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RESEARCH ARTICLE

C–H Bond Arylation of Pyrazoles at the *β*-Position: General Conditions and Computational Elucidation for a High Regioselectivity

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Supporting information for this article is given via a link at the end of the document.

Abstract: Direct arylation of most five-membered ring heterocycles are generally easily accessible and strongly favored at the *α*-position using classical palladium-catalysis. Conversely, regioselective functionalization of such heterocycles at the concurrent *β*-position remains currently very challenging. Herein, we report general conditions for regioselective direct arylation at the *β*-position of pyrazoles, while C–H *α*-position is free. By using aryl bromides as the aryl source and a judicious choice of solvent, the arylation reaction of variously *N*-substituted pyrazoles simply proceeds *via* *β*-C–H bond functionalization. The *β*-regioselectivity is promoted by a ligand-free palladium catalyst and a simple base without oxidant or further additive, and tolerates a variety of substituents on the bromoarene. DFT calculations revealed that a protic solvent such as 2-ethoxyethan-1-ol significantly enhances the acidity of the proton at *β*-position of the pyrazoles and thus favors this direct *β*-C–H bond arylation. This selective pyrazoles *β*-C–H bond arylation was successfully applied for the straightforward building of *π*-extended poly(hetero)aromatic structures *via* further Pd-catalyzed combined *α*-C–H intermolecular and intramolecular C–H bond arylation in an overall highly atom-economical process.

Introduction

Several very important drugs contain a 4-(hetero)arylpyrazole unit without substituent at the C5-position of the pyrazole ring (Figure 1).[1] For example, Crizotinib is an anti-cancer drug approved in 2011 for the treatment of some non-small cell lung carcinoma. Encorafenib is a drug approved in 2018 for the treatment of certain melanomas. Baricitinib is a drug approved in 2017 for the treatment of rheumatoid arthritis. Erdafitinib is investigated in the treatment of bile duct cancer, gastric cancer, non-small cell lung cancer, and esophageal cancer. Moreover, it was granted in March 2018, breakthrough therapy designation by the U.S. Food and Drug Administration for treatment of urothelial cancer and approved in 2019 for the treatment of bladder cancer. Finally, Avapritinib was approved in 2020 to treat patients with unresectable or metastatic gastrointestinal stromal tumors. In recent years, several methods for the preparation of substituted pyrazoles have been reported such as addition-cyclization, [2 + 2 + 1] annulation or ring-opening/cyclization.[2] However, there is still a need for simple and effective methods for the preparation of 4-arylpyrazoles.

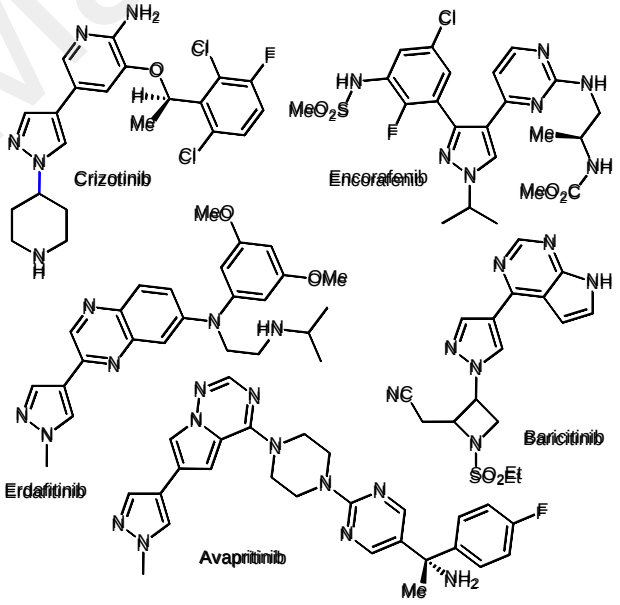


Figure 1. Examples of drugs containing a 4-(hetero)arylpyrazole unit.

Metal-catalyzed direct functionalization of (hetero)arene C–H bonds is a very powerful atom-economical synthetic method for the convergent synthesis of valuable polyaromatics.[3] Yet, the diversity of C–H bonds present in heterocycles may result in selectivity issues potentially very challenging to handle with. The inherent electronic bias of the heterocycle itself often orientates the regioselectivity of direct C–H bond arylation reaction. For example, in the C–H bond functionalization of furans, thiophenes, selenophenes, pyrroles, imidazoles and triazoles, palladium-catalyzed direct *α*-arylation is generally favored (Figure 2, left).[4,5] Interestingly, in a few cases it has been found that *β*-position is

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accessible for arylation by using specific conditions such as alternative coupling partners ($ArSiR_3$, $ArBR_2$, $ArSO_2R$) and/or specific catalysts, bases and additives (Figure 2, right). However, such regiodivergent reactions of five-membered heterocyclic rings, in the absence of introduced directing groups, remains limited to thiophenes,[6a] thiazoles,[6b] and selenophenes.[6c]

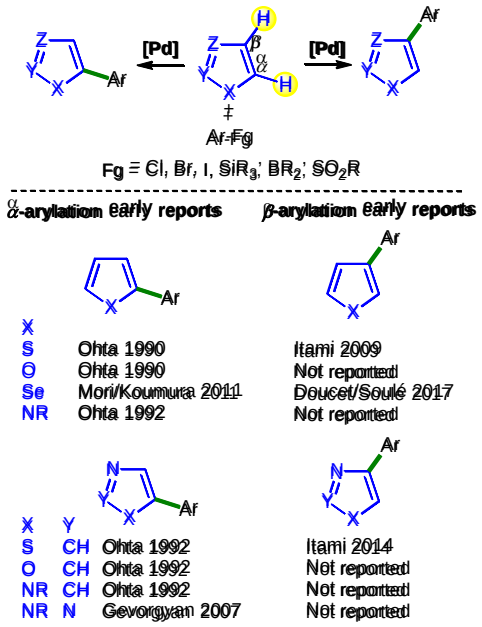
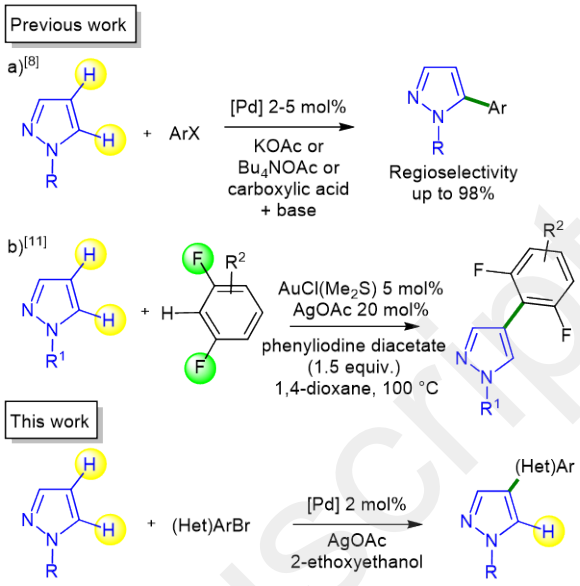


Figure 2. Palladium-catalyzed regiodivergent arylation reactions of five-membered heteroarenes.

