessary after the Pd-catalyzed reaction. The products that are obtained (**5**) contain two different nucleophilic positions, but are readily alkylated or

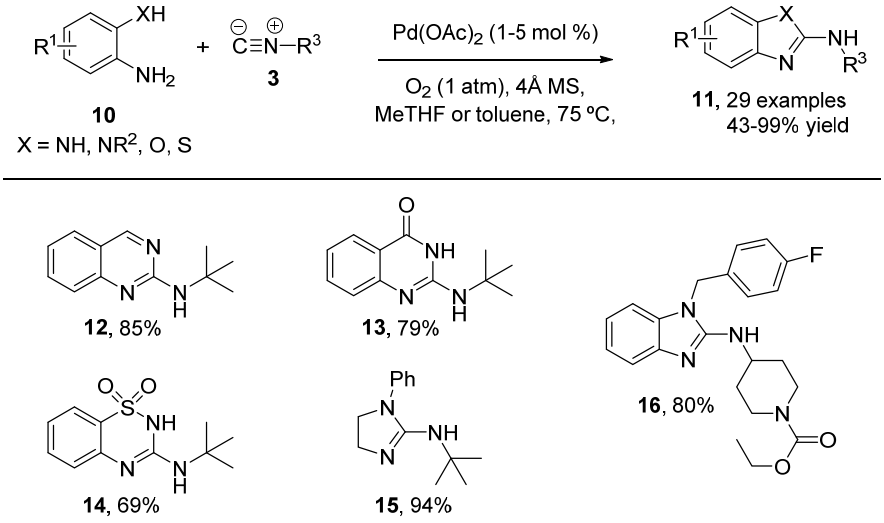
arylated at the more acidic N2-position. In this way, a two step synthesis leads to highly functionalized APOs containing a free 4-amino group (**6** and **7**) that can be derivatized as desired. To demonstrate the power of multicomponent reactions we also showed that **5** can be used in the complexity-generating Groebke-Bienaymé-Blackburn reaction to afford unexplored tricyclic products (**8**) in just two steps from commercial compounds.



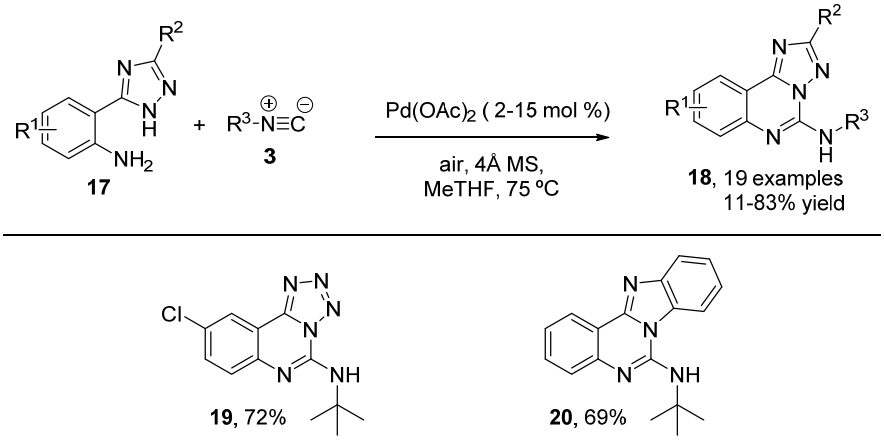
Scheme 2. Follow-up chemistry on the APO scaffold.

The guanidine motif is present in various scaffolds that are frequently found in pharmaceuticals and exhibit a wide range of therapeutic applications. The prevalent synthesis of this type of products has significant drawbacks, such as the availability or toxicity of reagents, and narrow substrate scope and/or product range. Moreover, these procedures suffer from poor atom and/or step efficiency, making them unattractive from a sustainability point of view. In **Chapter 5** a new approach towards guanidine-containing heterocycles, based on Pd-catalyzed isocyanide insertion, is

outlined. A wide range of bisnucleophiles (**10**) are oxidatively coupled with isocyanides in the presence of a simple Pd^{II} catalyst (Scheme 3). Most notably, the conditions are highly sustainable owing to the low catalyst loading, renewable solvent and absence of base. Molecular oxygen, the most abundant and sustainable oxidant available, is used as stoichiometric oxidant and only water is produced as a byproduct. The utility of this method was shown by the synthesis of **16**, which is a known precursor for the antihistamines norastemizole and astemizole.



