C–H Activation

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Ligand-controlled Regiodivergent C–H Alkenylation of Pyrazoles and its Application to the Synthesis of Indazoles

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Abstract: *Regioselective C4-, C5-, and di-alkenylations of pyrazoles were achieved. An electrophilic Pd catalyst generated by trifluoroacetic acid (TFA) and 4,5-diazafluoren-9-one (DAF) leads to C4-alkenylation, whereas KOAc and mono-protected amino acid (MPAA) ligand Ac-Val-OH give C5-alkenylation. A combination of palladium acetate, silver carbonate, and pivalic acid affords dialkenylation products. Annulation through sequential alkenylation, thermal 6π-electrocyclization, and oxidation gives functionalized indazoles. This comprehensive strategy greatly expands the range of readily accessible pyrazole and indazole derivatives, enabling useful regiodivergent C–H functionalization of pyrazoles and other heteroaromatic systems.*

Pyrazole is an important heterocycle that is frequently found in drugs and ligands for transition metals.[1] Synthetic methods for conveniently accessing highly functionalized pyrazoles are therefore desirable. Cross-coupling reactions have previously been utilized,[2] but they require pre-functionalized building blocks that are costly, not readily available, and often unstable. Direct C–H functionalization is an alternative, but this heterocyclic core presents a challenge for regioselectivity.[3] Generally, electrophilic aromatic substitution favors the C4 position, whereas strong-base-mediated substitution favors the C5 position (Figure 1 A).[4] The nucleophilicity at the C4 position and the acidity of the C–H bond at the C5 position make both positions susceptible to Pd catalysts,[5] and C–C bond forming catalysis often gives mixtures of mono- and disubstituted products.[6,7] To date, it has not been possible to exploit the electronic difference between the (C4/C5)–H bonds for a regiodivergent synthetic methodology.[8]

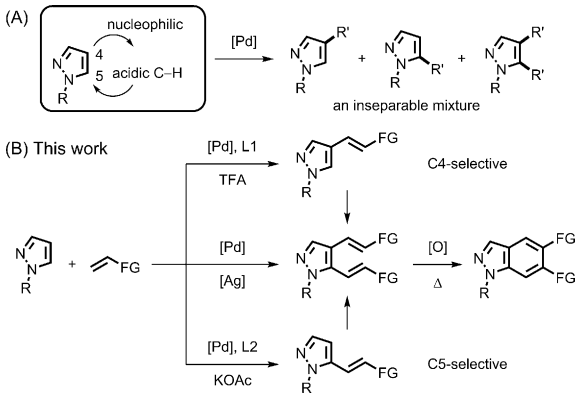

Figure 1. A) General reactivity of pyrazole. B) Strategies for C4-, C5-, and di-alkenylation and synthesis of indazoles. FG = functional group.

We developed regioselective C4-, C5-, and C4,5-alkenylation of simple pyrazoles (Figure 1 B)[9] by recognizing that an electrophilic Pd catalyst may prefer the nucleophilic C4 position, whereas efficient deprotonation may enable alkenylation at the C5 position. Moreover, an appropriate transition-metal carboxylate may facilitate metalation at both the C4 and C5 positions[10] to give multifunctionalized indazoles, which are pharmacologically important heterocycles.[11]

Extensive catalyst screening identified the regiodivergent alkenylation of *N*-methyl pyrazole with *n*-butyl acrylate (Table 1). From the outset, we were intrigued by the mechanism involving electrophilic Pd^{II} species $[Pd(TFA)]^+$ that has been applied to the C3-alkenylation of indoles.[12] Interestingly, the reaction was sensitive to the addition of trifluoroacetic acid (TFA), resulting in pronounced C4 regioselectivity (entry 1), and the 4,5-diazafluoren-9-one (DAF) ligand was critical (entry 2).[13] Thus, both TFA and DAF promoted the regioselective C4-alkenylation of the pyrazole (entry 3). While the model reaction including *N*-methyl pyrazole and butyl acrylate did not require 1,4-benzoquinone (BQ; entry 4), it increases the yields with other substrates by about 5–10%.[14] The addition of TFA maintained the C4 selectivity with mono-N-protected amino acid (MPAA) ligands, such as Ac-Val-OH (entry 5), in contrast to the high C5 selectivity of the same ligand in the presence of base (see below).

