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Pd-Catalyzed [3+2] cycloaddition of ketoimines with alkynes *via* directed sp^3 C–H bond activation†

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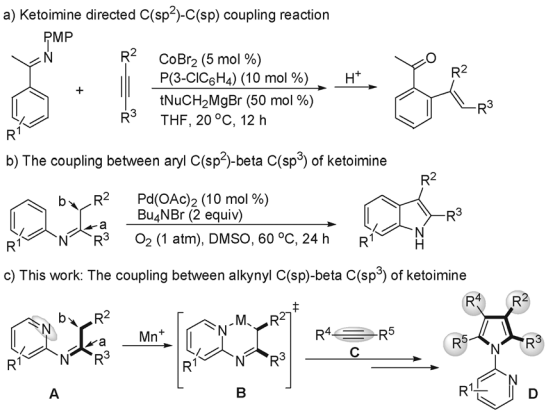
The Pd(II)-catalyzed oxidative [3+2] cycloaddition of *N*-(2-pyridyl) ketoimines with internal alkynes has been developed. The transformation is tolerant of extensive substitution on halogen, alkene, alkyne, hydroxyl, aryl and acyl groups, and allows facile assembly of multisubstituted pyrroles.

Pyrroles are among the most commonly used heterocyclic feedstocks for assembling complex biologically active molecules and pharmaceuticals.[1] Therefore, a myriad of catalytic reactions have been developed for the functionalization of pyrroles.[2] Among the different synthetic strategies, transition-metal catalyzed direct oxidative coupling reactions by the selective activation of C–H bonds have emerged as a powerful method for constructing pyrroles.[3] For example, the Pd(II), Ru(II) or Rh(III)-catalyzed cross-coupling cyclization of C–H/N–H bonds with internal alkynes could give pyrroles *via* cyclometalated intermediates.[4] However, despite enormous progress in this field, all methods for installing different types of substituents into specific positions of pyrroles cannot be accessed by a single type of transformation. Developing a new, more concise approach to multisubstituted pyrroles is a subject of great importance.

Imines are of great importance in organic chemistry, and their corresponding C–X coupling reactions (X = C and N) are widely utilized in constructing various kinds of nitrogen-containing compounds.[5] Recently, Yoshikai reported that Co(II)-catalyzed C(sp^2)–C(sp) coupling of aryl ketoimines with alkynes could furnish trisubstituted olefins *via* a C–H activation process, in which ketoimines were employed as directing groups (Scheme 1a).[6] Very recently, they further found that Pd(II) could directly enhance the intramolecular cyclization of *N*-aryl ketoimines to give benzopyrroles through aryl C (sp^2)–alkyl C (sp^3) coupling (Scheme 1b);[7] these results imply that β-C(sp^3)



Scheme 1 The direct C–C coupling strategies of ketoimines.

of ketoimines instead of imine carbon (α-C) or imine nitrogen[5c,8] could be directly coupled with unsaturated carbon–carbon bonds *via* a C–H activation process. Although the direct C(sp^3)–C(sp) coupling between unfunctionalized alkanes and alkynes has remained a considerable challenge,[9] inspired by earlier studies,[6,7,9] and in combination with the fact that pyridine could be used as a directing group to realize versatile C–H functionalization,[5i,k,10] we reasoned that a metallacyclic species (**B**) could be achieved *via* β-C(sp^3)–H activation if a pyridyl group from ketoimine (**A**) is employed as an anchor (Scheme 1c), then the corresponding cyclometalated species (**B**) will be possibly trapped by C(sp)-containing alkyne (**C**) through inserting into the carbon–carbon triple bond. To identify this hypothesis, herein we report a novel Pd-catalyzed [3+2] cycloaddition of 2-ketoiminopyridines with alkynes; this protocol can be readily used for constructing multisubstituted pyrroles (**D**).