Several procedures for the Pd-catalyzed regioselective *α*-arylation of pyrazoles have been reported (Scheme 1a).[7,8] The use of pyrazole unit in palladium- or rhodium-catalyzed alkenylations *via* C-H bond activation has also been described.[9] Conversely, only a few examples of *β*-arylation of pyrazoles have been reported, which involve *α*-substituted pyrazoles.[10] Alternatively, coupling reactions using Au/Ag catalyzed dehydrogenative process with polyfluoroarenes as the aryl source have been described by Zhu and co-workers (Scheme 1b), which strongly limit the scope of the reaction.[11] Clearly, general synthetic conditions for the regioselective direct arylation at *β*-position of unsubstituted pyrazoles with non-fluorinated aryl sources, are highly desirable (Scheme 1, bottom).[12,13]



Scheme 1. Direct *α*- or *β*-arylation reactions of pyrazoles.

Accordingly, we report herein on the influence of several reaction conditions on the regioselectivity in the Pd-catalyzed arylation of pyrazoles *via* C–H bond functionalization. The decisive role of the solvent and base at the origin of the regiodivergent selectivities observed was evaluated through DFT computations.

Results and Discussion

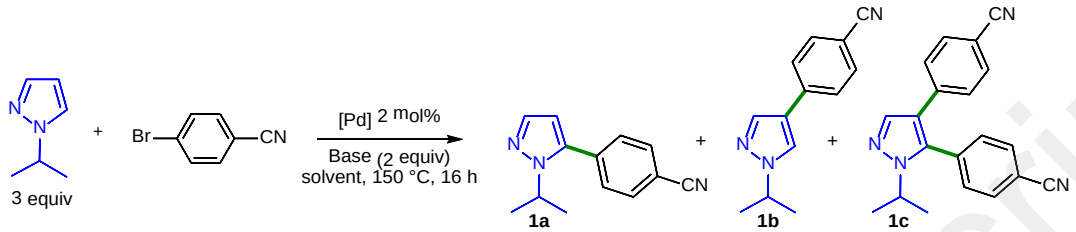
Under standard C–H functionalization conditions,[8b] we examined the regioselectivity of the arylation of 3 equiv of 1-isopropylpyrazole with 4-bromobenzonitrile, in DMA at 150 °C during 16 h (Table 1). Unsurprisingly, by using 2 mol% of $Pd(OAc)_2$ or $PdCl_2(MeCN)_2$ as catalysts, and 2 equiv of KOAc as the base, intractable mixtures of *α*- and *β*-arylated pyrazoles **1a**, **1b**, plus diarylated pyrazole **1c** were obtained. The *α*-arylated pyrazole **1a** was mostly obtained in any case (Table 1, examples in entries 1 and 2). Using K_2CO_3 as base, a poor conversion of the aryl bromide was obtained with $PdCl_2(MeCN)_2$, and again, the *α*-arylated product **1a** was the major regioisomer (Table 1, entry 3). Pleasingly, the use of AgOAc as the base with $PdCl_2(MeCN)_2$ gave *β*-arylated pyrazole **1b** with a ratio **1a**:**1b** of 20:80, and only a low amount of was **1c** formed (Table 1, entry 4); however, a partial conversion of the bromoarene below 50% was noticed. The use of mixtures of bases, such as 2 equiv of KOAc or K_2CO_3 associated with 0.1 equiv of AgOAc, did not improved the regioselectivity in *β*-C–H arylated regioisomer **1b** (Table 1, entries 5 and 6).

Therefore, the influence of solvents was examined, especially for improving the substrate conversion. In 2-ethoxyethan-1-ol, using AgOAc as a base, a quantitative conversion of 4-bromobenzonitrile was achieved with a regioselectivity favoring the desired product **1b**. $Pd(OAc)_2$ and $PdCl_2(MeCN)_2$ catalysts, allowed the formation of **1b**, which was isolated in 57% and 61% yield, respectively (Table 1, entries 7 and 8). In 2-ethoxyethan-1-ol, KOAc could be used as base without regioselectivity modification compared with AgOAc, but the undesired formation of (1,1'-biphenyl)-4,4'-dicarbonitrile was also observed from

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homocoupling of 4-bromobenzonitrile (Table 1, entry 9). Notably, using a Pd(0) source (such as $[Pd(dba)_2]$) instead of a Pd(II) provided the products **1a**-**1c** with a regioselectivity conserved, suggesting that the mechanism is likely to proceed *via* a Pd(0)/Pd(II) catalytic cycle (Table 1, entry 10). The selectivity of the reaction using other palladium catalysts, bases and solvents is described in the Table S1 in the supporting information.

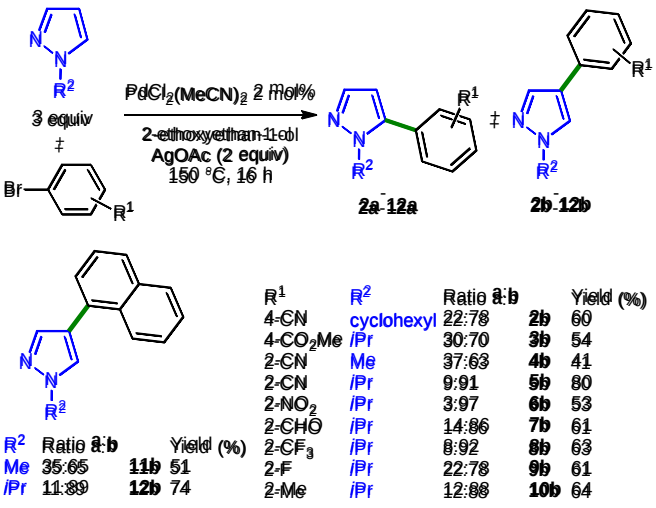
Table 1. Influence of the reaction conditions on the regioselectivity of the C–H bond arylation of 1-isopropylpyrazole.[a]



Entry	[Pd] (2 mol%)	Base (2 equiv)	Solvent	Conv. (%)	Ratio **1a**:**1b**:**1c**	Yield in **1b** (%)
1	$Pd(OAc)_2$	KOAc	DMA	73	41:31:28	19
2	$PdCl_2(MeCN)_2$	KOAc	DMA	68	35:29:36	15
3	$PdCl_2(MeCN)_2$	K_2CO_3	DMA	13	78:22:0	-
4	$PdCl_2(MeCN)_2$	AgOAc	DMA	54	19:75:6	38
5	$PdCl_2(MeCN)_2$	K_2CO_3 + AgOAc (0.1 equiv)	DMA	43	79:21:0	-
6	$PdCl_2(MeCN)_2$	KOAc + AgOAc (0.1 equiv)	DMA	31	40:60:0	17
7	$Pd(OAc)_2$	AgOAc	2-ethoxyethan-1-ol	99	20:66:14	57
8	$PdCl_2(MeCN)_2$	AgOAc	2-ethoxyethan-1-ol	99	19:68:13	61
9	$PdCl_2(MeCN)_2$	KOAc	2-ethoxyethan-1-ol	93	20:75:5	26[b]
10	$Pd(dba)_2$	AgOAc	2-ethoxyethan-1-ol	88	19:72:9	-