In order to selectively functionalize the acidic (C5)–H bond, a base was added. Although the selectivity of the DAF ligand switched to favor the C5 position with KOAc, the yield

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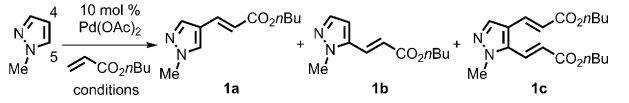
Table 1: Optimization of regiodivergent C–H alkenylation of *N*-methyl pyrazole.



Entry	Ligand	Additive	Oxidant	Solvent	Yield [%][a] 1a	1b	1c
1[b]	–	TFA	O_2	1,4-dioxane	53	–	6
2[b]	DAF	–	O_2	1,4-dioxane	52	13	31
3[b]	DAF	TFA	O_2	1,4-dioxane	90	–	3
4[b,c]	DAF	TFA	O_2, BQ	1,4-dioxane	88	2	5
5[b]	Ac-Val-OH	TFA	O_2	1,4-dioxane	67	1	6
6[d]	DAF	KOAc	air	DMA:1,4-dioxane (2:1)	8	32	19
7[d]	Ac-Val-OH	KOAc	air	DMA	–	53	11
8[d]	Ac-Val-OH	KOAc	air	DMA:1,4-dioxane (2:1)	1	87	5
9[d]	Ac-Ile-OH	KOAc	air	DMA:1,4-dioxane (2:1)	3	79	6
10[d]	Ac-Leu-OH	KOAc	air	DMA:1,4-dioxane (2:1)	12	74	1
11[e]	–	–	$Cu(OAc)_2$	1,4-dioxane	43	5	32
12[e]	–	PivOH	$Cu(OAc)_2$	1,4-dioxane	47	6	41
13[e]	–	–	AgOAc	1,4-dioxane	28	9	6
14[e]	–	–	Ag_2CO_3	1,4-dioxane	7	32	6
15[e]	–	PivOH	Ag_2CO_3	1,4-dioxane	14	8	71

DAF

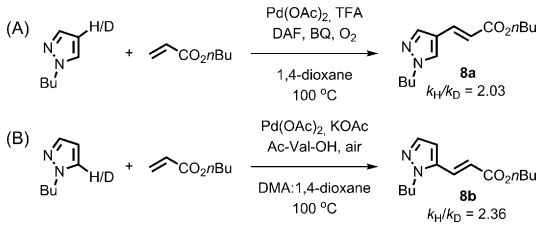
R = iPr: Ac-Val-OH
s-Bu: Ac-Ile-OH
iBu: Ac-Leu-OH

[a] ^{1}H NMR yield. [b] 1.5 equiv of butyl acrylate, 10 mol% of $Pd(OAc)_2$, 10 mol% of ligand, 20 mol% of additive, under 1 atm of O_2, solvent (0.50 M), at 100 °C, 24 h. [c] 30 mol% of BQ was added. [d] 1.5 equiv of butyl acrylate, 10 mol% of $Pd(OAc)_2$, 20 mol% of ligand, 1.0 equiv of additive, solvent (0.17 M), open to air, at 100 °C, 12 h. [e] 3.0 equiv of butyl acrylate, 10 mol% of $Pd(OAc)_2$, 2.0 equiv of additive, 2.5 equiv of oxidant, solvent (0.17 M), at 120 °C, 12 h. DMA = *N*,*N*-dimethylacetamide.

was low (entry 6). In conjunction with a base, the MPAA ligands showed distinctive C5 selectivity (entry 7),[15] showing negligible amounts of C4-alkenylation product. Mixing DMA and 1,4-dioxane (2:1) enhanced the C5 selectivity (entry 8) and in this mixed solvent system, Ac-Val-OH performed better (entries 9 and 10).

Finally, the C4,5-dialkenylation was optimized (entry 15) by combining pivalic acid and silver carbonate to give a good yield of the corresponding dialkenyl pyrazole **1c**, while synthetic methods based on other oxidants were not efficient (entries 11–14). The in situ formation of AgOPiv from Ag_2CO_3 and PivOH presumably promotes the C–H cleavage step.[16]

Preliminary mechanistic studies indicate that in the catalytic cycles for both C4- and C5-alkenylation, the palladation is rate-limiting based on kinetic isotope effects (Scheme 1). DFT calculations (Figure 2 and the Supporting Information)[5] fully support our conceptual proposal and show that C–H activation through concerted metalation–deprotonation (CMD) determines the regiochemistry. **1a** is formed by (DAF)Pd via the transition state **i-TS-ii** at



Scheme 1. Kinetic isotope effects.

