Domino Reactions

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Palladium-Catalyzed Annulation of Acyloximes with Arynes (or Alkynes): Synthesis of Phenanthridines and Isoquinolines**

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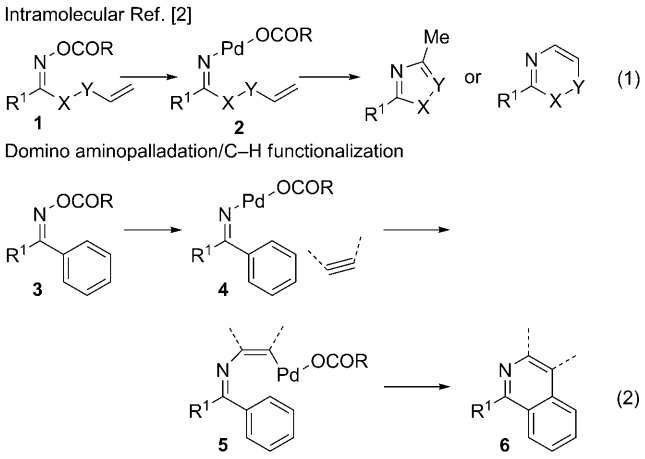
Palladium-catalyzed carbon–heteroatom bond formation has been the subject of intense research for the past decades.[1] Kitamura and Narasaka have developed an elegant palladium-catalyzed carbon–nitrogen bond-forming process by exploring the chemistry of readily accessible acyloximes.[2] In contrast to other palladium-catalyzed reactions where the nitrogen atom of C=N-containing substrates[3] acted as a nucleophile, the acyloximes act firstly as an electrophile to add oxidatively to the Pd^0 complex. The newly generated azapalladium(II) complex could then react with internal olefins to form cyclic product [Scheme 1, Eq. (1)].[4] This novel



Scheme 1. Palladium-catalyzed transformation of acyloximes.

palladium-catalyzed intramolecular amino-Heck process allows rapid elaboration of pyrroles,[5] pyridines,[6] and various aza-heterocycles.[7] This process has recently been used in a total synthesis of cycloheptylprodigiosin.[8] However, to the best of our knowledge, this chemistry has been limited to intramolecular processes and no report on the intermolecular trapping of a $\{R^1R^2C{=}N{-}Pd\}$ species by carbon–carbon multiple bonds was known.[9] In connection with our research program dealing with the transition-metal-catalyzed C–X bond formation[10] and domino processes,[11] we became interested in exploring the reactivity of the transient $\{R^1R^2C{=}N{-}Pd\}$ species in an intermolecular process.[12] We report herein the first example of such a process which leads to a rapid construction of functionalized phenanthridines and isoquinolines by a domino aminopalladation/C–H functionalization sequence.[13] The underlying principle is shown in Scheme 1 [Eq. (2)]. The intermolecular aminopalladation of benzynes (and other alkynes) by a $\{R^1R^2C{=}N{-}Pd\}$ species, resulting from the oxidative addition of acyloxime to Pd^0, would afford the vinylpalladium intermediate **5**. The subsequent C–H functionalization would then provide the cyclic product.

Benzynes have been widely used in organic synthesis.[14] Since the seminal work of Guitiàn, Perez, and co-workers, it has been established that arynes participate in palladium-catalyzed processes[15] and the versatility of such transformations is rapidly expanding.[16] Combining the unstable and reactive $\{R^1R^2C{=}N{-}Pd\}$ species with yet another highly reactive benzyne intermediate seemed to be a highly demanding endeavor—as many side reactions of both species are known. However, we expected that the subsequent C–H functionalization step, which would afford the heteroaromatic compound, could provide the driving force for the overall heteroannulation process.

