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Angewandte International Edition

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201709162
Angew. Chem. 10.1002/ange.201709162

Link to VoR: http://dx.doi.org/10.1002/anie.201709162
http://dx.doi.org/10.1002/ange.201709162

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

Hyun Tae Kim,[a] Hyeri Ha,[a] Geunhee Kang,[a] Og Soon Kim,[a] Ho Ryu,[b] Abul Kalam Biswas,[b] Sang Min Lim,*[c] Mu-Hyun Baik,*[b] and Jung Min Joo*[a]

Abstract: Regioselective C4-, C5-, and di-alkenylation of pyrazoles was achieved. Electrophilic Pd catalyst generated by TFA and 4,5-diazafluoren-9-one (DAF) led to C4-alkenylation, whereas KOAc and mono-protected amino acid (MPAA) ligand, Ac−Val−OH gave C5-alkenylation. Combining palladium acetate with silver carbonate and pivalic acid, dialkenylation products were formed. Annulation via sequential alkenylation, thermal 6π-electrocyclization, and oxidation gave functionalized indazoles. This comprehensive strategy greatly expanded 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 frequently found in drugs and ligands to 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 not readily available, costly 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 prefers the C5 position (Figure 1A).[4] The nucleophilicity of 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 di-substituted products.[6,7] To date, it has not been possible to exploit the electronic difference of the (C4/C5)−H bonds for a regiodivergent synthetic methodology.[8]

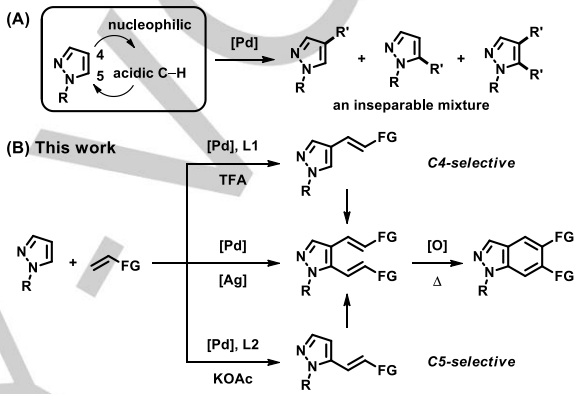

Figure 1. (A) General reactivity of pyrazole. (B) Strategies for C4-, C5-, and di-alkenylation and synthesis of indazoles (FG=functional group).

We developed regioselective C4-, C5-, and C4,5-alkenylation of simple pyrazoles (Figure 1B),[9] 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] easily leading to multi-functionalized indazoles that 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 increased the yields of 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 (vide infra).

In order to selectively functionalize the acidic (C5)−H bond, bases were added. Although the selectivity of the DAF ligand

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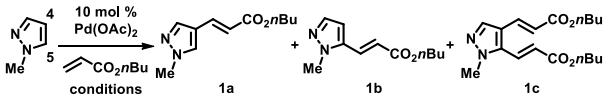
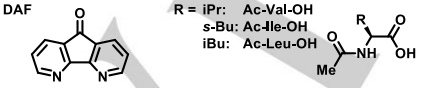
switched to favor the C5 position with KOAc, yield was low (entry 6). In conjunction with a base, the MPAA ligands showed distinctive C5-selectivity (entry 7),[15] showing negligible amounts of C4-alkenylation product. Mixing DMA and 1,4-dioxane (2:1) enhanced the C5 selectivity (entry 8) and in this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

Table 1. Optimization of Regiodivergent C−H Alkenylation of *N*-methyl Pyrazole

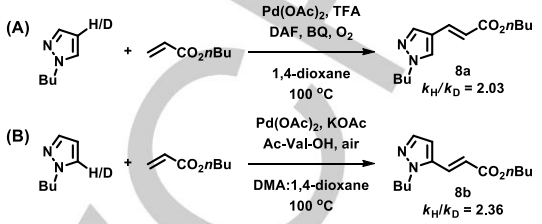


entry	ligand	additive	oxidant	solvent	yield [%][a] 1a	1b	1c
1[b]	–	TFA	O_2	1,4-dioxane	53	–	6
2[b]	DAF	–	O_2	1,4-dioxane	52	13	31
3[b]	DAF	TFA	O_2	1,4-dioxane	90	–	3
4[b],[c]	DAF	TFA	O_2, BQ	1,4-dioxane	88	2	5
5[b]	Ac−Val−OH	TFA	O_2	1,4-dioxane	67	1	6
6[d]	DAF	KOAc	air	DMA:1,4-dioxane (2:1)	8	32	19
7[d]	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



[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.