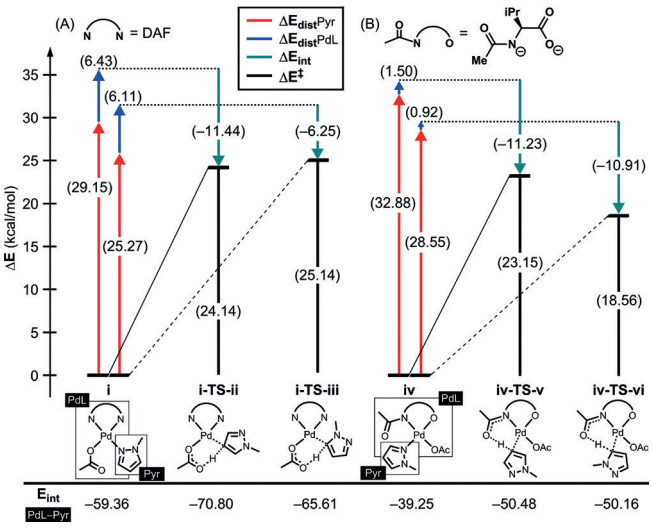
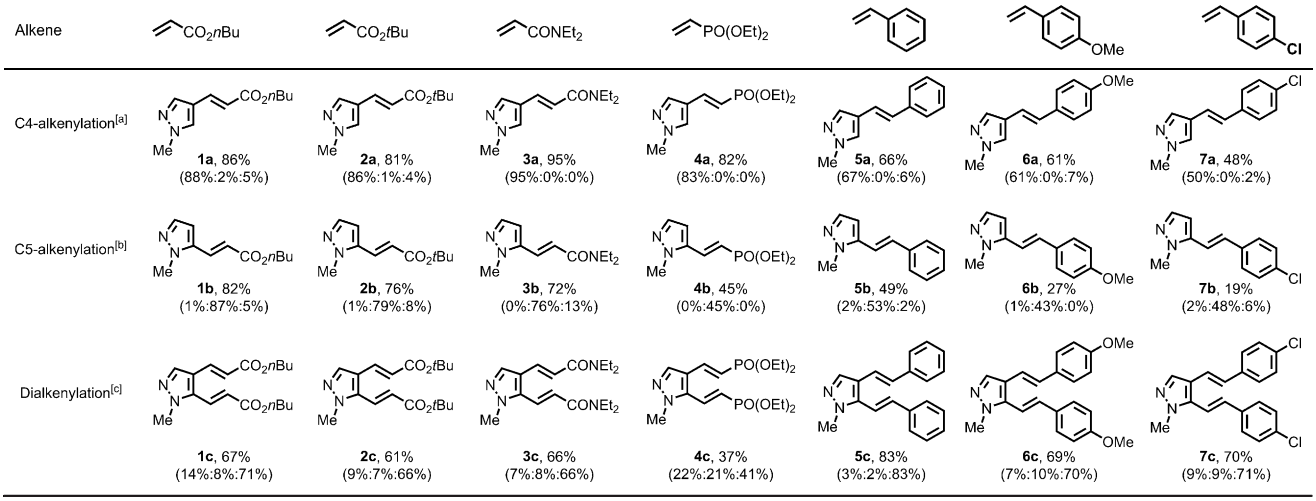


Figure 2. Computed electronic energy diagrams for C–H cleavage in kcal mol^{-1}. A) DAF ligand. B) Ac-Val-OH ligand (Pyr = pyrazole).

24.1 kcal mol^{-1}, which is around 1 kcal mol^{-1} lower than **i-TS-iii**, which gives **1b**, thus correctly suggesting that the DAF ligand preferentially affords **1a**. In contrast, the dianionic MPAA ligand lowers the CMD transition state **iv-TS-vi** to 18.6 kcal mol^{-1}, which is nearly 5 kcal mol^{-1} lower than **iv-TS-v**. Whereas these computed energies should be taken with some caution, the predicted regioselectivity values are meaningful. The energy component analysis reveals that the neutral DAF ligand renders the Pd highly electrophilic, with Pd–pyrazole interaction energies (E_{int}) around 65–70 kcal mol^{-1}, which is nearly 20 kcal mol^{-1} stronger than in the MPAA–Pd analogue. The Pd–pyrazole interaction energy in **i-TS-ii** is −11.4 kcal mol^{-1} and is much stronger than the −6.3 kcal mol^{-1} found in **i-TS-iii**: the more nucleophilic C4 carbon binds to Pd more strongly. The dianionic MPAA ligand makes the Pd much less electrophilic and the difference in nucleophilicity between C4 and C5 has no impact. Instead, the energies of **iv-TS-v/vi** are determined by the MPAA-mediated deprotonation, which is directly correlated to the distortion of pyrazole (ΔE_{dist}Pyr). Here, the higher acidity of the C5 proton lowers the energy of **iv-TS-vi** compared to **iv-TS-v**.