[a] [Pd] 2 mol%, 1-isopropylpyrazole (3 equiv), 150 °C, 16 h, conversion based on consumption of 4-bromobenzonitrile, conversions and ratios of **1a**:**1b**:**1c** determined by GC and NMR of the crude mixtures, isolated yields. [b] (1,1'-Biphenyl)-4,4'-dicarbonitrile was formed in high yield (60%).

Based on the high conversion and good regioselectivity conditions we determined, the substrate scope and the functional tolerance of *β*-C–H pyrazole arylation was investigated. First, the influence of the substituent hold on the nitrogen atom of pyrazole was determined (Scheme 2). Using 4-bromobenzonitrile as the aryl source, similar results were obtained with isopropyl and cyclohexyl substituents. A decrease of selectivity was observed for the arylation of 1-methylpyrazole compared to 1-isopropylpyrazole with 2-bromobenzonitrile (ratio **4a**:**4b** 37:63 *vs* **5a**:**5b** 9:91). The substituents on the aryl bromide also significantly influence the regioselectivity of the arylation. For example, the use of 2-bromonitrobenzene or 2-(trifluoromethyl)bromobenzene gave the regioisomers **6b** and **8b** in notably high 97% and 92% regioselectivity, respectively. Conversely, the use of 2-bromofluorobenzene gave the regioisomer **9b** in 78% selectivity. The reaction tolerates several other functions on the aryl bromide such as ester and formyl groups, affording **3b** and **7b** in 54% and 61% yield, respectively. The reaction of 1-isopropylpyrazole with 1-bromonaphthalene also afforded the desired *β*-arylated pyrazole **12b** in a high regioselectivity of 89%.

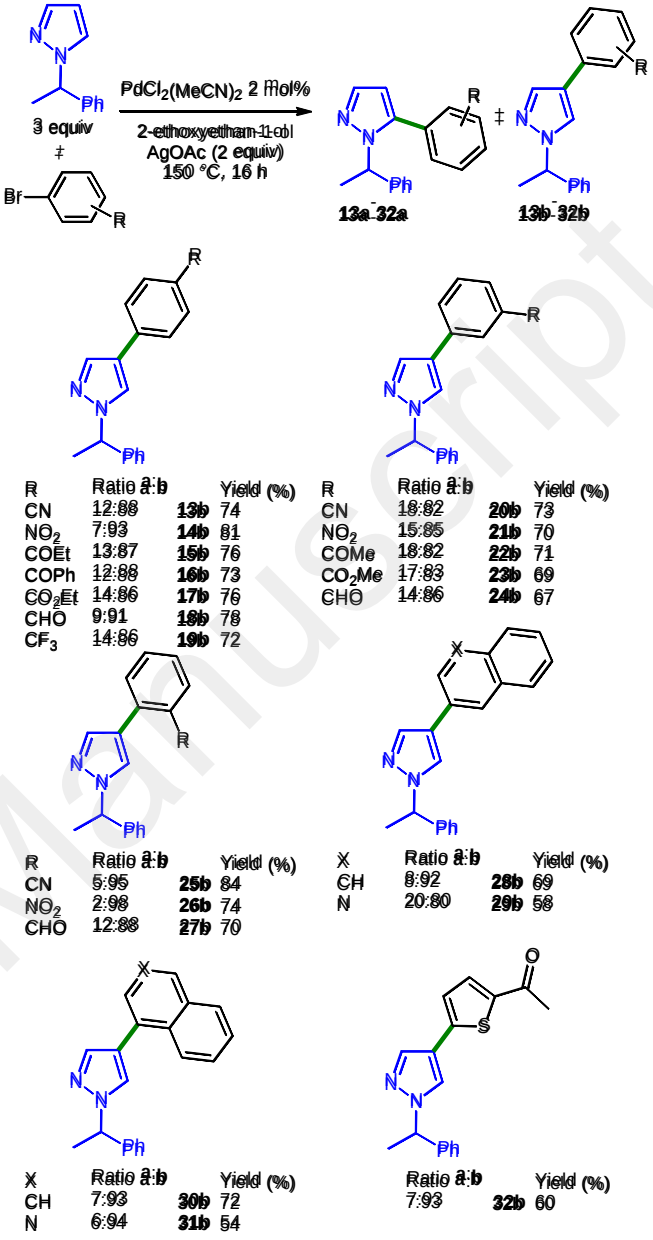


Scheme 2. Scope of *β*-arylation of 1-alkylpyrazole derivatives.

1-Phenylethyl substituent hold on the nitrogen atom of heteroaromatic substrates is a protecting group that can be removed by several convenient methods.[14] Therefore, the

