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Ligand-Promoted C(sp^3)–H Olefination en Route to Multi-functionalized Pyrazoles

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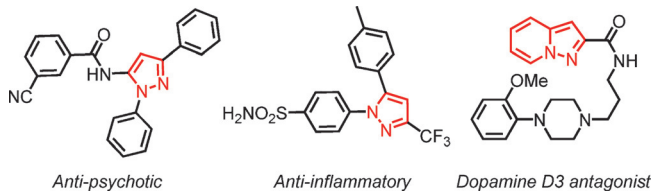
Dedicated to Professor Barry Sharpless on the occasion of his 75th birthday

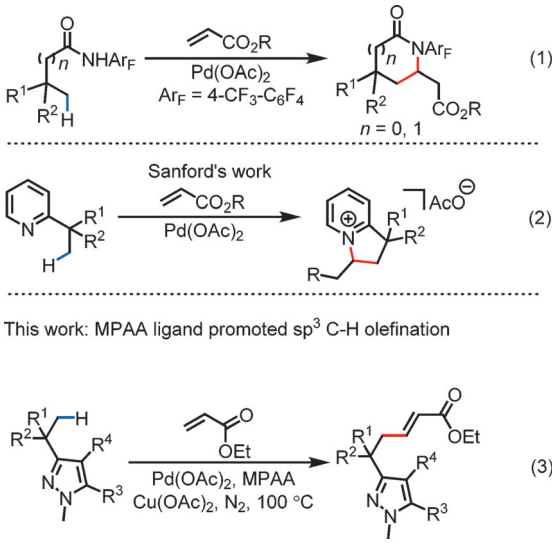
Abstract: A Pd-catalyzed/N-heterocycle-directed C(sp^3)–H olefination has been developed. The monoprotected amino acid ligand (MPAA) is found to significantly promote Pd-catalyzed C(sp^3)–H olefination for the first time. $Cu(OAc)_2$ instead of Ag^+ salts are used as the terminal oxidant. This reaction provides a useful method for the synthesis of alkylated pyrazoles.

Late-stage alkylation of heterocycles is a significant challenge in synthesis especially in the context of medicinal chemistry. The state-of-art-the-art relies mainly on cross-coupling of heteroaryl halides with alkyl boron and zinc reagents.[1] As alkyl halide coupling partners are often incompatible with nucleophilic heterocycles, direct C–H alkylation of heterocycles remains underdeveloped with only a handful of examples documented.[2] Inspired by the diversity of pharmacologically active pyrazole scaffolds (Scheme 1),[3] we set out to develop pyrazole-directed C(sp^3)–H olefination reaction of pendant alkyl groups to deliver diverse alkylated pyrazoles from a small number of commercially available pyrazoles.



Scheme 1. Biologically active pyrazoles and pyrazolo[1,5-*a*]pyridines.

The challenges associated with achieving this goal are two-fold. First, C(sp^3)–H olefination is among one of the most challenging C–H functionalization processes with only two precedents to date [Scheme 2, Eq. (1) and (2)].[4] Second, pyrazole-directed C–H activation reactions,[5] especially C(sp^3)–H activation, are rare.[5j] Herein we report the first example of Pd-catalyzed pyrazole-directed C(sp^3)–H olefination using $Cu(OAc)_2$ as the terminal oxidant. The mono-protected amino acid ligands (MPAA) are shown to promote C(sp^3)–H olefination for the first time. In contrast to previous work which reported the formation of aza-Michael cyclization products, this C(sp^3)–H olefination method can provide immediate access to products with intact olefins, which can be used as substrates for additional chemistry or potentially as covalent modifiers of proteins[6] [Eq. (3)].



Scheme 2. Pd-catalyzed sp^3 C–H olefination.