We used the reaction of benzophenone *O*-perfluorobenzoyl oxime[17] (**3a**) with *O*-(trimethylsilyl)phenyl triflate (**7a**) as a probe for evaluating the reaction conditions. Under reaction conditions previously reported for the carbopalladation of benzynes ($[Pd(dba)_2]$ (5 mol%), P(*o*-tolyl)$_3$ (5 mol%), CsF (3.0 equiv), in MeCN/toluene 1:9, 110°C for 24 h),[18] only a trace amount of the desired product **6a** was detected (Table 1, entry 1). A significant amount of triphenylene, resulting from the palladium-catalyzed cyclotrimerization of benzyne, was isolated using $PdCl_2$ as a precatalyst (data not shown). When allylpalladium(II) chloride dimer (APC = $[\{(allyl)PdCl\}_2]$)[19,20] was used as a precatalyst, analytically pure phenanthridine **6a** was isolated, albeit in low yield (Table 1, entry 2). Increasing the amount of MeCN in the solvent system (MeCN/toluene 1:1) increased the yield of product (Table 1, entries 4 and 5).[21] However, using MeCN alone as the solvent (at reflux) led to the formation of triphenylene as a major product and a significant amount of acyloxime was recovered. Reasoning that the reaction temperature may be a key factor for the desired transformation, propiononitrile (b.p. 97°C) and butyronitrile (b.p. 115–117°C) were then examined, and the latter was found to be optimum. This solvent not only allowed a slow

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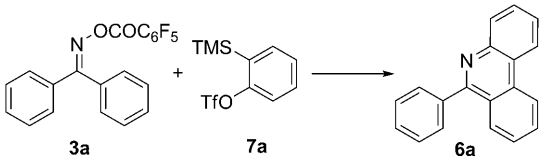
Table 1: A survey of the reaction conditions.[a]



3a **7a** **6a**

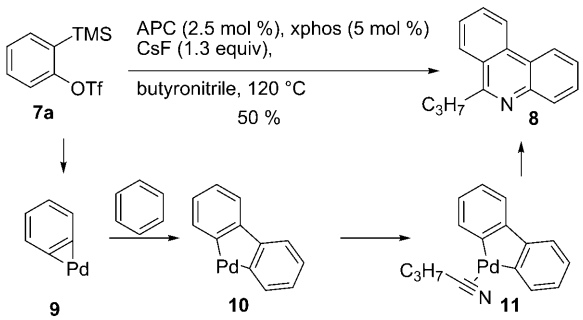
Entry	Pd	Ligand	Pd/ligand	Solvent (ratio)	*T* [°C]	Yield [%][b]
1	$[Pd(dba)_2]$	P(*o*-tolyl)$_3$	1:1	CH_3CN/tol (1:9)	110	trace
2	APC	P(*o*-tolyl)$_3$	1:2	CH_3CN/tol (1:9)	110	10[g]
3[c]	APC	P(*o*-tolyl)$_3$	1:2	CH_3CN/tol (1:9)	110	trace
4	APC	P(*o*-tolyl)$_3$	1:2	CH_3CN/tol (1:1)	110	27
5	APC	xphos	1:2	CH_3CN/tol (1:1)	110	30
6[c]	APC	dppp		CH_3CN	80	trace
7[d]	APC	P(*o*-tolyl)$_3$	1:2	C_2H_5CN	100	40
8[d]	APC[e]	P(*o*-tolyl)$_3$	1:2	C_3H_7CN	100	40
9[d]	APC	P(*o*-tolyl)$_3$	1:2	C_3H_7CN	120	67
10[d]	$[Pd(PPh_3)_4]$		–	C_3H_7CN	120	65
11[d]	APC[e]	dppp	1:1	C_3H_7CN	120	53
12[d]	APC[e]	xphos	1:2	C_3H_7CN	120	53
13[d]	APC[e]	–		C_3H_7CN	120	60
14	APC[e]	P(*o*-tolyl)$_3$	1:2	C_3H_7CN	120	70
15[f]	APC[e]	P(*o*-tolyl)$_3$	1:2	C_3H_7CN	120	74
16	–	–		C_3H_7CN	120	0

