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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(sp³)–H activation for the first time.

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Keywords

Pyrazole; C–H activation; cascade; benzo[*e*]indazole

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] 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. While developing a powerful directing group to override the cyclometalation directed by the heterocycle is an important future direction in achieving the desired regio-selectivity, developing conditions to allow C–H activation events to proceed in an orchestrated sequence at different positions could be fruitful towards 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(sp³)–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 are rich in functionality and 3-dimensionality would be of high value to both synthetic and medicinal chemistry.^[3]

To date pyrazole-directed C–H activation reactions have been largely limited to C(sp²)–H bonds of the aryl attached to the pyrazole nitrogen (Scheme 2).^[4, 5] The pyrazole-directed C(sp³)–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).

Our design aimed to investigate two possible reaction pathways. Pathway **a** relies on the pyrazole-directed C(sp³)–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. Based on 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 was obtained as the exclusive product (eq 1). This result suggests that the intrinsic directing power of the pyrazole can be over-ridden by the amide bearing the Wasa-Yu auxiliary under these conditions. Unfortunately, the anticipated subsequent C–H activation reactions depicted in pathway **b** did not occur.

[Eq. 1]

Considering the difficulty of activating the sp^3 C–H bonds using pyrazole as the directing group, we elected to focus on identifying conditions for arylating the methyl C–H bonds of the *t*-Butyl group. We found that the reaction of **1** with Pd(OAc)₂ (10 mol%), Ag₂CO₃ 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, Ag₂O is most effective affording the cascade product in 71% yield (Table 1, entry 4). Nitrogen or oxygen atmosphere has little influence on the reactivity (Table 1, entries 5 and 6).

Pd(OTf)₂(MeCN)₄ was identified as the most effective catalyst affording 83% NMR yield and 76% isolated yield (Table 1, entries 7–9). Further screening of solvents confirmed that the use of AcOH as the solvent is crucial for this reaction (Table 1, entries 10–13). Other commonly used oxidants including BQ, Cu(OAc)₂ and Cu(OTf)₂ are not suitable for this reaction leading to recovery of the starting material only.

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. Substitutions with phenyls or methoxy groups decreased the yields to the range of 45–52% (**2e–h**). The use of fluorinated, chlorinated, and brominated aryl iodides gave the desired products in 61–83% yields (**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.

3-*tert*-butylpyrazole **1** was initially chosen based on previous successes in pivalic acid functionalization.^[6] In our efforts to broaden the scope of this method, we found that substituting the *tert*-butyl with *i*-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 proceeded to give a variety of benzo[*e*]indazoles (**2p–w**). Notably, this reaction could also be applied to the synthesis of spiro compound albeit in lower yield (**2x**). We also found that the reaction is quite sensitive to the steric effects of the *N*-alkyl group. While the *N*-ethyl group was tolerated (**2a₁–b₁**), the *N*-isopropyl group decreased the yield to 32% (**2c₁**) while further beta-branching (eg. *N*-cyclopropylmethyl) completely abolished reactivity. These observations are consistent with

proposed pathway that the reaction starts with the pyrazole-directed C(sp³)-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 as competing C-H activation processes directed by two directing groups could give a mixture of multiple products. The preferential activation of the C(sp³)-H directed by pyrazole is surprising considering the lack of such examples. To obtain evidence in support of reaction pathway **a** (Scheme 3), we subjected the ester substrate **6** to the standard conditions and the arylation of the methyl group occurs to give mono- and di-arylation products with a ratio of 2:1 (Scheme 4). As expected the subsequent C-H activation did not proceed without using the amide directing group. The mono-arylated product **7** 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, the proposed intermediate **4** in pathway **b**, when subjected to the standard conditions, only led to arylation at the methyl group without forming the cascade product. These combined results are consistent with the first step of C(sp³)-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**).

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(sp³)-H activation directed by pyrazoles followed by a dual C-H activation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

sp² C-H activation
Pd, Ru, Rh
Several reports

sp² C-H carbonylation
Ru, 28% yield
One report

sp³ C-H activation
No report

Scheme 2.
Pyrazole-directing C-H activations.

Proposed transformation:

Scheme 3.

Triple C-H activation reactions using two directing groups.

Scheme 4.
Mechanistic investigations.

Scheme 5.
Proposed catalytic pathway.

Table 1

Optimization studies of Pd-catalyzed dual C–H activation

Entry ^[a]	Catalyst	Additive	Solvent	Yield
1	Pd(OAc) ₂	Ag ₂ CO ₃	AcOH	50%
2	Pd(OAc) ₂	AgOAc	AcOH	54%
3	Pd(OAc) ₂	AgNO ₃	AcOH	0%
4	Pd(OAc) ₂	Ag ₂ O	AcOH	71%
5 ^[b]	Pd(OAc) ₂	Ag ₂ O	AcOH	72%
6 ^[c]	Pd(OAc) ₂	Ag ₂ O	AcOH	68%
7	PdCl ₂	Ag ₂ O	AcOH	68%
8	Pd(TFA) ₂	Ag ₂ O	AcOH	68%
9 ^[d]	Pd(OTf)₂(MeCN)₄	Ag₂O	AcOH	83%
10	Pd(OTf) ₂ (MeCN) ₄	Ag ₂ O	Toluene	Trace
11	Pd(OTf) ₂ (MeCN) ₄	Ag ₂ O	DCE	0%
12	Pd(OTf) ₂ (MeCN) ₄	Ag ₂ O	DMF	0%
13	Pd(OTf) ₂ (MeCN) ₄	Ag ₂ O	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)	K ₂ S ₂ O ₈	AcOH	0%

^[a] ArF = (4-CF₃)C₆F₄. 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 the ¹H NMR using CH₂Br₂ as the internal standard.

^[b] The reaction was performed in N₂.

^[c] The reaction was performed in O₂.

^[d] Isolated yield is 76%.

^[e] Acetoxylation of *tert*-butyl with 44% isolated yield.

Table 2Scope and limitations of Pd-catalyzed dual C–H activation^[a]

^[a] Ar_F = (4-CF₃)C₆F₄. Reaction conditions: amide **1** (0.1 mmol), phenyl iodide (0.3 mmol), Pd catalyst (10 mol %), Ag₂O (0.20 mmol) and AcOH (1.0 mL) at 120 °C for 24 h. Yields were isolated yield.

Table 3

Scope and limitations of Pd-catalyzed dual C–H activation^[a]

^[a] Ar_F = (4- 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 $120\text{ }^\circ\text{C}$ for 24 h. Yields were isolated yield.