Next, the substrate scope with respect to alkenes was examined (Table 2), including a wide range of olefins, such as acrylates, acrylamides, vinyl phosphonates, and styrenes. Upon simply switching the catalysts, *N*-methyl pyrazole provided the corresponding C4-, C5-, and C4,5-alkenylation products in good yields. The strength of this strategy is

Table 2: Substrate scope: alkenes



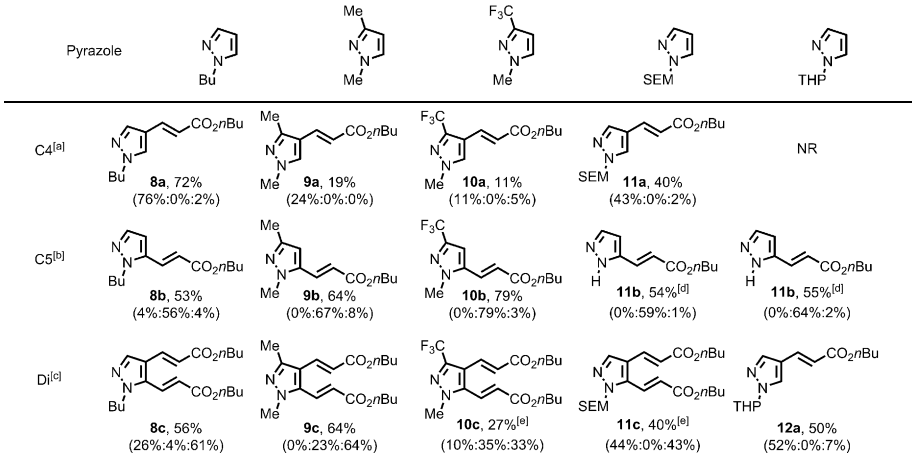
[a] Reaction conditions: *N*-methyl pyrazole (1.0 mmol), alkene (1.5 mmol), $Pd(OAc)_2$ (0.10 mmol), DAF (0.10 mmol), TFA (0.20 mmol), BQ (0.30 mmol), 1,4-dioxane (2.0 mL), 1 atm of O_2, 100 °C, 24 h. [b] Reaction conditions: *N*-methyl pyrazole (0.50 mmol), alkene (0.75 mmol), $Pd(OAc)_2$ (0.050 mmol), Ac-Val-OH (0.10 mmol), KOAc (0.50 mmol), 1,4-dioxane (1.0 mL), DMA (2.0 mL), air, 100 °C, 12 h. [c] Reaction conditions: *N*-methyl pyrazole (0.50 mmol), alkene (1.5 mmol), $Pd(OAc)_2$ (0.050 mmol), PivOH (1.0 mmol), Ag_2CO_3 (1.25 mmol), 1,4-dioxane (3.0 mL), 120 °C, 12 h. Yields in parentheses (C4:C5:di) were determined by ^{1}H NMR analysis with an internal standard.

demonstrated in the diversity of the resulting pyrazoles obtained from commercially available, inexpensive pyrazoles and alkenes in a single step. In addition, the alkenylation reactions could be generally applied to pyrazole derivatives with different substituents at the N1 and C3 positions (Table 3), although the C4-alkenylation appeared to be sensitive to steric effects by the C3 substituents. It was also feasible to access C3-alkenyl pyrazoles from the corresponding C5-alkenylation products of SEM pyrazole through N-methylation and SEM removal (see the Supporting Information).[7a] It is notable that the dialkenylation conditions produced the C4-alkenylation product of THP pyrazole that could not be obtained under the acidic C4-alkenylation conditions.