[a] All reactions were carried out under an argon atmosphere using Pd (5 mol%), **7a** (2 equiv), CsF (3 equiv), $c = 0.42$ M for 20 hours. [b] Yield of isolated product. [c] Slow addition of **7a** over 4 h. [d] **7a** (3 equiv) and CsF (4 equiv). [e] 2.5 mol%. [f] $c = 0.25$ M in the presence of M.S. (4 Å). [g] Similar yields were obtained when dppe, P(2-furyl)$_3$, dppp, and johnphos were used as supporting ligands. dba = *trans*,*trans*-dibenzylideneacetone, dppe = ethane-1,2-diylbis(diphenylphosphane), dppp = propane-1,3-diylbis(diphenylphosphane), johnphos = 2-(di-*tert*-butylphosphino)biphenyl, Tf = triflate, tol = toluene, TMS = trimethylsilyl, xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

generation of the benzyne resulting from the poorer solubility of CsF in butyronitrile (as compared with the solubility in MeCN), but also allowed us to carry out the reaction at a higher temperature than the reactions in acetonitrile and propionitrile (Table 1, entries 8 and 9 versus entries 6 and 7). By performing the reaction in butyronitrile at reflux in the presence of 0.025 equivalents of APC, the yield of **6a** was not significantly affected by the structure of the supporting ligands, and the reaction occurred even without the ligand (Table 1, entry 13). Nonetheless, P(*o*-tolyl)$_3$ stood out as the ligand of choice. The addition of 4-Å molecular sieves (M.S.) into the mixture further improved the efficiency of the reaction and led to **6a** in 74% yield (Table 1, entry 15). Overall, the optimal reaction conditions were: $[\{(allyl)PdCl\}_2]$ (2.5 mol%), P(*o*-tolyl)$_3$ (5 mol%), CsF (3.0 equiv) in butyronitrile ($c = 0.42$ M) at 120°C, in the presence of M.S. (4 Å).

Several points deserved further comment regarding this transformation: 1) less reactive benzophenone *O*-benzoyloxime was a poor substrate that afforded a low yield of the annulation product, 2) use of the butyronitrile soluble tetrabutylammonium triphenyldifluorosilicate (TBAT), instead of CsF only led to the formation of triphenylene and degradation products, 3) the Beckmann rearrangement product was not isolated under the optimized reaction conditions,[22] 4) we were initially concerned that the product might interfere with benzyne because a variety of nitrogen-containing heterocycles, including pyridines[23] and quinolines,[24] have been shown to react with benzynes, however, this side reaction was not observed, 5) the presence of palladium catalyst is necessary, because in its absence the same reaction afforded a complex mixture of products (Table 1, entry 16),[25] 6) during the optimization studies 6-propylphenanthridine (**8**) was frequently observed as a side product, especially when xphos and dppp were used as supporting ligands.[26] Indeed, compound **8** can be produced in up to 50% yield when the oxime was omitted, as illustrated in Scheme 2. The reaction most probably goes via the η^2-metallocyclopropene intermediate **9**[27] which reacted with a second equivalent of benzyne to form the palladacycle **10**. Subsequent insertion of butyronitrile into **10** would then afford the observed product **8**.

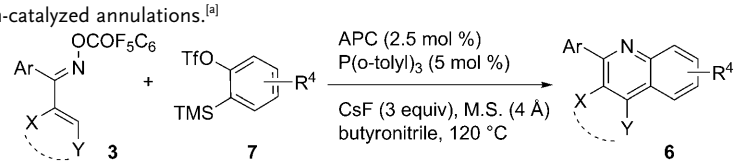
The generality of this novel domino transformation was examined by varying the electronic and steric properties of each reactant, and the results are summarized in Table 2. The required ketoxime *O*-pentafluorobenzoates were easily prepared by the condensation of ketones[28] with hydroxylamine and subsequent acylation with pentafluorobenzoyl chloride.

