Synthetic Methods

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Palladium-Catalyzed Coupling of Aldehyde-Derived Hydrazones: Practical Synthesis of Triazolopyridines and Related Heterocycles**

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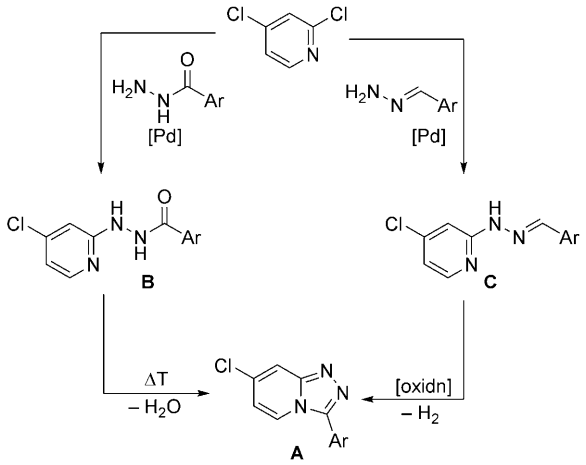
In memory of Keith Fagnou

Triazolopyridines constitute an important class of heteroaromatic compounds. The [1,2,4]triazolo[4,3-*a*]pyridine moiety[1] can be found in a variety of biologically active compounds, including antibacterial, antithrombotic, antiinflammatory, antiproliferative, and herbicidal agents.[2] To access this class of compounds we became interested in the palladium-catalyzed coupling reactions of 2-chloropyridines with hydrazine derivatives and we recently reported the use of hydrazides as nucleophiles in palladium-catalyzed reactions.[3] Herein, we describe the use of aldehyde hydrazones for the efficient synthesis of triazolopyridines and related heterocycles.

Buchwald and co-workers have reported the palladium-catalyzed reaction of benzophenone hydrazone with aryl halides for the synthesis of indoles,[4a,b] and *N-tert*-butylhydrazones that are derived from aryl aldehydes were reported to undergo intermolecular palladium-catalyzed C–C-coupling as acyl-anion equivalents to afford diarylketones.[5] However, to the best of our knowledge, the use of aldehyde-derived un-substituted hydrazones in palladium-catalyzed intermolecular C–N coupling reactions has not previously been reported.[6]

Our initial targets were 7-chloro-3-aryl-1,2,4-triazolo[4,3-a]pyridines **A**, which can serve as useful templates for the rapid generation of analogues, because the chloro group offers the possibility of introducing further substituents through additional palladium-catalyzed coupling reactions. We sought to prepare these compounds in a highly efficient fashion starting from 2,4-dichloropyridine as a cheap precursor. Palladium-catalyzed reactions on this substrate have been shown to occur selectively at the 2-position,[7] whilst thermal substitution reactions slightly favor displacement at the 4-position.[8] We recently reported the reactions of chloropyridines with benzoic hydrazide but, owing to competing side-reactions, only mediocre yields (30–50%) of the desired coupling product were obtained with 2,4-dichloropyridine.[3] As oxidative approaches to triazoles are known,[1,9] the intermediate **C** seemed to be a suitable candidate to explore this synthetic approach (Scheme 1). Attempts to access this intermediate by introduction of the hydrazine through palladium-catalyzed coupling with benzophenone hydrazone, followed by benzophenone hydrolysis and condensation with benzaldehyde, failed at the benzophenone-deprotection step. To succeed with this approach, the previously unreported coupling of aldehyde-derived hydrazones had to be developed.



Scheme 1. Different approaches to triazolopyridine **A**.

In the initial screen of reaction conditions, the commercially available benzophenone hydrazone was selected as a coupling partner. Based on the previously established superiority of bidentate ligands for the coupling of benzophenone hydrazone with aryl halides[4] or chloropyridines,[10] the dppf (1,1′-bis(diphenylphosphino)ferrocene) ligand was deemed a suitable entry point; indeed, this ligand afforded the desired 2-functionalized products in good yields. The undesired bis(addition) of the nucleophile was significantly less-pronounced with K_2CO_3, as compared to Na_2CO_3 or Cs_2CO_3. Importantly, the conditions could be applied with our C–N coupling partners, aldehyde-derived hydrazones, with equal success (Scheme 2). Furthermore, the only coupling product that was detected resulted from substitution at the 2-position of 2,4-dichloropyridine.[11] The low solubility of the products allowed for direct isolation by crystallization. Gratifyingly, the