Finally, the C4,5-dialkenylation was optimized (entry 15) by combining pivalic acid and silver carbonate to 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 promoted the C−H cleavage step.[16]



Scheme 1. Kinetic Isotope Effects

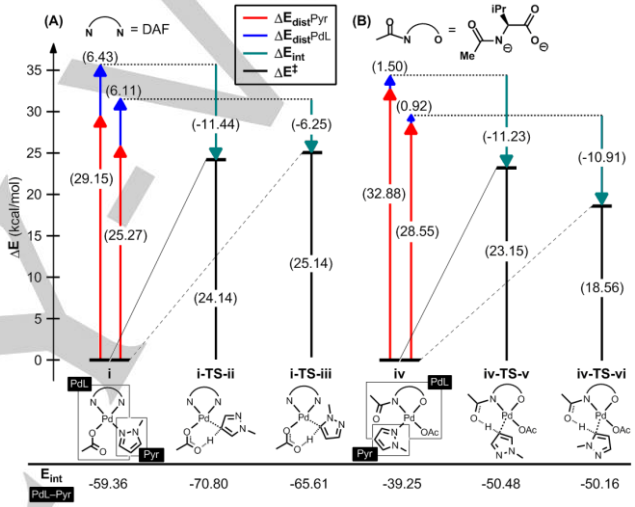


Figure 2. Computed electronic energy diagram of C–H cleavage in kcal/mol. (A) DAF ligand (B) Ac-Val-OH ligand (Pyr=pyrazole).

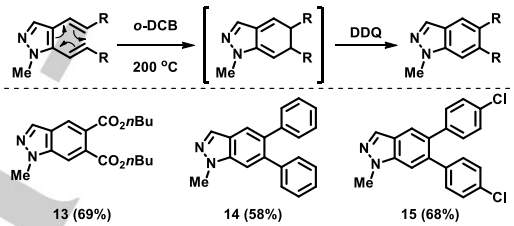
Preliminary mechanistic studies indicate that in both catalytic cycles for C4- and C5-alkenylation, the palladation was rate-limiting based on kinetic isotope effects (Scheme 1). DFT calculations (Figure 2 and Supporting Information)[5] fully support our conceptual proposal and show that the C−H activation via concerted metalation-deprotonation (CMD) determines the regiochemistry. **1a** is formed by (DAF)Pd via the transition state **i-TS-ii** at 24.1 kcal/mol, which is ~1 kcal/mol lower than **i-TS-iii** that 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, nearly 5 kcal/mol lower than **iv-TS-v**. Whereas these computed energies should be taken with some caution, the predicted regioselectivities are meaningful. The energy component analysis reveals that the neutral DAF ligand renders the Pd highly electrophilic with Pd−pyrazole interaction energies (E_{int}) being ~65-70 kcal/mol, nearly 20 kcal/mol stronger than in the MPAA−Pd analogue. The Pd−pyrazole interaction in **i-TS-ii** is -11.4 kcal/mol and is much stronger than -6.3 kcal/mol 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 nucleophilicity difference of C4/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 **iv-TS-vi** compared to **iv-TS-v**.

Next, the substrate scope of alkenes was examined (Table 2), including a wide range of olefins, such as acrylates, acrylamides, vinyl phosphonates, and styrenes. By 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 well 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 having 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 using *N*-methylation and SEM-deprotection (see Supporting Information).[7a] It was 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 multi-substituted 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 having different substituents (Scheme 3). The second alkenylation of the C4- and C5-alkenylation products, **5a** and **1b**, respectively, by using the [Pd]/[Ag] dialkenylation protocol 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 to 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 with alkenes offers flexibility in the design and synthesis of indazoles and related polycyclic benzo-fused pyrazoles.



Scheme 2. Synthesis of Indazoles by 6π-Electrocyclization/Oxidation of Dialkenylation Products

Table 2. Substrate Scope: Alkenes

Alkene	CO_2nBu	CO_2tBu	$CONEt_2$	$PO(OEt)_2$		OMe	Cl
C4-alkenylation[a]	1a, 86% (88%:2%:5%)	2a, 81% (86%:1%:4%)	3a, 95% (95%:0%:0%)	4a, 82% (83%:0%:0%)	5a, 66% (67%:0%:6%)	6a, 61% (61%:0%:7%)	7a, 48% (50%:0%:2%)
C5-alkenylation[b]	1b, 82% (1%:87%:5%)	2b, 76% (1%:79%:8%)	3b, 72% (0%:76%:13%)	4b, 45% (0%:45%:0%)	5b, 49% (2%:53%:2%)	6b, 27% (1%:43%:0%)	7b, 19% (2%:48%:6%)
Dialkenylation[c]	1c, 67% (14%:8%:71%)	2c, 61% (9%:7%:66%)	3c, 66% (7%:8%:66%)	4c, 37% (22%:21%:41%)	5c, 83% (3%:2%:83%)	6c, 69% (7%:10%:70%)	7c, 70% (9%:9%:71%)

[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.

