Cascade C–H Activation

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Orchestrated Triple C–H Activation Reactions Using Two Directing Groups: Rapid Assembly of Complex Pyrazoles**

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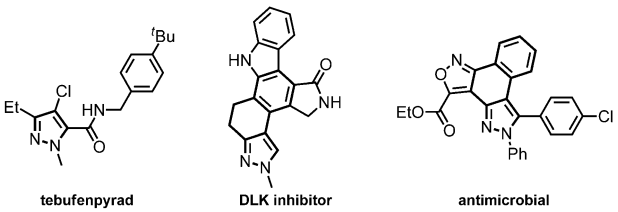
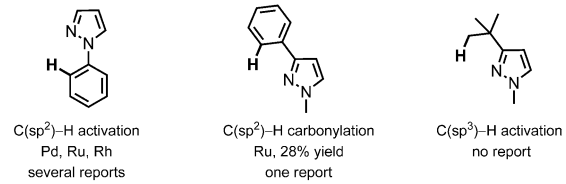
Abstract: *A sequential triple C–H activation reaction directed by a pyrazole and an amide group leads to the well-controlled construction of sterically congested dihydrobenzo[e]indazole derivatives. This cascade reaction demonstrates that the often problematic competing C–H activation pathways in the presence of multiple directing groups can be harvested by design to improve step economy in synthesis. Pyrazole as a relatively weak coordinating group is shown to direct C_{sp^3}–H activation for the first time.*

C–H activation reactions on heterocyclic substrates directed by simple functional groups are often complicated by competing C–H activation events due to the intrinsic directing ability of the heterocycles themselves.[1] The lack of methods to activate C–H bonds at positions other than those *ortho* to heterocycles hampers their applications in medicinal chemistry and organic synthesis. Whereas the development of a powerful directing group to override the cyclometalation directed by the heterocycle is an important future direction in achieving the desired regioselectivity, the development of conditions that allow C–H activation events to proceed in an orchestrated sequence at different positions could be fruitful for constructing complex structures in a cascade manner. Indeed, cascade C–H activation reactions using both Pd^0/ArI and Pd^{II} catalysts has been elegantly exploited to assemble complex molecules.[2] Herein we report a Pd^{II}-catalyzed sequential pyrazole-directed C_{sp^3}–H arylation followed by an intramolecular dual amide-directed C–H activation–cyclization event to afford complex dihydro benzo[*e*]indazole derivatives. Facile access to such ring systems which possess a high number of functional groups would be of high value to both synthetic and medicinal chemistry (Scheme 1).[3]

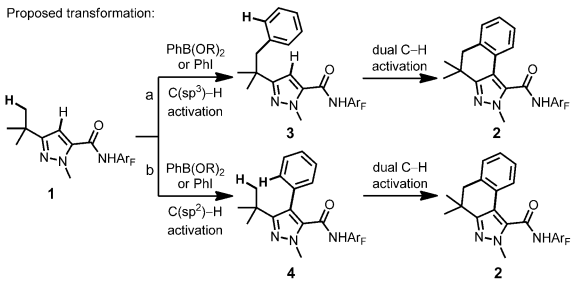
To date pyrazole-directed C–H activation reactions have been largely limited to C_{sp^2}–H bonds of the aryl attached to the pyrazole nitrogen (Scheme 2).[4,5] The pyrazole-directed C_{sp^3}–H activation has not yet been demonstrated. The orchestration of the sequential C–H activation directed by the pyrazole and the Wasa–Yu auxiliary in the desired order and regioselectivity is challenging and may critically depend on the reaction conditions and choice of coupling partners (Scheme 3).



Scheme 1. Biologically active pyrazoles and benzo[*e*]indazole derivatives.



Scheme 2. Pyrazole-directing C–H activations.



Scheme 3. Triple C–H activation reactions using two directing groups.

Our design aimed at investigating two possible reaction pathways. Pathway a relies on the pyrazole-directed C_{sp^3}–H arylation to be the initiating step. Alternatively, in pathway b the amide would be the dominant directing group leading to directed C–H arylation at the 4-position as the first step. In both pathways, we anticipate that subsequent C–H activation directed by the amide or pyrazole could trigger an intramolecular dual C–H activation to form complex dihydro benzo[*e*]indazoles **2** bearing a quaternary carbon center.