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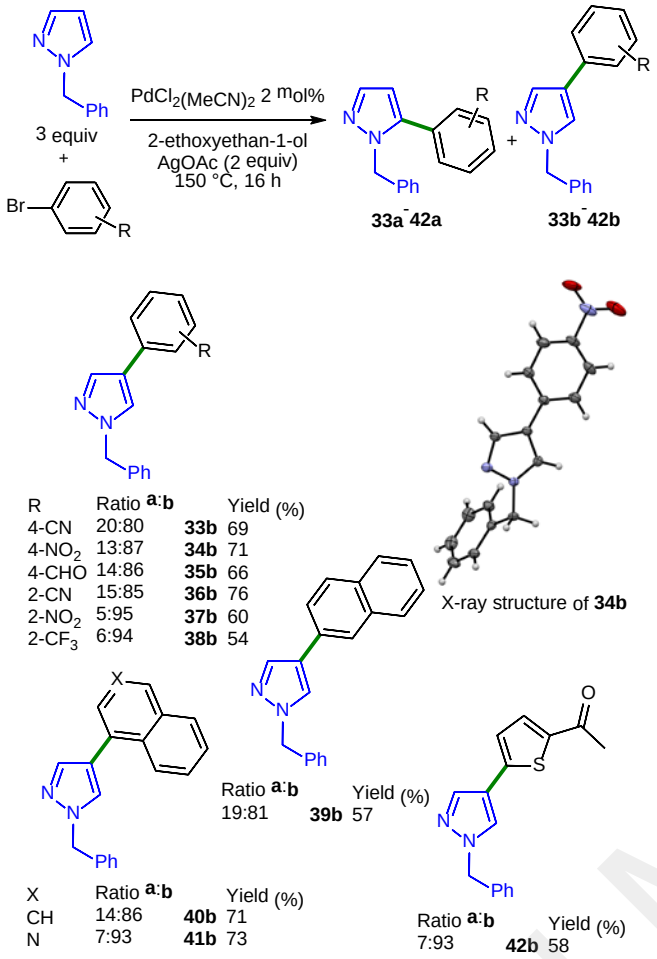
reactivity and regioselectivity of 1-(1-phenylethyl)pyrazole as the pyrazole source was investigated under our general conditions (Scheme 3). Pleasingly, in most cases, high regioselectivity favoring *β*-arylations was achieved. Direct arylation from bromoarenes bearing cyano, nitro, propionyl, benzoyl, ester, formyl or trifluoromethyl *para*-substituents, gave the expected 4-arylpyrazoles **13b**-**19b** in 86-93% regioselectivity, isolated in 72-81% yields. Substituents at *meta*-position were also well tolerated, with 3-bromobenzonitrile, 3-bromonitrobenzene and 3-bromoacetophenone giving the products **20b**-**22b** with 82-85% regioselectivity, isolated in 70-73% yields. In general, the use of a more hindered aryl bromide afforded 4-arylpyrazole with higher regioselectivity. 2-Cyano- and 2-nitro-substituted aryl bromides gave the products **25b** and **26b** in 95% and 98% regioselectivity, respectively. We examined the opportunity to extend the *β*-functionalization to heteroaryl bromides using our catalytic conditions. Both 3-bromoquinoline and 4-bromoisoquinoline gave the desired biheteroaryls **29b** and **31b** with high regioselectivity (80% and 94%, respectively). From 2-acetyl-5-bromothiophene, compound **32b** was also obtained in a high regioselectivity (93%) and in good yield (60%).



Scheme 3. Scope of the *β*-arylation of 1-(1-phenylethyl)pyrazole.

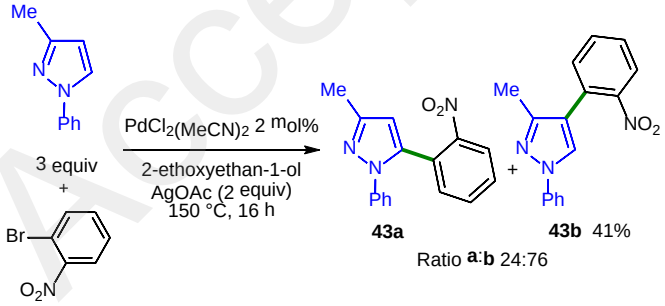
Since benzyl is also a common protecting group of heteroarenes[15] the regioselectivity of the arylation of 1-benzylpyrazole was further examined (Scheme 4). In most cases, slightly lower regioselectivity, still in favor of *β*-arylation, were observed under our conditions. However, in general reasonable to good yields of arylpyrazole can be obtained. Thus, reaction using 4- and 2-bromobenzonitriles afforded the products **33b** and **36b** in 69% and 76% yield, respectively (80-85% selectivity). Highly selective *β*-arylation was observed with the congested aryl bromides 2-bromonitrobenzene and 2-(trifluoromethyl)bromobenzene (95% and 94%). Using the heteroaryl bromides 4-bromoisoquinoline and 2-acetyl-5-bromothiophene the regioselectivity for coupling 1-(1-phenylethyl)pyrazole (products **31b** and **32b**) and 1-benzylpyrazole (products **41b** and **42b**) were similarly above 90%.

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Scheme 4. Scope of the *β*-arylation of 1-benzylpyrazole.

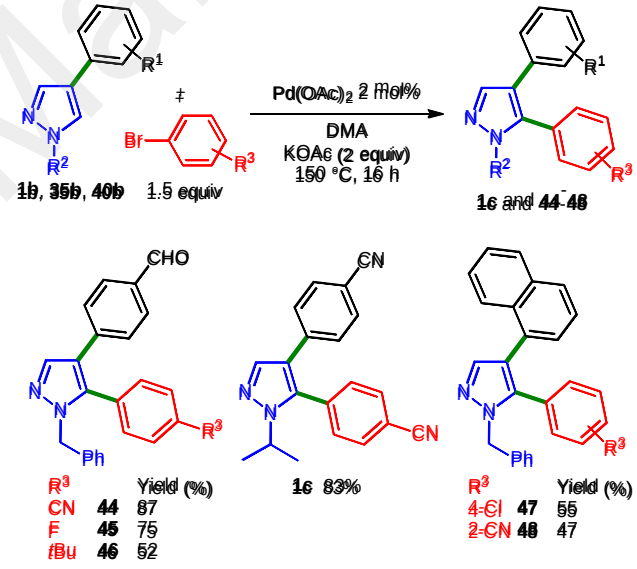
The regioselectivity of the arylation of a 3-substituted pyrazole was also studied (Scheme 5). From 3-methyl-1-phenylpyrazole and 2-bromonitrobenzene, the C4-arylated pyrazole **43b** was obtained in 76% regioselectivity and in 41% yield, revealing that the presence of a methyl substituent at the pyrazole C3-position has a negative influence on the regioselectivity.



Scheme 5. *β*-Arylation of a 3-substituted pyrazole.

It should be mentioned that the reactivity of the *N*-heterocycle substituted pyrazole 1-(tetrahydro-2H-pyran-2-yl)pyrazole was also examined, as the tetrahydropyranyl unit is a convenient protecting group. However, very low yields in coupling products, which could not be isolated, were detected by GC/MS analysis of the crude mixtures using 4-bromobenzonitrile or 1-bromonaphthalene as the reaction partners in the presence of 2 mol% $PdCl_2(MeCN)_2$, AgOAc (2 equiv.) in 2-ethoxyethan-1-ol at 150 °C during 6 h. The use of NMP, DEC or DMA as the solvent also led to very poor conversions of the aryl bromides.

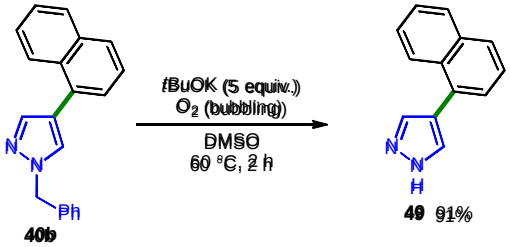
α-C–H bond position of pyrazoles is known to be reactive for direct arylation reactions with aryl halides using palladium catalysis in the presence of acetate bases.[8] We thus examined the opportunity to further *α*-C–H functionalize the 4-arylpyrazoles previously formed, this possibly leading to valuable unsymmetrically polysubstituted heteroaromatics (Scheme 6).[16,17] Compound **35b** was reacted with a set of aryl bromides in the presence of 2 mol% of $Pd(OAc)_2$ catalyst, and KOAc as the base in DMA. The *α*,*β*-diarylated products **44**-**46** were obtained in 52-87% yields using the electron-poor 4-bromobenzonitrile, 4-fluorobromobenzene and the electron-rich 4-*tert*-butylbromobenzene. The lower yield obtained with 4-*tert*-butylbromobenzene was due to a partial conversion of this unactivated aryl bromide. From **1b** and 4-bromobenzonitrile, the *α*,*β*-diarylpyrazole bearing two identical aryl groups was obtained in 83% yield. Conversely, the *α*-arylation of 4-naphthylpyrazole **40b** gave the products **47** and **48** in moderate yields (**48**, 47%).