Despite the extensive studies on Pd^{II}-catalyzed C(sp^2)–H olefination reactions involving either electrophilic palladation or C–H insertion pathways,[7] the translation of these methods into saturated C(sp^3)–H system has been largely unsuccessful. In the two previous examples of C(sp^3)–H olefination,[4] the newly installed olefin unit further reacts with the nucleophilic-directing group to give the undesired Michael cyclization products. A powerful extension of this methodology would exploit the intrinsic directing ability of a 5-membered azole ring which may avoid undesired cyclization due to ring strain. Additionally, this methodology enables late-stage functionalization of quaternary carbon centers that would have been otherwise ac-

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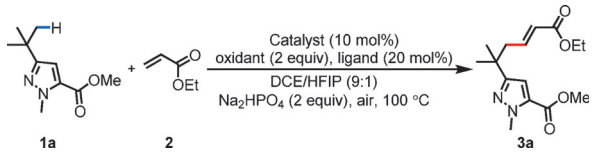
cessed by lengthy de novo azole ring preparations. To improve the scope and efficiency of this synthetically powerful sp^3 C–H olefination reaction, it is crucial to identify a suitable ligand that can promote and modulate the reactivity. We therefore investigated the two classes of ligands that have been developed to promote C–H activation, namely, MPAA[8] and quinoline ligands.[9] Based on the presence of multiple vectors for exploration, we selected the commercially available methyl 3-(*tert*-butyl)-1-methyl-1*H*-pyrazole-5-carboxylate (**1a**) as the model substrate. Thus, olefination of **1a** with ethyl acrylate was examined under various conditions (see the Supporting Information). In the presence of 10 mol% $[Pd(OTf)_2(MeCN)_4]$ and 20 mol% ligand, the reaction proceeded to give the olefinated product **3a** in 50% yield (Table 1, entry 1). Removal of the ligand reduced the yield to 21%, suggesting a beneficial role of the ligand in the reaction (entry 2). Encouraged by this observation, we screened a set of commercially available N-protected amino acids with different backbones (entries 3–6). The product **3a** was obtained in 60% yield when Ac-Ile-OH was used. Changing *N*-acetyl to other protecting groups resulted in significant decrease in yields (entries 7–9). Replacement of $[Pd(OTf)_2(MeCN)_4]$ by $Pd(OAc)_2$ did not affect the reaction under these conditions (entry 10). Reducing the amount of ligand to 10 mol% increased the yield to 66% (entry 11). Running the reaction under N_2 instead of air gave significantly lower yield, indicating the beneficial effect of molecular O_2 (entry 12). Other Pd sources were significantly less effective (entries 13–15). During the investigation of different oxidants, we found that less expensive oxidant $Cu(OAc)_2$ also afforded the product in 37% yield (entry 19). Further examination of this reaction revealed that the combination of $Cu(OAc)_2$ with O_2 decomposed the starting material. Further exploration of impact of oxidants on the reaction revealed that the use of $Cu(OAc)_2$ as the sole oxidant under N_2 improved the yield to 76% (entry 20). Under the optimized conditions, omission of the ligand reduced the yield to 35% confirming a noticeable ligand effect in this C(sp^3)–H olefination reaction (entry 21).

We next examined the scope of pyrazoles for this ligand-promoted C(sp^3)–H olefination (Table 2). This catalytic system can tolerate pyrazole esters, pyrazole amides, as well as simple pyrazoles (**3a**–**3c**). Both electron-donating and electron-withdrawing substituents at the 4-position of the pyrazole ring afforded the corresponding products (**3d**–**3f**) in good yields (65–71%). Other tertiary alkyls[10] at the 3-positions are also reactive (**3g**–**3i**), although secondary and primary alkyls are not reactive under current conditions. However, functional groups on the tertiary alkyls including acetate and methoxyl are compatible (**3j**, **3k**). Interestingly, the fused tricyclic 4,5-dihydro-2*H*-benzo[*e*]indazole prepared from our previous C–H activation cascade[5j] also gives the product **3l**, albeit in lower yield (37%). The reduced reactivity of **1l** is likely due to geometric constraints hindering the formation of the desired co-planar transition state. Successful application of C(sp^3)–H olefination on pharmaceutically relevant benzo[*d*]oxazole, pyrazolo[1,5-a]pyridine scaffolds in the presence of additional polar functionality proceeds to give the desired products (**3m**–**3n**). To the best of our knowledge, these heterocycles have not been used to direct C–H activation. To further demonstrate the potential utility of this reaction, olefination of the highly functionalized pyrazole scaffold **1o** proceeded in good yield (64%) with no obvious interference of either the nitro or carbamate groups on the reaction.

Table 1. Optimization studies of Pd-catalyzed C(sp3)–H olefination.