Initially we focused on investigating whether the palladium-catalyzed cycloaddition of imine **1a** with diphenylacetylene **2a** could lead to the corresponding pyrrole **3a**. Reactions were usually carried out in the presence of *n*-Bu$_4$NBr and PhI(OAc)$_2$. After an initial screening of various palladium catalysts (Table 1, entries 1–5), we quickly found that Pd(OAc)$_2$ (10 mol%) could afford 13% yield of the desired product **3a** by using toluene as a solvent at 60 °C for

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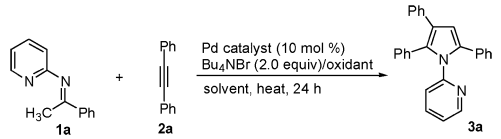
† Electronic supplementary information (ESI) available. CCDC 1004595. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc04676e

Table 1 Optimization of the reaction parameters[a]



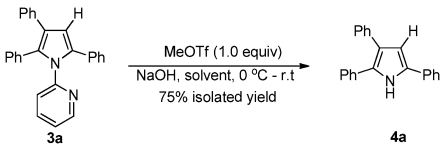
Entry	Catalyst	Oxidant	Solvent	Yield[b] (%)
1	$PdCl_2$	$PhI(OAc)_2$	Toluene	5
2	$Pd(TFA)_2$	$PhI(OAc)_2$	Toluene	Trace
3	$PdCl_2(CH_3CN)_2$	$PhI(OAc)_2$	Toluene	Trace
4	$PdCl_2(PPh_3)_2$	$PhI(OAc)_2$	Toluene	Trace
5	$Pd(OAc)_2$	$PhI(OAc)_2$	Toluene	13
6	$Pd(OAc)_2$	$PhI(OAc)_2$	CH_3CN	21
7	$Pd(OAc)_2$	$PhI(OAc)_2$	Dioxane	Trace
8	$Pd(OAc)_2$	$PhI(OAc)_2$	EtOAc	10
9	$Pd(OAc)_2$	$PhI(OAc)_2$	DMSO	22
10	$Pd(OAc)_2$	Ag_2CO_3	DMSO	13
11	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	11
12	$Pd(OAc)_2$	BQ[c]	DMSO	57
13	$Pd(OAc)_2$	O_2	DMSO	59
14	$Pd(OAc)_2$	O_2	DMSO	83[d]
15	$Pd(OAc)_2$	O_2	DMSO	91[e]
16	$Pd(OAc)_2$	O_2	DMSO	78[f]
17	$Pd(OAc)_2$	O_2	DMSO	43[e,g]
18	$Pd(OAc)_2$	O_2	DMSO	62[e,h]

[a] Unless otherwise noted, all the reactions were carried out using ketoimine (**1a**) (0.10 mmol) and alkyne (**2a**) (0.10 mmol) with Pd catalysts (10 mol%) in the presence of an oxidant (1.0 equiv.) and a solvent (1.0 mL) at 60 °C for 24 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO_2. [b] Isolated yield. [c] BQ stands for 1, 4-benzoquinone. [d] The reaction temperature is 80 °C. [e] The reaction temperature is 100 °C. [f] The reaction temperature is 120 °C. [g] The additive is *n*-Bu_4NCl instead of *n*-Bu_4NBr. [h] The additive is *n*-Bu_4NI instead of *n*-Bu_4NBr.

24 h (entry 5). Subsequently, further improvement of the reaction (22% yield of **3a**) was achieved when DMSO was employed as the solvent (compare entries 5–8 with 9). Considering that a proper oxidant is essential for enhancing this transformation, various oxidants were evaluated in the DMSO solvent system. To our delight, the yield of product **3a** could be significantly increased to 59% using molecular oxygen as an oxidant (compare entries 9–12 with 13). Finally, the best yield (91% yield of **3a**) was obtained by increasing the reaction temperature to 100 °C (compare entries 13 and 14 with 15), while higher temperature (120 °C) gave a slightly lower yield (compare entry 15 with 16). It is worth noting that switching additives from *n*-Bu_4NBr to *n*-Bu_4NCl or *n*-Bu_4NI could not further improve the yield of **3a** (entries 17 and 18).