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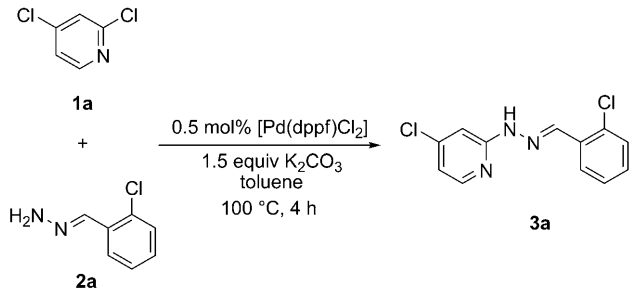
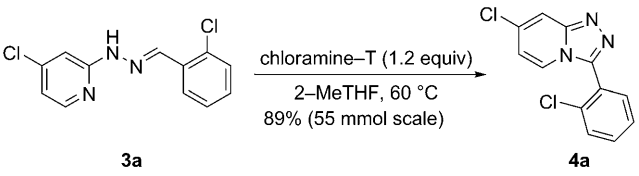


Scheme 2. Optimized conditions for the palladium-catalyzed coupling reaction.

reaction was robust, and the products were isolated in excellent yields on large laboratory scale (86% on 54 g scale).

With suitable conditions for the palladium-catalyzed coupling reaction in hand, our focus shifted to identifying mild conditions for the oxidative cyclization. Previously iodobenzene diacetate,[9a] copper(II) chloride,[9b] bromine,[9c,d] lead(IV) acetate,[9d] and chloramine-T[9e] have been utilized for this transformation. Most of these reagents suffer from the formation of large amounts of toxic by-products, which can impact product isolation and have a negative environmental impact. In our hands, chloramine-T afforded rapid conversions (< 2 h) and high yields (> 85%) in most solvents (ethanol, tetrahydrofuran, and ethyl acetate). The reaction work-up was initially complicated by the need to remove the stoichiometric toluenesulfonamide by-product. This issue was overcome by utilizing 2-methyltetrahydrofuran as a reaction solvent. Taking advantage of the immiscibility of this solvent with water, a basic-aqueous workup was used to remove the toluenesulfonamide. Thereafter, the product could be isolated by simple crystallization on addition of heptane. Significantly, no decrease in the yield of isolated product was observed when the reaction was performed on a 15 g scale (Scheme 3).

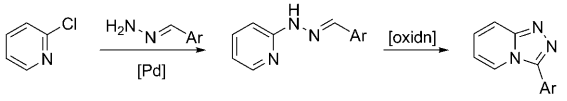


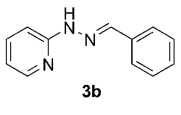
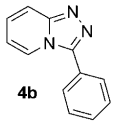
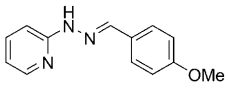
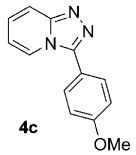
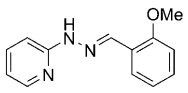
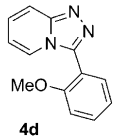
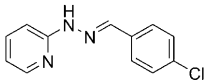
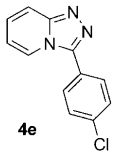
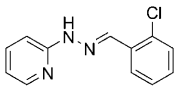
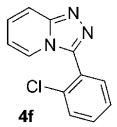
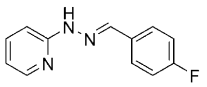
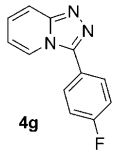
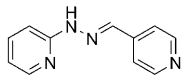
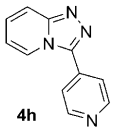
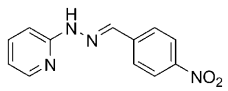
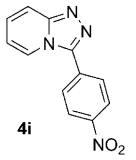
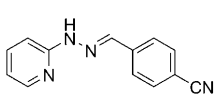
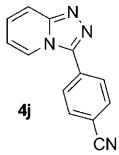
Scheme 3. Optimization of the oxidative cyclization reaction.

These optimized conditions could be applied to a wide variety of chloropyridines. Various substituted benzaldehyde-derived hydrazones were competent nucleophiles in the coupling reactions with 2-chloropyridines. The palladium-catalyzed coupling and oxidative cyclization reactions tolerated electron-donating (Table 1, entries 2 and 3), and electron-withdrawing substituents (Table 1, entries 7–9). Additional halogenation in the form of a chloro or fluoro substituent on the nucleophile did not interfere with the reaction (Table 1, entries 4–6).