Scheme 6. Scope of the *α*-arylation of 4-aryl-1-(1-benzyl)pyrazoles or 4-(1-isopropylpyrazol-4-yl)benzonitrile.

A variety of methods for the deprotection of benzyl-substituted heteroarenes have been reported,[15] and accordingly the deprotection of 1-benzyl-4-(naphthalen-1-yl)pyrazole **40b** was very efficiently achieved in short reaction time (Scheme 7). The reaction of **40b** with *t*BuOK with O_2 bubbling afforded the desired 4-(naphthalen-1-yl)pyrazole **49** in 91% yield.

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Scheme 7. Deprotection of 1-benzyl-4-(naphthalen-1-yl)pyrazole **40b**.

In order to gain more insight into the origin of the divergent regioselectivity in this Pd-catalyzed direct *β*-C–H bond arylation, we used Density Functional Theory (see Computational Details) to compute the Gibbs free energy profiles for direct arylation involving Pd(0) and 4-bromobenzonitrile in DMA (Figure 3) and 2-ethoxyethan-1-ol (Figure 4).

The mechanism depicted in Figure 3 begins with the oxidative addition (OA) of 4-bromobenzonitrile (**Ar1**) to Pd(pyrazole)$_2$. The OA starts from the initial Pd(0)-π-complex **add-π** (5.8 kcal mol^{-1}), which is then transformed into the Pd(II) complex **int1** in a highly exergonic process (ΔG = −24.8 kcal mol^{-1}). This transformation takes place through a typical three-membered transition state **ts-OA** with the simultaneous formation of the Pd−C and the Pd−X bonds. The concerted metalation−deprotonation (CMD) step then takes place similarly to previously reported.[18-23] It is noteworthy that the pyrazole involved in the CMD step is already coordinated to the palladium atom. Both **ts1-C*β*** and **ts1-C*α*** transition states proceed with a five-membered structure, associated with the simultaneous Pd–C and O–H bond formation and C…H bond breaking. The activation barriers differs only by 0.5 kcal mol^{-1} in favor of **ts1-C*α*** ($\Delta G^{\ddagger}$ = 21.3 kcal mol^{-1} for *β*-position and $\Delta G^{\ddagger}$ = 20.8 kcal mol^{-1} for *α*-position). The arylation at *α*-position is thus slightly favored. Under kinetic control this 0.5 kcal mol^{-1} difference leads to a *α*:*β* product ratio of 65:35, which reasonably agrees with the experimental observations (Table 1, entries 1-3 and 5-6).

This preference comes from the fact that the proton in *α*-position is more acidic. This is also characterized by **ts1-C*α*** being an *early* transition state (TS), structurally closer to reagents than products, contrary to **ts1-C*β***. Thus, C–H and Pd–O bonds to be broken are shorter in **ts1-C*α*** than in the *late* TS **ts1-C*β***: C–H = 1.29 Å and Pd–O = 2.18 Å in **ts1-C*α*** *vs* C–H = 1.39 Å and Pd–O = 2.22 Å in **ts1-C*β***.

The reductive elimination takes place to give the final products **1a** and **1b**. To this end, the HOAc/L ligand exchange generates **int4** in an exergonic process. From **int4** the formation of final product takes place through the reductive elimination involving the **ts2**. The **ts2-C*β*** and **ts2-C*α*** transition states are associated with the simultaneous formation of the C–C bond and the Pd–C$_{Ar1}$ and Pd–C$_{Ar2}$ bond breaking. Notably, these results indicate that in DMA, in the absence of silver participation, the *α*-arylation is kinetically favored, in full agreement with the experimental results.

Interestingly, when 2-ethoxyethan-1-ol is used as solvent (Figure 4), the computed CMD activation barriers are reversed compared to the DMA case and differ by 1.4 kcal mol^{-1}: $\Delta G^{\ddagger}$ = 20.8 kcal mol^{-1} for *β*-arylation, and $\Delta G^{\ddagger}$ = 22.2 kcal mol^{-1} for *α*-arylation. The arylation at *β*-position is more clearly favored, in agreement with experimental results. This inversion in selectivity from *α*-favored to *β*-favored induced by the solvent, comes from the protic nature of the 2-ethoxyethan-1-ol. The hydrogen bonding N…H–O (1.77 Å for **ts1-C*α*** and 1.75 Å for **ts1-C*β***), as shown in Figure 4 (and SI for full profile), involving the lone pair of pyrazole nitrogen with the hydroxyl group of 2-ethoxyethan-1-ol strongly modifies the heterocycle electronic features. This is well-illustrated by the very different change of partial charges occurring at the protons in *α* and *β*-position. The solvation change from DMA to 2-ethoxyethan-1-ol makes the partial charge of the proton in *β*-position increasing by 28% (from 0.043 to 0.055 coulomb), while at the same time the partial charge of the proton in *α*-position increases by only 9% (from 0.083 C to 0.090 C). Additionally, the entropic effects destabilize more the early TS **ts1-C*α*** (Figure 4, C–H 1.30 Å) than the late TS **ts1-C*β*** (Figure 4, C–H 1.39 Å).

The combination of this *β*-acidity increase and **ts1-C*α*** destabilization is decisive in the regioselectivity inversion in 2-ethoxyethan-1-ol. Consistently, under kinetic control the computed Gibbs free energy difference of 1.4 kcal mol^{-1} leads to an estimated theoretical *α*:*β* product ratio of 15:85, in fair agreement with the general trends of all the experimental cross-couplings conducted in 2-ethoxyethan-1-ol. The resulting catalytic cycle is shown in Figure 5.