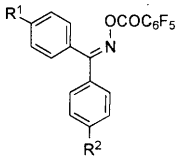
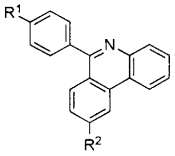
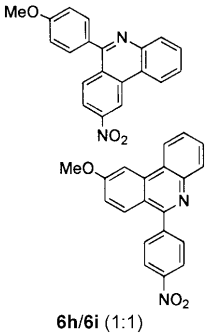
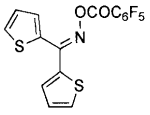
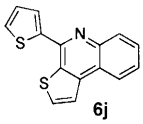
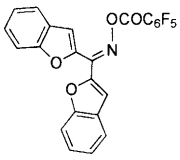
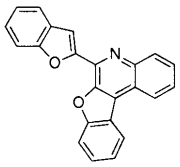
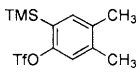
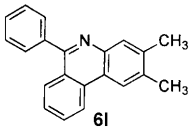
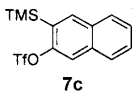
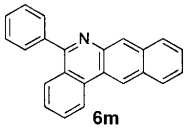
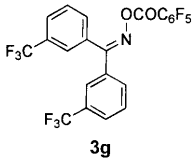
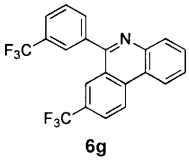
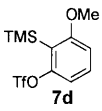
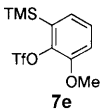
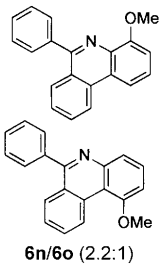


Scheme 2. Synthesis of 6-propylphenanthridine.

Symmetrical 4,4′-substituted benzophenone-derived oximes bearing electron-withdrawing groups smoothly underwent the annulation process to generate the expected phenanthridines (Table 2, entries 1–4). In the case of **3c**, an appreciable amount of ketone was isolated, thus explaining the somewhat reduced yield of **6c** (Table 2, entry 2). The presence of a chlorine atom did not alter the reaction pathway, thus indicating that acyloxime **3** is more prone to undergo oxidative addition to Pd^0 than the aryl chloride (Table 2, entry 3). A weakly electron-donating methyl group was tolerated in the reaction (Table 2, entry 5), but a strongly electron-donating group like a methoxy group was incompatible with the domino sequence as no desired compound could

Table 2: Scope of the palladium-catalyzed annulations.[a]



Entry	Oxime	Aryne	Product	Yield [%][b]	Entry	Oxime	Aryne	Product	Yield [%][b]
1	 **3b**: R^1=R^2=F	**7a**	 **6b**: R^1=R^2=F	69	7	(*E*)- or (*Z*)-**3h**: $R^1=NO_2$, $R^2=OMe$	**7a**	 **6h/6i** (1:1)	67
2	**3c**: $R^1=R^2=CF_3$	**7a**	**6c**: $R^1=R^2=CF_3$	43	8	 **3j**	**7a**	 **6j**	41
3	**3d**: $R^1=R^2=Cl$	**7a**	**6d**: $R^1=R^2=Cl$	66	9	 **3k**	**7a**	 **6k**	43
4	**3e**: $R^1=R^2=CN$	**7a**	**6e**: $R^1=R^2=CN$	70	10	**3a**	 **7b**	 **6l**	67
5	**3f**: $R^1=R^2=CH_3$	**7a**	**6f**: $R^1=R^2=CH_3$	30	11	**3a**	 **7c**	 **6m**	51
6	 **3g**	**7a**	 **6g**	45	12	**3a**	 **7d** or  **7e**	 **6n/6o** (2.2:1)	44