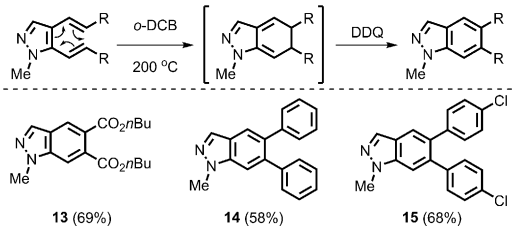
The alkenylation of pyrazoles offers the opportunity to construct multisubstituted indazoles, which are a clinically validated but under-represented heterocycle in modern medicinal chemistry (Scheme 2).[17] Thermal 6π-electrocyclization of the dialkenylation products followed by oxidation using DDQ formed the anticipated indazole cores, giving **13**–**15** in good yields.[18]

The successful oxidative cyclization reaction inspired the preparation of indazoles with different substituents (Scheme 3). A second alkenylation of the C4- and C5-alkenylation products, **5a** and **1b**, respectively, by using the [Pd]/[Ag] dialkenylation method affords the common product **16** (Scheme 3A). This result suggested that both C4–C5 and C5–C4 alkenylation sequences may be adopted for the sequential alkenylation of pyrazoles. The resulting dialkenylation product **16** readily underwent ring-closure to give indazole **17**. Furthermore, simple pyrazoles could be converted into polycyclic π-extended fused pyrazoles, which have been under-explored as functional materials.[19] Subsequent to sequential alkenylation and oxidative cyclization, the intramolecular C–H arylation of **20** provided the corresponding π-extended triphenylene-fused pyrazole **21** (Scheme 3B).[20] This synthetic strategy based on the sequential alkenylation of pyrazoles

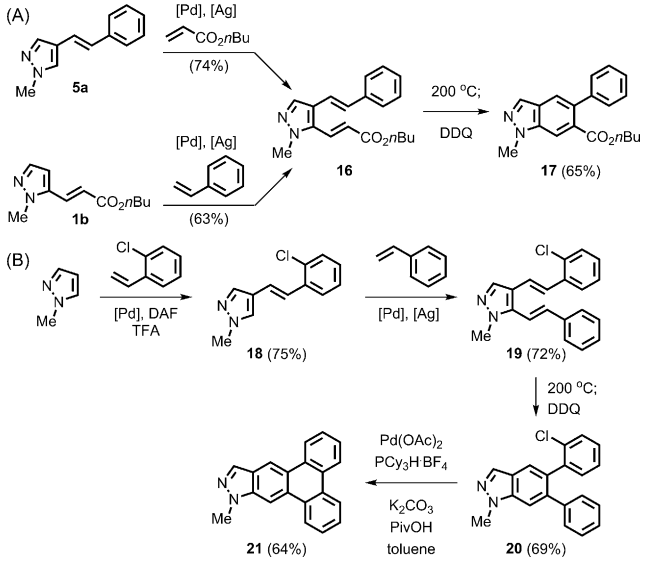
Table 3: Substrate scope: pyrazoles



[a] C4-alkenylation conditions as in Table 2. [b] C5-alkenylation conditions as in Table 2. [c] Dialkenylation conditions as in Table 2. [d] The product was isolated after deprotection due to an isolation problem. [e] The reaction was performed in *N*,*N*- dimethylformamide (DMF) instead of 1,4-dioxane. NR = no reaction. SEM = 2-(trimethylsilyl)ethoxymethyl. Yields in parentheses (C4:C5:di) were determined by ^{1}H NMR analysis with an internal standard.



Scheme 2. Synthesis of indazoles through 6π-electrocyclization/oxidation of dialkenylation products. DCB = 1,2-dichlorobenzene, DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.



Scheme 3. Synthesis of functionalized indazoles enabled by sequential alkenylation followed by 6π-electrocyclization and oxidation.

with alkenes offers flexibility in the design and synthesis of indazoles and related polycyclic benzo-fused pyrazoles.

In conclusion, we have developed regioselective C–H alkenylation reactions of pyrazoles by exploiting the electronic differences of C–H bonds in the heterocycle. Three distinctive Pd catalysts enable C4-, C5-, and di-alkenylation of commercially available, low-cost pyrazoles using alkenes. Preliminary mechanistic studies showed that the C–H cleavage step is the rate- and regio-determining step. These results have broad implications for the C–H functionalization of pyrazoles and the application of DAF and amino acid ligands for Pd-catalyzed regiodivergent coupling reactions. A sequence involving thermal 6π-electrocyclization of dialkenyl pyrazoles and oxidation afforded indazoles. This comprehensive strategy provides a wide range of pyrazole and indazole derivatives for applications in medicinal chemistry and the development of functional materials.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenylation · C–H activation · indazole · palladium · pyrazole

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[20] In the synthesis of diarylindazole **14**, the formation of the corresponding triphenylene structure **21** was not detected after extended heating.

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