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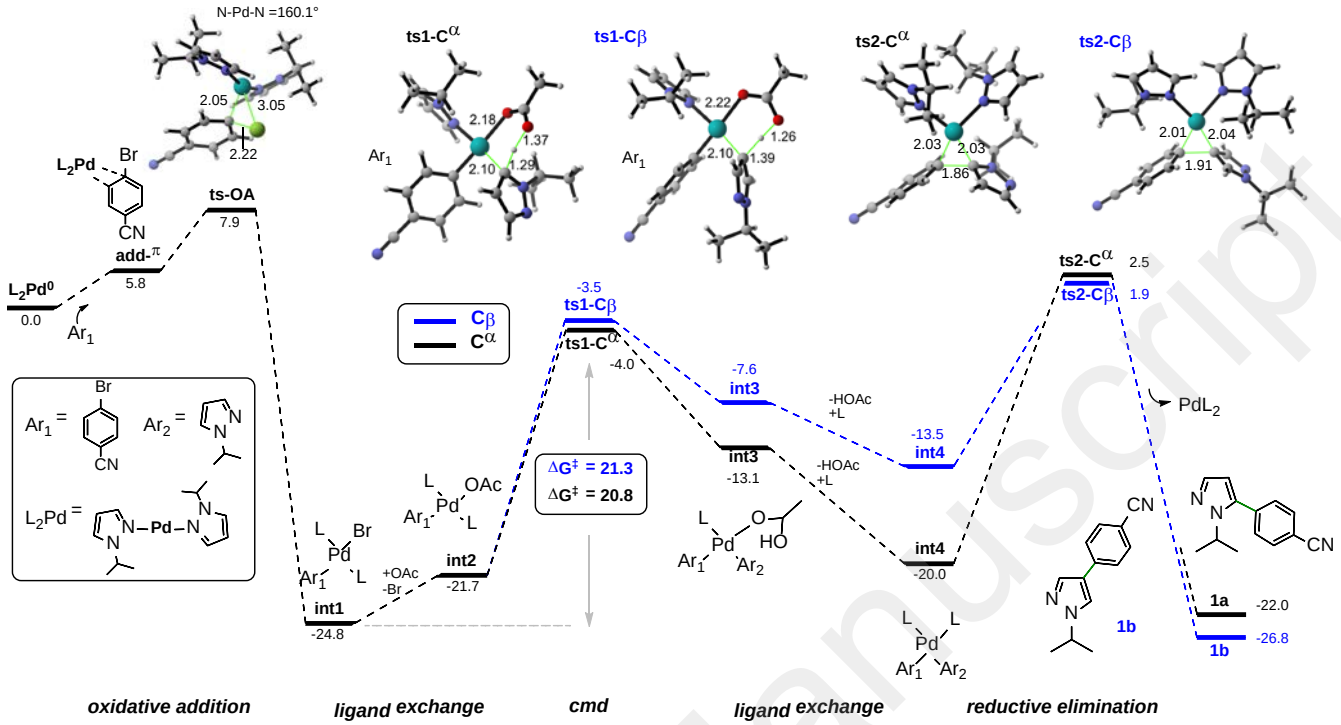


Figure 3. Gibbs free energy profile (kcal mol^{-1}) computed for the Pd-catalyzed arylation at 150 °C in DMA. Key distances are given in Å. Atom color code: C = grey, H = white, N = blue, O = red, Pd = cyan and Br = green.

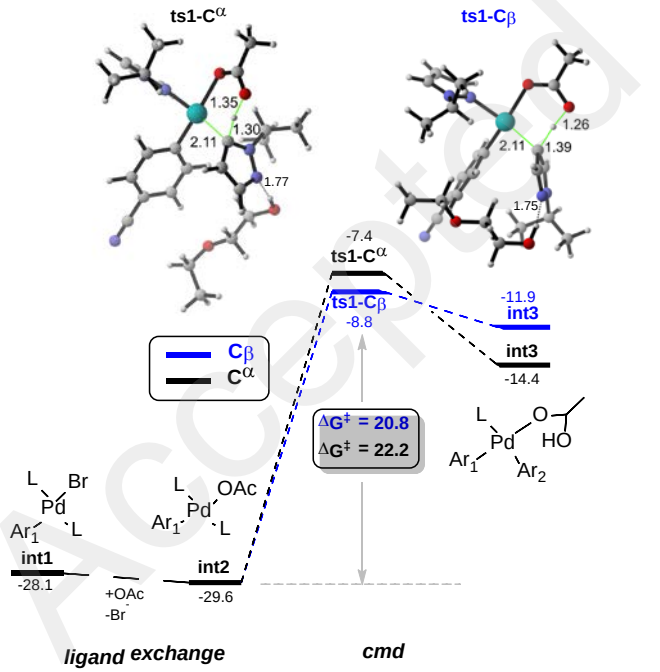


Figure 4. Gibbs free energy profile for the C–H activation computed in 2-ethoxyethan-1-ol at T = 150 °C. Selected pertinent distances are given in Å.

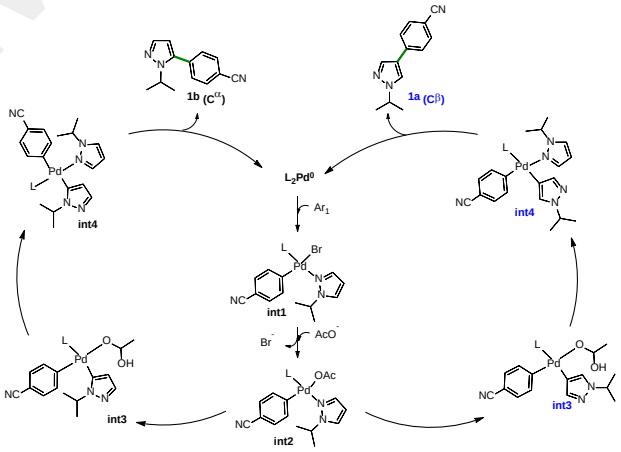


Figure 5*. Proposed catalytic cycle without silver salt.*

We also further considered the role of silver salts in the arylation of 1-isopropylpyrazole. In our hands, a silver promoted process was not amenable to a highly efficient catalytic process with *β*-C–H arylation regioselectivity. Experimentally, a stoichiometric amount of AgOAc was necessary and 0.1 equiv was detrimental to the conversion (see Table 1), while the absence of palladium was ineffective. As detailed in the Supplementary Information, silver can be involved in many ways.[24] We found that it could activate the *β* position by binding to the lone pair of the pyrazole similarly to the action of the 2-ethoxyethan-1-ol solvent (Figure 6 in 2-ethoxyethan-1-ol, and Figure S3-Th in DMA in ESI). A lower activation barrier was calculated for C–H activation occurring at the *β*-C ($\Delta G^{\ddagger}$ = 29.3 kcal mol^{-1}) in comparison to *α*-C ($\Delta G^{\ddagger}$ = 30.0 kcal mol^{-1}); this both in DMA and 2-ethoxyethan-1-ol. These

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results suggest that in DMA the regiodivergence is partly due to the complexation of silver to pyrazole. Conversely, in 2-ethoxyethan-1-ol, the *β*-arylation process is favored with or without the participation of silver.