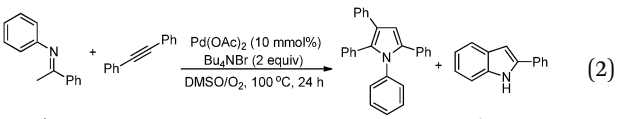
Having established an efficient reaction protocol that enables the smooth Pd-catalyzed [3+2] cycloaddition of **1a** with **2a**, we next investigated the scope and generality of this transformation under the optimized conditions. As shown in Table 2, common functional groups on the benzene rings (Ar) attached to the imine carbon, including alkyl, alkoxy, hydroxyl, ester, nitro, halogen, and acetal groups, were all compatible with this cycloaddition and gave moderate to excellent yields of pyrroles (entries 1 and 2). The *meso* or the *ortho*-substituted benzene ring (Ar) led to a lower yield presumably due to the increased steric hindrance around the ketoimine (entry 1, compare **3e** with **3f** and **3g**). Moreover, aromatic heterocycle (Ar) substituted ketoimines (such as Ar = 2-thiophene and 2-furan) could also give the desired pyrroles **3m** and **3n** in 47–56% yields (entry 4). Worthy of note was that when R^2 was changed to the methyl group (CH_3–), the corresponding five-substituted pyrrole **3l** could be produced in 52% yield (entry 3), and its structure was already unambiguously assigned by its single crystal X-ray analysis [see the ESI† for more details]. Then, we investigated the substitution effects of the pyridine ring on this transformation, and found that the electron-rich pyridine offered higher yield of product (**3o**), while electron-deficient substrates inhibited cycloaddition performance (entry 5, compare **3o** with **3p**–**3r**). In addition, 2-ketoiminopyrimidine was also a suitable substrate for this transformation and provided 48% yield of the desired pyrrole **3s** (entry 6).

Subsequently, the scope of the procedure with regard to various internal alkynes was additionally explored with **1a** particularly. Gratifyingly, we found that alkyl, aryl, alkoxycarbonyl, hydroxymethyl, acyl, alkenyl and alkynyl substituted alkynes were all tolerated for this transformation, and provided good to excellent yield of the desired products **3t**–**3z** (Table 2, entries 7–9). Notably, when ketoimine **1l** and alkenylalkyne **2i** were used as the substrates in this reaction system, the desired 1, 2, 3, 4, 5-differently substituted group-containing pyrrole **3za** was obtained in 43% yield (entry 10). Finally, the pyridyl moiety of **3a** could be very easily removed under basic conditions (MeOTf–NaOH, 0 °C–r.t) to provide the free N–H pyrrole **4a** in 75% yield [eqn (1)].

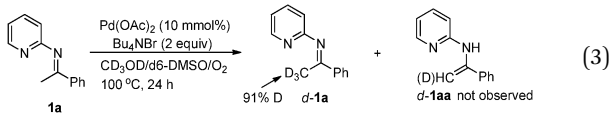


(1)

To further probe the reaction mechanism, several controlled experiments were carried out. First, we tried the [3+2] cycloaddition of *N*-phenyl imine (**1t**) with diphenylacetylene (**2a**) under our standard conditions. Unfortunately, we only got 65% yield of indole derivative **4d** which was from the oxidative cyclization of **1t**, and no pyrrole product **4c** was observed [eqn (2)]. These results clearly indicated that the pyridyl group played a significant directing role in forming pyrroles. Second, when the H/D exchange of *N*-pyridyl ketoimine **1a** was conducted in the Pd(II)–CD_3OD system for 24 h in the absence of alkyne **2a**, 91% deuterium incorporation was observed at the imino methyl group of **1a** (see the ESI for more details), and no ^1H NMR trace from enamine ***d*-1aa** was detected [eqn (3)];[11] this experiment suggested that the Csp^3–H insertion step was involved in the transformation in this reaction system. Finally, the intermolecular isotope effect (K_H/K_D = 1.52) suggested Csp^3–H bond cleavage occurred in the rate-limiting step [eqn (4)] (see the ESI† for more details).[12]