The reaction sequence also had a broad scope with regards to the electrophile. 2,3-Dichloropyridine (Table 2, entry 1), 2,4-dichloropyridine (Table 2, entries 2–4), and 2,5-dichloropyridine (Table 2, entry 5) were all competent cou-

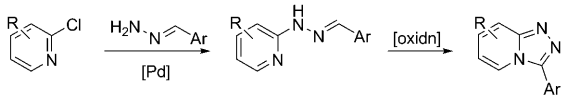
Table 1: Scope of the coupling and cyclization reaction with 2-chloropyridines.[a]

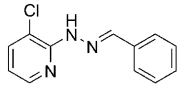
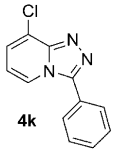
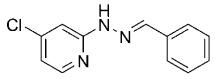
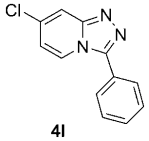
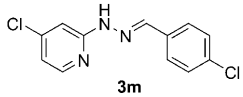
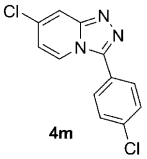
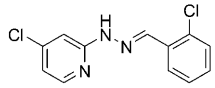
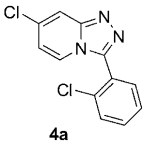
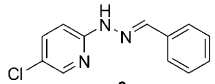
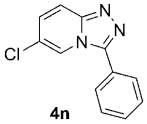
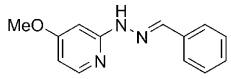
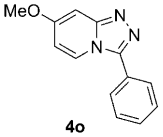


Entry	Coupling product	Yield [%][b]	Cyclization product	Yield [%][c]
1	 **3b**	47(81) 89(97)[d]	 **4b**	91
2	 **3c**	67(77)	 **4c**	82
3	 **3d**	69(74)	 **4d**	87
4	 **3e**	85(92)	 **4e**	83
5	 **3f**	77(79)	 **4f**	90
6	 **3g**	64(81)	 **4g**	88
7	 **3h**	64(77)	 **4h**	84
8	 **3i**	84(94)	 **4i**	75
9	 **3j**	94(95)	 **4j**	89

[a] General reaction conditions: [Pd] = 0.5 mol% [Pd(dppf)Cl_2], K_2CO_3, toluene, 100°C; [oxidn] = chloramine-T, 2-Me-THF, 60°C. [b] Yield of isolated product. Assay yield, determined by HPLC, given in brackets. [c] Yield of isolated product. [d] Reaction in DME at 80°C. THF = tetrahydrofuran, DME = 1,2-dimethoxyethane.

Table 2: Scope of the coupling and cyclization reaction with disubstituted 2-chloropyridines.[a]



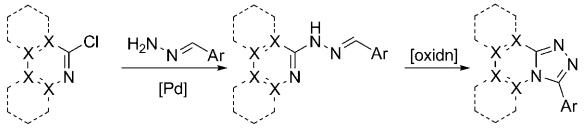
Entry	Coupling product	Yield [%][b]	Cyclization product	Yield [%][c]
1	 **3k**	42(71)	 **4k**	95
2	 **3l**	73(84)	 **4l**	81
3	 **3m**	78(86)	 **4m**	80
4	 **3a**	86	 **4a**	89
5	 **3n**	58(65)	 **4n**	93
6	 **3o**	57(64)	 **4o**	95

[a] For general reaction conditions, see Table 1. [b] Yield of isolated product. Assay yield, determined by HPLC, given in brackets. [c] Yield of isolated product.

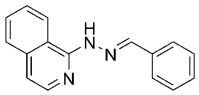
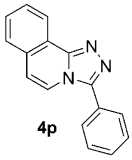
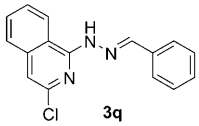
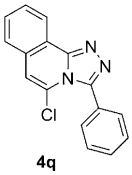
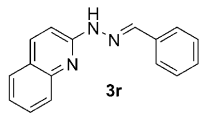
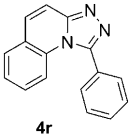
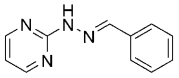
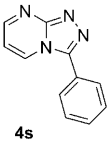
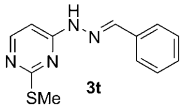
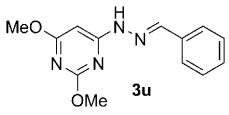
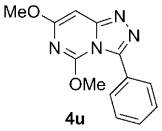
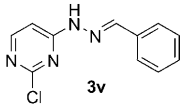
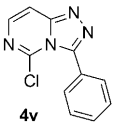
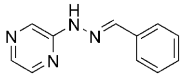
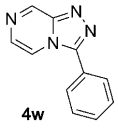
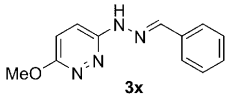
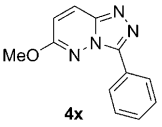
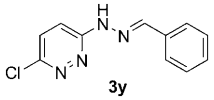
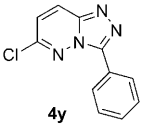
pling partners. Such scope is particularly useful as the products provide versatile scaffolds that have the potential to be utilized in subsequent palladium-catalyzed coupling reactions with more-active catalysts. 2-Chloro-4-methoxypyridine also performs well in the reaction (Table 2, entry 6).