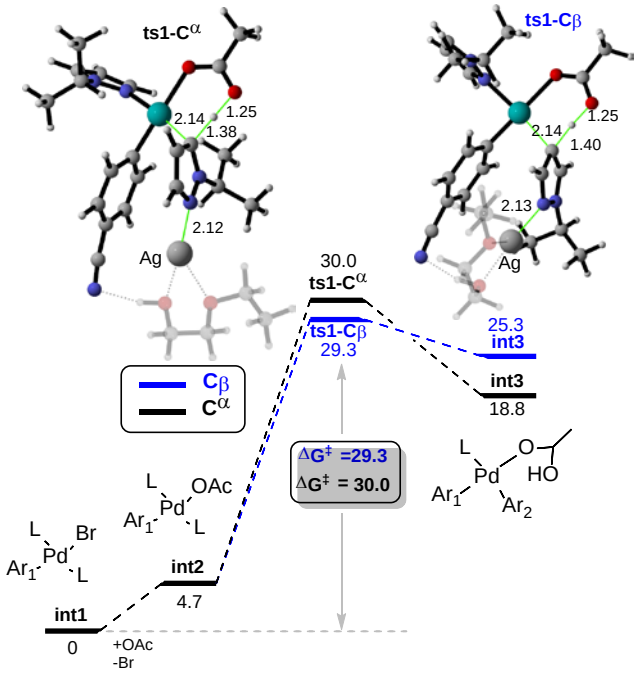
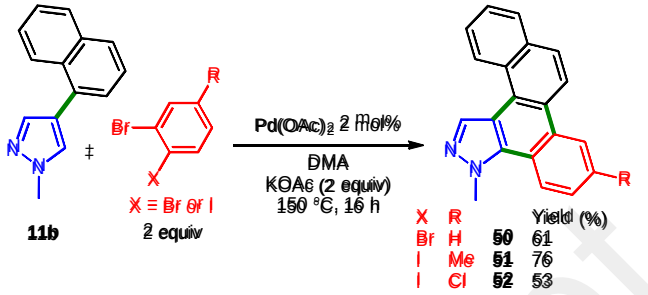


Figure 6. Gibbs free energy profile (kcal mol^{-1}) for CMD process assisted by silver in 2-ethoxyethan-1-ol at T = 150 °C. Selected pertinent distances are given in Å.

Palladium-catalyzed intermolecular arylation associated with intramolecular C–H bond arylation is a straightforward method in the building of *π*-extended (hetero)polyaromatic structures, overwhelming more classical divergent multistep procedures.[17] Thanks to the present alternative regioselectivity provided by our conditions, and usually of difficult access, we applied a Pd-catalyzed combined methodology to the synthesis of dibenzo[*e*,*g*]indazoles (Scheme 8). From *N*-methyl-4-(naphthalen-1-yl)pyrazole **11b** and 1,2-dibromobenzene in the presence of 2 mol% of $Pd(OAc)_2$ catalyst, the targeted benzo[*g*]naphtho[1,2-*e*]indazole **50** was obtained in 61% yield. The use of 1-bromo-2-iodobenzene reagents allows to selectively introduce a substituent at the *C*3-position of the benzo[*g*]naphtho[1,2-*e*]indazole, as the oxidative addition to palladium is faster for the C–I bond than for the C–Br. Thus, using 1-bromo-3-methyl-6-iodobenzene, methyl-aryl compound **51** was obtained in very good 76% yield. Similarly, the chloro-substituted benzo[*g*]naphtho[1,2-*e*]indazole **52** was obtained in 53% yield from 1-bromo-3-chloro-6-iodobenzene. The C–Cl bond remained untouched potentially allowing for further functionalization.



Scheme 8. Two steps, three C–H bond arylation, straightforward synthesis of benzo[*g*]naphtho[1,2-*e*]indazoles.

Conclusion

Overall, we disclosed simple general conditions for the palladium-catalyzed regioselective direct arylation at the *β*-position of pyrazoles, while until now the more acidic *α*-position was the only one selectively reachable. This inedited regioselectivity is highly dependent on the nature of the solvent and the base. With ligand-free $Pd(OAc)_2$ catalyst and AgOAc as base in 2-ethoxyethan-1-ol, the *β*-arylated pyrazoles were obtained in 70-98% regioselectivity with pyrazoles bearing isopropyl, cyclohexyl, benzyl, or 1-phenylethyl substituents on the nitrogen atom. This procedure tolerates a variety of useful substituents on the aryl bromide. Due to the wide availability of diversely substituted pyrazoles and aryl bromides at an affordable cost, such simple reaction conditions (easily available catalyst, base and solvent) should be very attractive for synthetic chemists, giving a robust access to *β*-arylated pyrazoles. From the 4-arylpyrazole compounds formed, a second palladium-catalyzed C–H bond functionalization at carbon C5 of the pyrazole ring gives an alternative synthetic pathway to unsymmetrically substituted 4,5-diarylpyrazoles. DFT computations showed that the 2-ethoxyethan-1-ol solvate exacerbates the acidity of the proton in *β*-position which eventually favors arylation in *β*-position. However, in DMA the *β*-arylation is only favored in the presence of AgOAc. Computations suggested in such cases, that the regioselectivity determining CMD step could be –at least partially– assisted by silver complexes. Ultimately, this new *β*-C–H arylation method was applied for the easy synthesis of *π*-extended benzo[*g*]naphtho[1,2-*e*]indazoles by using 4-arylpyrazoles C–C coupling in a Pd-catalyzed intermolecular associated to intramolecular double C–H bond arylation.

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Keywords: catalysis • *β*-C–H arylation • heterocycle • palladium • solvent effect

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[1] a) A. Shaw, U. Yasothan, P. Kirkpatrick, *Nat. Rev. Drug Discov.* **2011**, *10*, 897-898; b) K. Garber *Nat. Biotechnol.* **2013**, *31*, 3-4; c) P. Sidaway *Nat. Rev. Clin. Oncol.* **2018**, *15*, 344-345.

[2] For recent preparation methods of pyrazoles: a) D. Y. Li, X. F. Mao, H. J. Chen, G. R. Chen, P. N. Liu, *Org. Lett.* **2014**, *16*, 3476-3479; b) M. C. Pérez-Aguilar, C. Valdés, *Angew. Chem., Int. Ed.* **2015**, *54*, 13729-13733; c) R. S. Thombal, Y. R. Lee, *Org. Lett.* **2018**, *20*, 4681-4685; d) J. Liu, E. Xu, J. Jiang, Z. Huang, L. Zheng, Z.-Q. Liu, *Chem. Commun.* **2020**, *56*, 2202-2005.