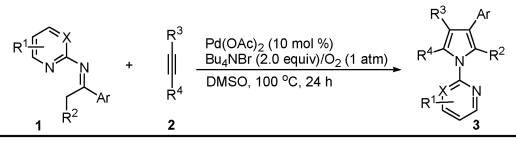


(2)



(3)

Table 2 Substrate scope for the Pd(II)-catalyzed [3+2] cycloaddition of ketoimines with alkynes[a]



1 2 3

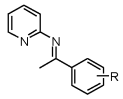
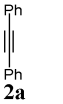
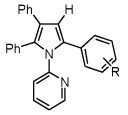
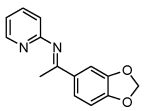
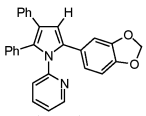
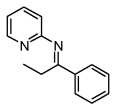
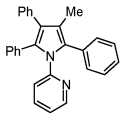
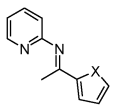
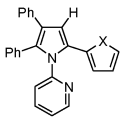
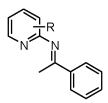
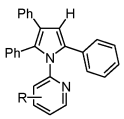
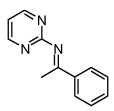
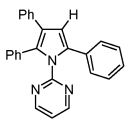
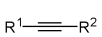
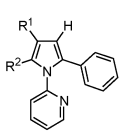
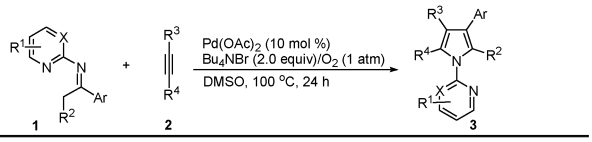
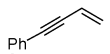
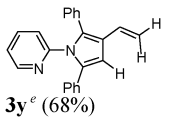
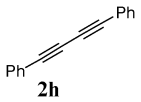
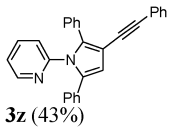
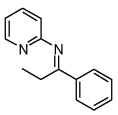
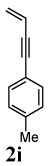
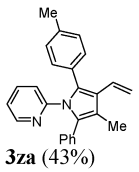
Entry	Ketoimine (1)	Alkyne (2)	Product (3)[b] (yield)
1	 1	 2a	 3
	1a: R = H	**2a**	**3a**: R = H (91%); (87%)[c]
	1b: R = *p*-Me	**2a**	**3b**: R = *p*-Me (93%)
	1c: R = *p*-MeO	**2a**	**3c**: R = *p*-MeO (93%)
	1d: R = *o*-OH	**2a**	**3d**: R = *o*-OH (44%)
	1e: R = *p*-Cl	**2a**	**3e**: R = *p*-Cl (78%)
	1f: R = *m*-Cl	**2a**	**3f**: R = *m*-Cl (59%)
	1g: R = *o*-Cl	**2a**	**3g**: R = *o*-Cl (54%)
	1h: R = *p*-Br	**2a**	**3h**: R = *p*-Br (84%)
	1i: R = *p*-CO_2Me	**2a**	**3i**: R = *p*-CO_2Me (70%)
	1j: R = *p*-NO_2	**2a**	**3j**: R = *p*-NO_2 (67%)
2	 1k	**2a**	 **3k** (91%)
3	 **1l**	**2a**	 **3l** (52%)
4		**2a**	
	1m: X = O	**2a**	**3m**: X = O (47%)
	1n: X = S	**2a**	**3n**: X = S (56%)
5		**2a**	
	1o: R = 5-Me	**2a**	**3o**: R = 5-Me (82%)
	1p: R = 5-Cl	**2a**	**3p**: R = 5-Cl (61%)
	1q: R = 5-Br	**2a**	**3q**: R = 5-Br (62%)
	1r: R = 5-CN	**2a**	**3r**: R = 5-CN (40%)
6	 **1s**	**2a**	 **3s** (48%)
7	**1a**	 **2**	 **3**
	1a	**2b**: R^1 = Et, R^2 = Ph	**3t**: R^1 = Et, R^2 = Ph (80%) (r.r = 9 : 1)[d]
	1a	**2c**: $R^1 = R^2$ = *n*-Pr	**3u**: $R^1 = R^2$ = *n*-Pr (66%)
	1a	**2d**: R^1 = Ph, R^2 = CO_2Me	**3v**: R^1 = Ph, R^2 = CO_2Me (71%)