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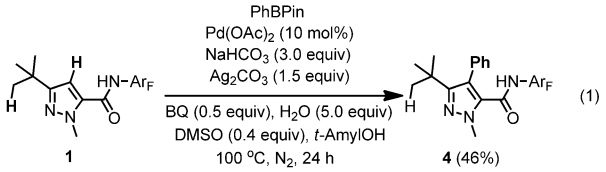
Based on the successful development of C–H activation on pivalic acid derivatives,[6] our initial investigation used 3-*tert*-butyl pyrazole-5-carboxamide (**1**) and phenyl boronate pinacol ester. Under standard conditions described previously by us[7] the amide-directed C–H arylation product **4** was obtained as the exclusive product [Eq. (1)]. This result

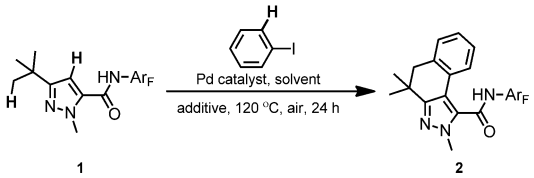


(1)

suggests that the intrinsic directing power of the pyrazole can be overridden by weakly coordinating amide as auxiliary under these conditions. Unfortunately, the anticipated subsequent C–H activation reactions depicted in pathway b did not occur.

Considering the difficulty of activating the C_{sp^3}–H bonds using pyrazole as the directing group, we decided to focus on identifying conditions for the arylation of the methyl C–H bonds of the *tert*-butyl group. We found that the reaction of **1** with $Pd(OAc)_2$ (10 mol%) and Ag_2CO_3 in AcOH at 120 °C gave product **2** in 50% yield (Table 1, entry 1). Apparently, the initially arylated product underwent subsequent dual C–H activation to furnish the cascade product as depicted in pathway a (Scheme 3). Among the oxidants tested, Ag_2O is most effective affording the cascade product in 71% yield (entry 4). Nitrogen or oxygen atmosphere has little influence on the reactivity (entries 5 and 6). $Pd(OTf)_2(MeCN)_4$ was identified as the most effective catalyst affording 83% NMR yield and 76% yield of the isolated product (entries 7–9). Further screening of solvents confirmed that the use of AcOH as the solvent is crucial for this reaction (entries 10–13). Other commonly used oxidants including benzoquinone (BQ), $Cu(OAc)_2$, and $Cu(OTf)_2$ are not suitable for this reaction leading to recovery of the starting material only.

Table 1: Optimization studies of Pd-catalyzed triple C–H activation.



Entry[a]	Catalyst	Additive	Solvent	Yield [%]
1	$Pd(OAc)_2$	Ag_2CO_3	AcOH	50
2	$Pd(OAc)_2$	AgOAc	AcOH	54
3	$Pd(OAc)_2$	$AgNO_3$	AcOH	0
4	$Pd(OAc)_2$	Ag_2O	AcOH	71
5[b]	$Pd(OAc)_2$	Ag_2O	AcOH	72
6[c]	$Pd(OAc)_2$	Ag_2O	AcOH	68
7	$PdCl_2$	Ag_2O	AcOH	68
8	$Pd(TFA)_2$	Ag_2O	AcOH	68
9[d]	**$Pd(OTf)_2(MeCN)_4$**	**Ag_2O**	**AcOH**	**83**
10	$Pd(OTf)_2(MeCN)_4$	Ag_2O	toluene	trace
11	$Pd(OTf)_2(MeCN)_4$	Ag_2O	DCE	0
12	$Pd(OTf)_2(MeCN)_4$	Ag_2O	DMF	0
13	$Pd(OTf)_2(MeCN)_4$	Ag_2O	HFIP	13
14	$Pd(OTf)_2(MeCN)_4$	BQ	AcOH	0
15	$Pd(OTf)_2(MeCN)_4$	$Cu(OAc)_2$	AcOH	0
16	$Pd(OTf)_2(MeCN)_4$	$Cu(OTf)_2$	AcOH	0
17[e]	$Pd(OTf)_2(MeCN)_4$	$K_2S_2O_8$	AcOH	0