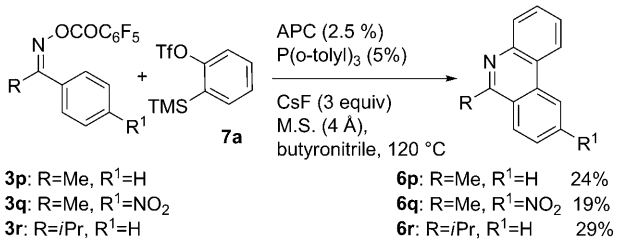
[a] All reactions were carried out under an argon atmosphere using benzyne precursor (**7**; 2 equiv), CsF (3 equiv), $c=0.42$ M in the presence of M.S. (4 Å) for 24 hours. [b] Yield of isolated product.

be isolated (not shown). When *meta*-substituted 3,3′-trifluoromethyl **3g** was employed, 8-(trifluoromethyl)phenanthridine **6g** was obtained at the expense of 10-(trifluoromethyl)phenanthridine, possibly because of steric reason (Table 2, entry 6). 2,2′-dithienyl and -dibenzofuranyl acylketoximes **3j** and **3k** have also successfully been employed in this reaction, thus affording reasonable yields of the corresponding heterocyclic compounds (Table 2, entries 8 and 9). These results are

noteworthy as both the starting materials and the products could act as ligands to sequester the palladium catalyst. Unsymmetrical acylketoximes were also evaluated. In the case of **3h**, bearing two groups that have opposing electronic properties, the reaction proceeded with good overall yield: the C–H annulation step occurring on both electron-rich and electron-poor aryl group, and afforded **6h** and **6i** in a 1:1 ratio (Table 2, entry 7).[29]

Substituted *O*-(trimethylsilyl)aryl triflates were also briefly examined. 4,5-dimethyl-2-(trimethylsilyl)phenyl triflate (**7b**) and 3-(trimethylsilyl)naphthalen-2-yl triflate (**7c**) furnished the desired product **6l** and **6m** in 67 and 51 % yields, respectively (Table 2, entries 10 and 11). When the 3-methoxy-2-trimethylsilyl trifluorosulfonate (**7d**) reacted with benzophenone *O*-perfluorobenzoyl oxime (**3a**), two isomers (**6n** and **6o**) were obtained in a 2.2:1 ratio (Table 2, entry 12). Similar results were obtained when **3a** reacted with 2-methoxy-6-trimethylsilyl trifluorosulfonate (**7e**), which is a regioisomer of **7d**. These results clearly suggest the intermediacy of an aryne species in the annulation process.[30]

Acetophenone-type acyloximes bearing an aryl and an alkyl group (**3p**–**3r**) were also subjected to the domino process (Scheme 3). They proved to be poor substrates and

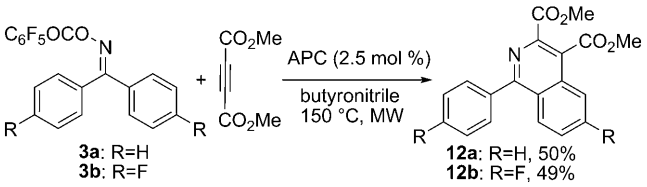


Scheme 3. Synthesis of 6-alkylphenanthridines.

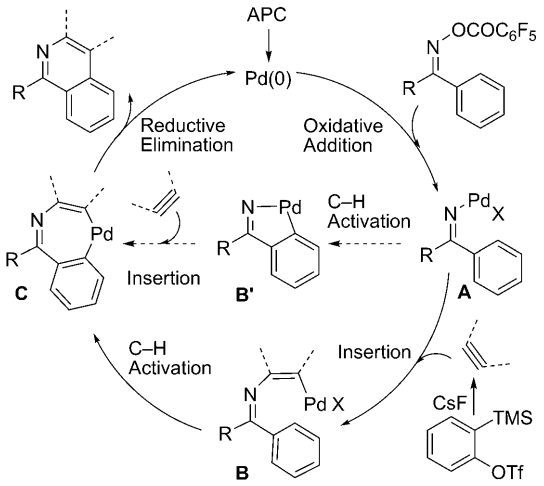
afforded the expected phenanthridines in low yields. Since the angle of the C=N–M moiety is almost linear, the geometry of the starting *N*-acyloxime should not be a concern. Indeed, control experiments using geometrically pure acyloxime (*E*)-**3h** and (*Z*)-**3h** afforded the same ratio of compounds **6h** and **6i** (Table 2, entry 7). We hypothesized that the presence of an enolizable alkyl substituent provided an opportunity for imine–enamine tautomerization, which could in turn led to some unproductive reaction pathways.[31]