Having established a robust synthesis of a diverse array of [1,2,4]triazolo[4,3-*a*] pyridines, we sought to explore if the approach could be extended to the synthesis of even more-complex heterocyclic scaffolds. Annulation on the pyridine core was not an impediment for the synthesis; both 1-chloroisoquinoline and 2-chloroquinoline performed well in the palladium-catalyzed coupling reaction to afford tricylic scaffolds after cyclization (Table 3, entries 1 and 3). The reaction with 1,3-dichloroisoquinoline proceeds selectively at the 1-position (Table 3, entry 2). Bicyclic heterocycles with four nitrogen atoms are particularly attractive in the development of biologically active compounds; representative exam-

Table 3: Scope of the coupling and cyclization reaction with other chloro-substituted nitrogen heterocycles.[a]



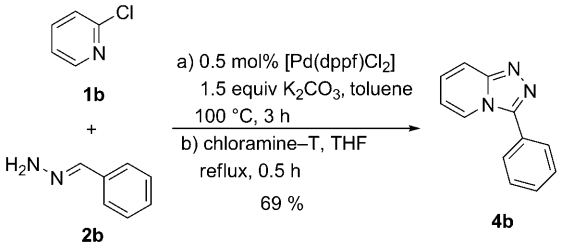
X = CH or N

Entry	Coupling product	Yield [%][b]	Cyclization product	Yield [%][c]
1	 **3p**	70(84)	 **4p**	59
2	 **3q**	81(91)	 **4q**	69
3	 **3r**	20(92)	 **4r**	92
4	 **3s**	63(71)	 **4s**	99
5	 **3t**	73(78)	 **4t**	91
6	 **3u**	90(95)	 **4u**	79
7	 **3v**	58(80)	 **4v**	77
8	 **3w**	87(91)	 **4w**	75
9	 **3x**	35	 **4x**	84
10	 **3y**	79(81)	 **4y**	82

[a] For general reaction conditions, see Table 1. [b] Yield of isolated product. Assay yield, determined by HPLC, given in brackets. [c] Yield of isolated product.

ples of their use include [1,2,4]triazolo[4,3-a]pyrimidines,[12a,b,c] [1,2,4]triazolo[4,3-c]pyrimidines,[12d] [1,2,4]triazolo[4,3-a]pyrazines,[12e] and [1,2,4]triazolo[4,3-b]pyridazines.[12b,f] The great versatility of our methodology is demonstrated by the fact that all these heterocyclic systems are available through the same two-step palladium-catalyzed-coupling/oxidative-cyclization sequence (Table 3, entries 4–10). The mildness of these reaction conditions in the oxidative cyclization is evidenced by the selective formation of the parent heterocycles, without evidence of the formation of Dimroth-type rearrangement products.[13]

Whilst the reaction sequence, including isolation of the intermediate addition product, is highly efficient as a two-step procedure, it can also be performed as a one-pot procedure. After performing the coupling under the standard conditions, the cyclization can be performed with tetrahydrofuran as a co-solvent, thus affording the product in 69% overall yield (Scheme 4).



Scheme 4. One-pot synthesis of triazolopyridine **4b**.

In conclusion, we have discovered a mild and selective palladium-catalyzed intermolecular coupling of aldehyde-derived hydrazones with chloro-substituted heterocycles. The coupled products undergo a clean oxidative cyclization to afford triazolopyridines and other related heterocycles. This novel reaction has a broad substrate scope and a large variety of six-membered heterocycles with different substituents were tolerated as reaction partners. This reaction is readily scalable and can be conducted as a one-pot process if desired. Based on the large number of commercially available α-chloroazines, this straightforward two-step reaction allows access to a broad variety of scaffolds that constitute useful templates in drug discovery.

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