1a 2 3a

Entry[a]	Catalyst	Ligand	Oxidant	Yield [%]
1	$[Pd(OTf)_2(MeCN)_4]$	Ac-Leu-OH	AgOAc	50
2	$[Pd(OTf)_2(MeCN)_4]$	–	AgOAc	21
3	$[Pd(OTf)_2(MeCN)_4]$	Ac-Ala-OH	AgOAc	45
4	$[Pd(OTf)_2(MeCN)_4]$	Ac-Val-OH	AgOAc	49
5	$[Pd(OTf)_2(MeCN)_4]$	Ac-Gly-OH	AgOAc	43
6	**$[Pd(OTf)_2(MeCN)_4]$**	**Ac-Ile-OH**	**AgOAc**	**60**
7	$[Pd(OTf)_2(MeCN)_4]$	Boc-Ile-OH	AgOAc	30
8	$[Pd(OTf)_2(MeCN)_4]$	Fmoc-Ile-OH	AgOAc	26
9	$[Pd(OTf)_2(MeCN)_4]$	For-Ile-OH	AgOAc	31
10	$Pd(OAc)_2$	Ac-Ile-OH	AgOAc	62
11[b]	$Pd(OAc)_2$	Ac-Ile-OH	AgOAc	66
12[b,c]	$Pd(OAc)_2$	Ac-Ile-OH	AgOAc	38
13[b]	$[Pd(TFA)_2]$	Ac-Ile-OH	AgOAc	41
14[b]	$[Pd(acac)_2]$	Ac-Ile-OH	AgOAc	26
15[b]	$PdCl_2$	Ac-Ile-OH	AgOAc	<5
16[b]	$Pd(OAc)_2$	Ac-Ile-OH	$AgNO_3$	32
17[b]	$Pd(OAc)_2$	Ac-Ile-OH	$K_2S_2O_8$	21
18[b]	$Pd(OAc)_2$	Ac-Ile-OH	BQ	16
19[b]	$Pd(OAc)_2$	Ac-Ile-OH	$Cu(OAc)_2$	37
20[b,c]	**$Pd(OAc)_2$**	**Ac-Ile-OH**	**$Cu(OAc)_2$**	**76**
21[b,c]	$Pd(OAc)_2$	–	$Cu(OAc)_2$	35

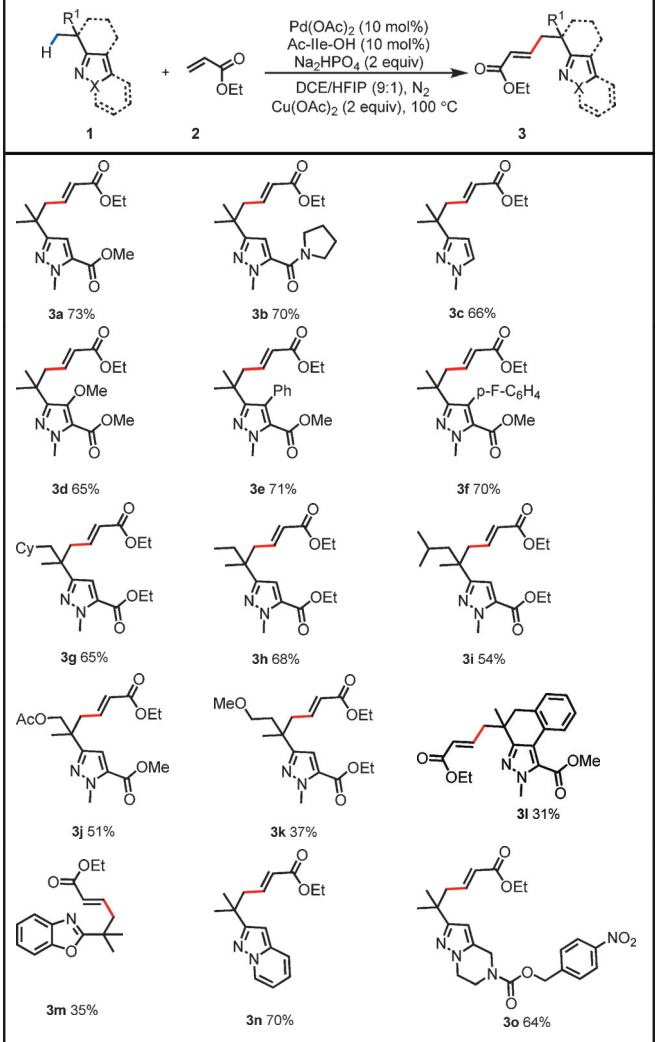
Reaction conditions: [a] pyrazole ester **1a** (0.05 mmol), ethyl acrylate (0.30 mmol), Pd catalyst (10 mol%), DCE/HFIP (9:1, 0.5 mL). All the reactions are carried out at 100 °C for 24 h. Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] 10 mol% ligand is used. [c] The reaction was performed in N_2.