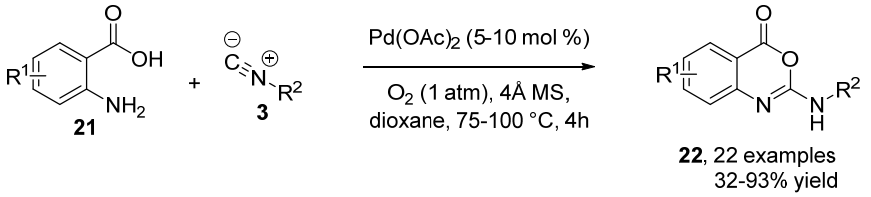
Scheme 3. Aerobic oxidative coupling of bisnucleophiles and isocyanides.



Scheme 4. Azoles as nucleophile in the oxidative coupling of bisnucleophiles and isocyanides.

It is possible to use an azole as one of the nucleophiles in the aerobic oxidative coupling of bisnucleophiles and isocyanides, as is described in **Chapter 6**. The use of azoles as substrates affords valuable azolo[*c*]quinazolines (Scheme 4), which have shown potential in the treatment of Parkinson's disease. An atmosphere of molecular oxygen is not required for this substrate class; a simple air atmosphere provides slightly better results and a much more convenient procedure. The high number of heteroatoms in the products is challenging for this chemistry because it offers several unproductive coordination sites for Pd^{II}. The relative ease with which the aerobic oxidative guanidine synthesis could be applied to these difficult substrates is indicative of the broad utility of this chemistry.

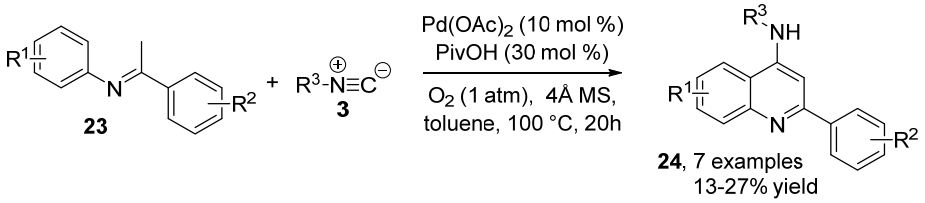
In **Chapter 7** we show that anthranilic acids (**21**) can also be coupled with isocyanides under aerobic oxidative Pd^{II} catalysis (Scheme 5). The resulting 2-aminobenzoxazinones (**22**) are valuable for medicinal chemistry purposes and our synthesis has advantages over other methodologies. It is, however, also another particularly challenging expansion of our guanidine synthesis due to the sensitivity of the benzoxazinone products to nucleophilic attack and the tendency of benzoic acids to undergo decarboxylative processes in the presence of Pd^{II}. In addition, benzoic acid derivatives may undergo Pd-catalyzed decarbonylative coupling with isocyanides at temperatures as low as 70 °C. Moreover, isocyanides have also been reported to react with anthranilic acids to produce 4-quinazolinones. The extension of our oxidative coupling of bisnucleophiles and isocyanides to such a challenging substrate class further illustrate the general applicability of this chemistry.



Scheme 5. Aerobic oxidative synthesis of 2-aminobenzoxazinones.

Chapter 8 describes our efforts to develop an imidoylative double C-H activation cascade reaction that provides products containing an imine/enamine moiety in a highly atom-economical manner. Only a few Pd-catalyzed isocyanide insertion reactions toward this structural motif are known, of which none is based on a double C-H activation cascade. We have realized this type of transformation by converting tautomerizable *N*-arylimines (**23**), that are readily activated at the α-position, to 4-aminoquinolines (**24**, Scheme 6). Unfortunately, the yields were low and

full conversion was not reached, indicating the catalyst is deactivated. Extensive optimization did not improve the catalytic efficiency, but nevertheless a proof-of-concept for the proposed imidoylative double C-H activation cascade is provided.



Scheme 6. Pd-catalyzed imidoylative double C-H activation cascade.

In summary, the results described in this thesis show that isocyanides are highly versatile and useful C_1 building blocks in palladium catalysis. The recent surge of interest in this field will undoubtedly lead to further developments and applications of this chemistry. We have contributed to the advancement of imidoylative palladium catalysis by the synthesis of various important heterocycles, demonstrating the potential for medicinal chemistry purposes, and the discovery of the first oxidative coupling of bisnucleophiles with isocyanides.