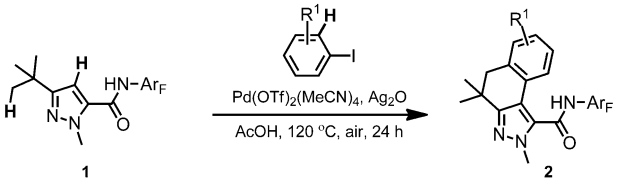
[a] $Ar_F = (4\text{-}CF_3)C_6F_4$. Reaction conditions: amide **1** (0.05 mmol), phenyl iodide (0.15 mmol), Pd catalyst (10 mol%), additive (0.10 mmol), and AcOH (0.5 mL) at 120 °C for 24 h. Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as the internal standard. [b] The reaction was performed in N_2. [c] The reaction was performed in O_2. [d] The yield of the isolated product is 76%. [e] Acetoxylation of *tert*-butyl with 44% yield. DCE = dichloroethane; DMF = dimethylformamide; HFIP = hexafluoro-2-propanol; TFA = trifluoroacetic acid.

With the optimized conditions in hand, we examined the scope of aryl iodides (Table 2). The cascade reaction with *para*- or *meta*-substituted aryl iodides afforded the desired benzo[*e*]indazoles in 62–78% yields (**2b–d**), whereas *ortho*-substituted aryl iodides were not compatible due to steric hindrance. The use of phenyl- or methoxy-substituted starting materials resulted in lower yields in the range of 45–52% (**2e–h**). The use of fluorinated, and chlorinated aryl iodides gave the desired products in 61–83% yield (**2i–k**). Phosphonate, acetate, and ester functionalities are all tolerated providing synthetically useful yields (**2l–o**). The intramolecular arylation with the newly installed aryl group consistently occurs at the less hindered position with complete regiochemical control.

The compound 3-*tert*-butylpyrazole (**1**) was initially chosen based on previous success in pivalic acid functionalization.[6] In our efforts to broaden the scope of this method, we found that substituting the *tert*-butyl with *iso*-propyl or ethyl groups led to complete loss of reactivity under current conditions. The lack of reactivity of these type of substrates has been attributed to the Thorpe–Ingold effect.[8] However, a variety of tertiary alkyls are compatible (Table 3). Arylation of these substrates with two representative aryl iodides bearing electron-withdrawing fluoro and electron-donating methyl groups proceeded to give a variety of benzo[*e*]indazoles (**2p–w**). Notably, this reaction could also be applied to the synthesis of a spiro compound **2x**, albeit in lower yield. Unfortunately, the replacement of one of the methyl groups in the substrate by an acetoxymethyl functional group decreased the reactivity, affording the desired product only in trace amount. We also found that the reaction is quite sensitive to the steric effects of the *N*-alkyl group. Whereas the *N*-ethyl group was tolerated (**$2a_1$–b_1**), the compound **$2c_1$** with an *N*-isopropyl group was obtained in a lower yield of 32%; further beta-branching (e.g., *N*-cyclopropylmethyl) completely abolished reactivity. These observations are consistent with the proposed pathway that starts with a pyrazole-directed C_{sp^3}–H activation, which can be hampered by the steric hindrance of the chelating nitrogen atom.

The successful orchestration of this cascade reaction critically depends on the selectivity of each C–H activation step, because competing C–H activation processes directed by two directing groups could give a mixture of multiple products. The preferential activation of the C_{sp^3}–H directed by pyrazole is surprising considering the lack of such examples. To obtain evidence in support of reaction pathway a

Table 2: Scope and limitations of Pd-catalyzed triple C–H activation.[a]



1 → 2

2a 76% | **2b** 78% | **2c** 72%

2d 62% | **2e** 50% | **2f** 46%

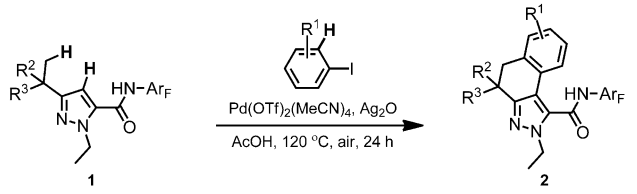
2g 45% | **2h** 52% | **2i** 83%

2j 75% | **2k** 61% | **2l** 63%

2m 61% | **2n** 47% | **2o** 60%

[a] $Ar_F = (4\text{-}CF_3)C_6F_4$. Reaction conditions: amide **1** (0.1 mmol), aryl iodide (0.3 mmol), Pd catalyst (10 mol%), Ag_2O (0.20 mmol), and AcOH (1.0 mL) at 120°C for 24 h. Yields are of isolated products.