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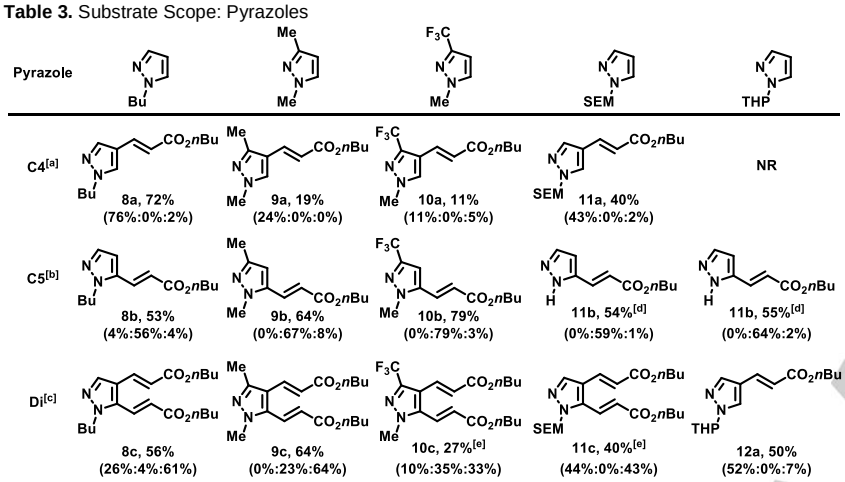
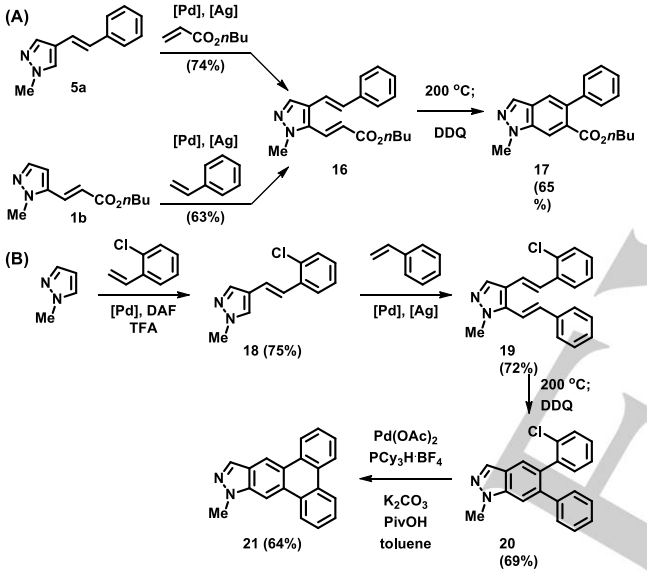
Table 3. Substrate Scope: Pyrazoles





Scheme 3. Synthesis of Functionalized Indazoles Enabled by Sequential Alkenylation Followed by 6π-Electrocyclization and Oxidation

In conclusion, we developed regioselective C−H alkenylation reactions of pyrazoles by exploiting the electronic differences of C−H bonds in the heterocycle. Three distinctive Pd catalysts enabled C4-, C5-, and di-alkenylation of commercially available, low-cost pyrazoles using alkenes. Preliminary mechanistic studies showed that the C−H cleavage step was the rate- and regio-determining step. These results have a broad implication in 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.

[a]C4-alkenylation conditions of Table 2. [b]C5-alkenylation conditions of Table 2. [c]Dialkenylation conditions of Table 2. [d]The product was isolated after deprotection due to an isolation problem. [e]The reaction was performed in DMF instead of 1,4-dioxane. NR=no reaction.

Acknowledgements

This research was supported by the National Research Foundation of Korea (NRF-2016R1D1A1B03930762), the Korea Institute of Science and Technology (KIST) Institutional Program (2E26850) and the Institute for Basic Science (IBS-R10-D1).

Keywords: pyrazole • indazole • palladium • alkenylation • C−H activation

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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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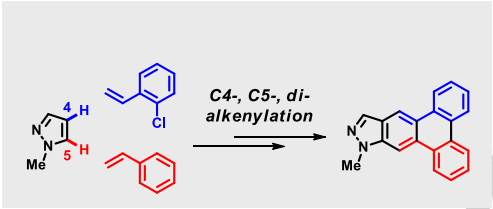
Regioselective C−H functionalization of pyrazoles has been developed to provide C4-, C5-, and di-alkenyl pyrazoles using three distinctive Pd catalytic systems. The systematic preparation of alkenyl pyrazoles enabled the synthesis of multi-functionalized indazoles and π-extended pyrazoles from readily available, inexpensive pyrazoles and olefins.



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