With respect to the olefin coupling partners, α,β-unsaturated ketones, and aldehydes are reactive, albeit with lower yields (**3p**–**3r**). These products have higher reactivity as Michael acceptors which may offer unique opportunities as covalent ligands of biologically interesting proteins (Table 3).[11]

On the basis of our previous mechanistic studies, a putative catalytic cycle is proposed for the pyrazole-directed C(sp^3)–H Heck-type olefination (Scheme 3). The pyrazole directs C(sp^3)–H activation to form 5-membered palladacycle intermediate **A**. Subsequent migratory insertion of **A** gives the olefinated product **3**. The Pd^0 formed from the β-hydride elimination and reductive elimination steps is oxidized by the Cu^{II} oxidant to close the catalytic cycle.

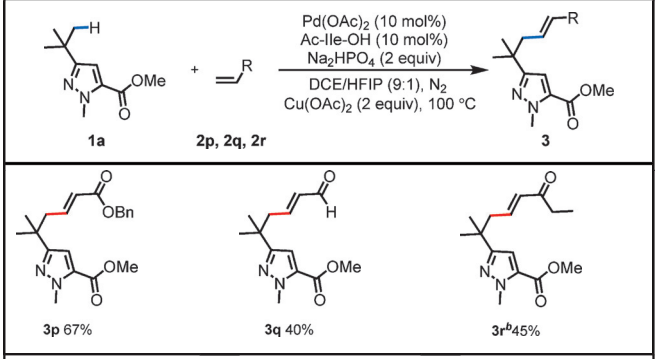
In conclusion, a pyrazole-directed C(sp^3)–H olefination has been developed for the first time. Our investigations revealed that mono-protected amino acid (MPAA) ligands are found to promote C(sp^3)–H olefination. The transformation has proven to be tolerant to a wide variety of functional groups thus enabling late stage diversification of candidate scaffolds.

Table 2. Scope of substrates in Pd-catalyzed C(sp^3)–H olefination.[a]

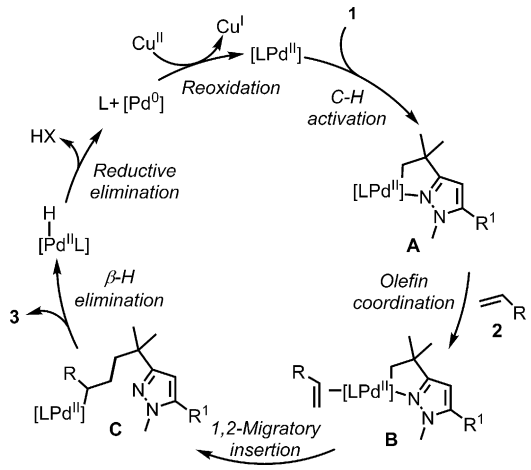


Reaction conditions: [a] heterocycles **1** (0.1 mmol), ethyl acrylate (0.60 mmol), Pd catalyst (10 mol%), ligand (10 mol%), DCE/HFIP (9:1, 1.0 mL). All reactions were carried out at 100 °C for 24 h. All yields are isolated yields.

Table 3. Scope of olefins in Pd-catalyzed C(sp^3)–H olefination.[a]



Reaction conditions: [a] Reaction conditions: heterocycles **1a** (0.1 mmol), olefins (0.60 mmol), $Pd(OAc)_2$ (10 mol%, **3r**). [b] 15 mol%), ligand (10 mol%), DCE/HFIP (9:1, 1.0 mL). All reactions were carried out at 100 °C for 24 h. All yields are isolated yields.



Scheme 3. Proposed catalytic pathway.

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Keywords: amino acid ligands · C–H activation · olefination · organic chemistry · pyrazole

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