Table 3: Scope and limitations of Pd-catalyzed triple C–H activation.[a]



1 → 2

2p 61% | **2q** 50% | **2r** 51%

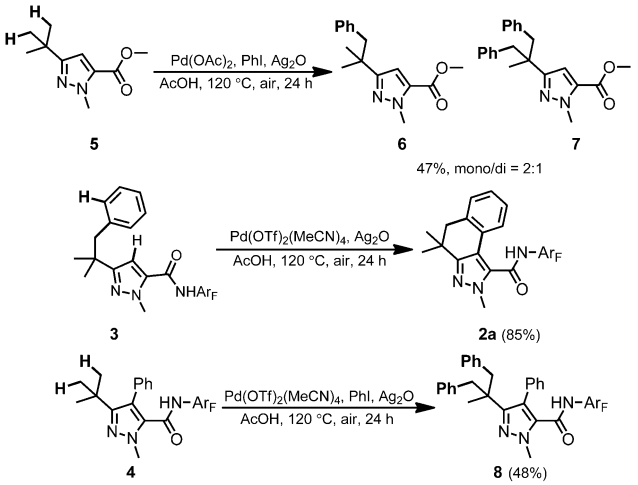
2s 46% | **2t** 67% | **2u** 60%

2v 70% | **2w** 67% | **2x** 28%

2a$_1$ 62% | **2b$_1$** 70% | **2c$_1$** 32%

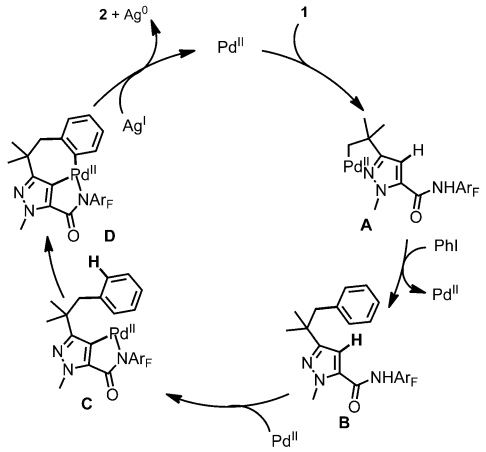
[a] $Ar_F = (4\text{-}CF_3)C_6F_4$. Reaction conditions: amides **1** (0.05 mmol), aryl iodide (0.15 mmol), Pd catalyst (10 mol%), Ag_2O (0.10 mmol), and AcOH (0.5 mL) at 120°C for 24 h. Yields are of isolated products.

(Scheme 3), we subjected the ester substrate **5** to the standard conditions and the arylation of the methyl group occurs to give mono- and diarylation products with a ratio of 2:1 (Scheme 4). As expected, the subsequent C–H activation did not proceed without the amide directing group. The mono-arylated product **6** was then converted to the amide **3** and subjected to the standard conditions. The desired cascade product **2a** was obtained in 85% yield supporting the intermediacy of **3**. In contrast, when the proposed intermediate **4** in pathway b was subjected to the standard conditions, only arylation at the methyl group and no formation of the cascade product was observed. These combined results are



Scheme 4. Mechanistic investigations.

consistent with the first step of C_{sp^3}–H activation directed by pyrazoles via Pd^{II}/Pd^{IV} catalysis (Scheme 5). The amide then directs the *ortho*-palladation to give the palladated intermediate, which further activates the *ortho*-phenyl C–H bond to give **D**. Reductive elimination from **D** gives the final product **2** (Scheme 3, pathway a).



Scheme 5. Proposed catalytic pathway.

In conclusion, we have demonstrated the feasibility to control the order of C–H activation at different positions in the presence of two competing directing groups. The successfully orchestrated cascade triple C–H activation reaction provides a short route for the synthesis of medicinally important benzo[*e*]indazole derivatives. Detailed mechanistic elucidation points to the involvement of an unprecedented C_{sp^3}–H activation directed by pyrazoles followed by a dual C–H activation.

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