Encouraged by the successful reaction between benzynes and acyloximes, the reaction of **3a** with dimethyl acetylenedicarboxylate (DMAD) was next examined. The best reaction conditions consisted of APC as a catalyst under microwave irradiation conditions.[32] Under optimal reaction conditions (APC, butyronitrile, MW, 150 °C), the desired isoquinoline **12a** was isolated in 50 % yield (Scheme 4). The addition of ligand reduced the yield of **12a**, while the presence of CsF led to a complete degradation of the starting materials. Unfortunately, diphenylacetylene failed to participate in this annulation reaction.

A possible scenario that could account for the formation of phenanthridine **6** and isoquinoline **12** is illustrated in Scheme 5. According to the proposal by Kitamura and



Scheme 4. Synthesis of dimethyl isoquinoline-3,4-dicarboxylates.



Scheme 5. Possible reaction pathways of the domino aminopalladation/C–H functionalization sequence.

Narasaka, oxidative insertion of palladium into the N–O bond of an acyloxime should lead to compound **A**. Two possible pathways can then be considered: 1) *cis*-Aminopalladation of benzyne or alkyne species would generate a second Pd^{II} intermediate **B** that could evolve into complex **C** by an intramolecular C–H activation process. A reductive elimination would close the catalytic cycle thereby producing the nitrogen-containing heterocycles. 2) Alternatively, a cyclopalladated intermediate **B′** could be formed from complex **A**. Such a complex is related to the numerous azapalladacycles which are well documented,[33] even if they usually bear a neutral nitrogen ligand. Triple bond insertion into complex **B′** could then lead to intermediate **C**, which after reductive elimination would afford the annulated compound. Another catalytic cycle involving the η^2-metallocyclopropene intermediate **9** may also be operative (see Scheme 2).[34] However, we believed that this kinetically viable pathway might not be responsible for the formation of the desired product.[35] Rather, it accounts for the formation of the side products such as triphenylene and 6-propylphenanthridine.

In summary, we have developed a novel palladium-catalyzed domino annulation process for the formation of biologically relevant phenanthridines and isoquinolines. To the best of our knowledge, this represented the first example wherein a $\{R^1R^2C{=}N{-}Pd\}$ species generated by oxidative addition of acyloxime to Pd^0 underwent intermolecular aminopalladation reaction of alkynes. The use of butyronitrile as the solvent was determinant to the success of the present aminopalladation/C–H functionalization process and we assumed that it could well be an effective solvent in other

palladium-catalyzed transformations involving benzyne intermediates.

Experimental Section

Typical procedure for the synthesis of phenanthridines: Benzophenone *O*-pentafluorobenzoyloxime **3a** (100 mg, 0.255 mmol, 1.0 equiv) and tri(*o*-tolyl)phosphine (3.9 mg, 0.013 mmol, 0.05 equiv) were added to a stirred suspension of [{(allyl)PdCl}$_2$] (2.3 mg, 0.006 mmol, 0.025 equiv) and molecular sieves (4 Å) in freshly distilled and degassed butyronitrile (0.6 mL) under argon. Then anhydrous CsF (116.4 mg, 0.770 mmol, 3.0 equiv) and 2-(trimethylsilyl)phenyltriflate **7a** (152.5 mg, 0.510 mmol, 2.0 equiv) were added. After stirring at reflux overnight, the reaction mixture was diluted with water and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with a saturated solution of NH_4Cl, dried over sodium sulfate and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (dichloromethane) afforded 6-phenylphenantridine **6a** as a white solid (49 mg, 74%).

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