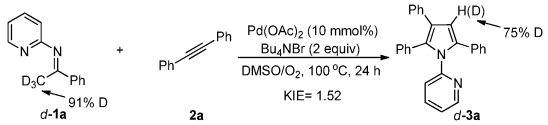
Table 2 (*continued*)



1 2 3

Entry	Ketoimine (1)	Alkyne (2)	Product (3)[b] (yield)
	1a	**2e**: R^1 = Ph, R^2 = CH_2OH	**3w**: R^1 = Ph, R^2 = CH_2OH (61%)
	1a	**2f**: R^1 = Ph, R^2 = PhCO	**3x**: R^1 = Ph, R^2 = PhCO (80%)
8	**1a**	 **2g**	 **3y**[e] (68%)
9	**1a**	 **2h**	 **3z** (43%)
10	 **1l**	 **2i**	 **3za** (43%)

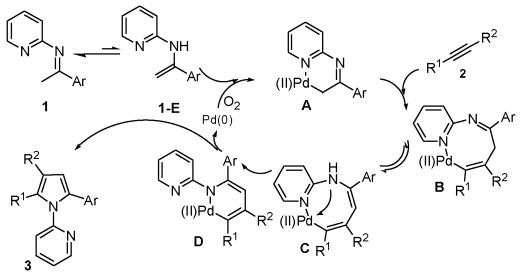
[a] All the reactions were carried out using ketoimine (**1**) (0.10 mmol) and alkyne (**2**) (0.10 mmol) with $Pd(OAc)_2$ (10 mol%) in DMSO (1.0 mL) at 100 °C for 24 h under 1 atm of O_2 in a sealed reaction tube, followed by flash chromatography on SiO_2. [b] Isolated yield. [c] The yield for a larger scale coupling product of **1a** (8.0 mmol) with **2a** (8.0 mmol). [d] Regioisomeric ratio (r.r) determined by ^{1}H NMR spectroscopy. [e] ^{1}H–^{1}H NOE NMR spectra of **3y** is available in the ESI.



(4)

From the above-mentioned experimental results, we proposed a possible mechanism that involved a Pd(II)/Pd(0) redox process (Scheme 2). At first, enamine **1-E** derived from imine/enamine-isomerization **7** would be electrophilically attacked by Pd(II) to form a six-membered palladacycle **A** *via* an intramolecular Csp^3–H palladation. Subsequently, the reactive palladium intermediate **A** will be inserted into an equivalent of alkyne **2** to form an 8-membered palladacycle **B**, which would further result into a six-membered ring cyclopalladated **D** through a N-ligand shift process.[13] Finally, Pd(II) intermediate **D** can reductively eliminate to form pyrrole **3** and generate a Pd(0) species which can be oxidized by O_2 to generate the catalytically active Pd(II) complex.

In summary, we have developed a facile palladium-catalyzed oxidative [3+2] cycloaddition reaction to assemble a multi-substituted pyrrole skeleton from readily available *N*-pyridyl substituted ketoimines and internal alkynes. This new approach tolerates a variety of useful functionalities including halogen, hydroxyl, alkyloxycarbonyl, alkenyl and alkynyl substituents which have not been easily accessible through existing synthetic methods. Since the pyridyl moiety could be removed under mild



Scheme 2 Possible mechanism for the reaction.

reaction conditions, a wide variety of free (N–H) pyrroles can be synthesized by using this protocol. Further investigation into the mechanism and synthetic application of this transformation is underway in our laboratory.

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