[3] For reviews on C–H bond functionalization: a) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315-1345; b) R. Rossi, F. Bellina, M. Lessi, C. Manzini, *Adv. Synth. Catal.* **2014**, *356*, 17-117; c) L. Djakovitch, F.-X. Felpin, *ChemCatChem* **2014**, *6*, 2175-2187; d) L. Theveau, C. Schneider, C. Fruit, C. Hoarau, *ChemCatChem* **2016**, *8*, 3183-3194; e) S. Agasti, A. Dey, D. Maiti, *Chem. Commun.* **2017**, *53*, 6544-6556; f) T. Gensch, M. J. James, T. Dalton, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 2296-2306; g) J. Kalepu, P. Gandeepan, L. Ackermann, L. T. Pilarski, *Chem. Sci.* **2018**, *9*, 4203-4216; h) K. Hirano, M. Miura, *Chem. Sci.* **2018**, *9*, 22-32; i) P. Gandeepan, T. Mueller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192-2452; j) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788-1887.

[4] S. Mao, H. Li, X. Shi, J.-F. Soulé, H. Doucet, *ChemCatChem* **2019**, *11*, 269-286.

[5] a) Y. Akita, A. Inoue, K. Yamamoto, A. Ohta, T. Kurihara, M. Shimizu, *Heterocycles* **1985**, *23*, 2327-2333; b) A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles* **1990**, *31*, 1951-1958; c) Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, J. Kunoh, R. Honma, Y. Akita, A. Ohta, *Heterocycles* **1992**, *33*, 257-272; d) S. Tamba, R. Fujii, A. Mori, K. Hara, N. Koumura, *Chem. Lett.* **2011**, *40*, 922-924; e) S. Chuprakov, N. Chernyak, A. S. Dudnik, V. Gevorgyan, *Org. Lett.* **2007**, *9*, 2333-2336.

[6] a) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc.* **2009**, *131*, 14622-14623; b) S. Tani, T. N. Uehara, J. Yamaguchi, K. Itami, *Chem. Sci.* **2014**, *5*, 123-135; c) A. Skhiri, R. Ben Salem, J.-F. Soulé, H. Doucet, *Chem. Eur. J.* **2017**, *23*, 2788-2791.

[7] For a study on the regioselectivity of the arylation of pyrazoles: R. Goikhman, T. L. Jacques, D. Sames, *J. Am. Chem. Soc.* **2009**, *131*, 3042-3048.

[8] For selected examples of Pd-catalyzed direct *α*-arylations of pyrazoles: a) C. Mateos, J. Mendiola, M. Carpintero, J. M. Minguez, *Org. Lett.* **2010**, *12*, 4924-4927; b) A. Beladhria, K. Beydoun, H. Ben Ammar, R. Ben Salem, H. Doucet, *Synthesis* **2011**, 2553-2560; c) F. Bellina, M. Lessi, C. Manzini, *Eur. J. Org. Chem.* **2013**, 5621-5630; d) E. T. T. Kumpulainen, A. Pohjakallio, *Adv. Synth. Catal.* **2014**, *356*, 1555-1561; e) H. Jung, S. Bae, H.-L. Jang, J. M. Joo, *Bull. Korean Chem. Soc.* **2014**, *35*, 3009-3014; f) S. Fuse, T. Morita, K. Johmoto, H. Uekusa, H. Tanaka, *Chem. Eur. J.* **2015**, *21*, 14370-14375; g) W. F. Vernier, L. Gomez, *Tetrahedron Lett.* **2017**, *58*, 4587-4590.

[9] For the use of pyrazole unit in C-H bond activation and related articles: a) H. T. Kim, H. Ha, G. Kang, O. S. Kim, H. Ryu, A. K. Biswas, S. M. Lim, M.-H. Baik, J. M. Joo, *Angew. Chem., Int. Ed.* **2017**, *56*, 16262-16266; b) H. Kim, R. S. Thombal, H. D. Khanal, Y. R. Lee, *Chem. Commun.* **2019**, *55*, 13402-13405; c) H. Cai, R. S. Thombal, X. Li, Y. R. Lee, *Adv. Synth. Catal.* **2019**, *361*, 4022-4032.

[10] For examples of Pd-catalysed direct *β*-arylations of 3,5-disubstituted pyrazoles: a) S. Kumar, H. Ila, H. Junjappa, *J. Org. Chem.* **2009**, *74*, 7046; b) Y. Fall, H. Doucet, M. Santelli *Synthesis* **2010**, 127-135; c) F. Derridj, J. Roger, S. Djebbar, H. Doucet, *Adv. Synth. Catal.* **2012**, *354*, 747-750.

[11] For Au/Ag catalyzed dehydrogenative *β*-arylation of pyrazoles with polyfluoroarenes: W. Li, D. Yuan, G. Wang, Y. Zhao, J. Xie, S. Li, C. Zhu, *J. Am. Chem. Soc.* **2019**, *141*, 3187-3197.

[12] For recent examples of synthesis of 4-arylpyrazoles using Suzuki reaction: a) Y. Liang, M. Wispelaere, M. Carocci, Q. Liu, J. Wang, P. L. Yang, N. S. Gray, *ACS Med. Chem. Lett.* **2017**, *8*, 344-349; b) S. Mah, J. H. Park, H.-Y. Jung, K. Ahn, S. Choi, H. S. Tae, K. H. Jung, J. K. Rho, J. C. Lee, S.-S. Hong, S. Hong, *J. Med. Chem.* **2017**, *60*, 9205-9221; c) V. Trivedi-Parmar, M. J. Robertson, J. A. Cisneros, S. G. Krimmer, W. L. Jorgensen, *ChemMedChem* **2018**, *13*, 1092-1097; d) Y. Shan, R. Si, J. Wang, Q. Zhang, H. Zhou, J. Song, J. Zhang, Q. Chen, *Eur. J. Med. Chem.* **2019**, 440-447.

[13] For the synthesis of 4-arylpyrazoles using Negishi reaction: C. Wiethan, W. C. Rosa, H. G. Bonacorso, M. Stradiotto, *Org. Biomol. Chem.* **2016**, *14*, 2352-2359.

[14] For selected examples of deprotection of 1-phenylethyl-substituted heteroarenes: a) A. J. Smith, A. Young, S. Rohrbach, E. F. O'Connor, M. Allison, H.-S. Wang, D. L. Poole, T. Tuttle, J. A. Murphy, *Angew. Chem., Int. Ed.* **2017**, *56*, 13747-13751; b) S. Haldar, S. Saha, S. Mandal, C. K. Jana, *Green Chem.* **2018**, *20*, 3463-3467.

[15] For selected examples of deprotection of benzyl-substituted heteroarenes: a) A. A. Haddach, A. Kelleman, M. V. Deaton-Rewolinski, *Tetrahedron Lett.* **2002**, *43*, 399-402; b) R. S. Foster, H. Adams, H. Jakobi, J. P. A. Harrity, *J. Org. Chem.* **2013**, *78*, 4049-4064; c) A. W. Brown, M. Fisher, G. M. Tozer, C. Kanthou, J. P. A. Harrity, *J. Med. Chem.* **2016**, *59*, 9473-9488; d) O. Obulesu, K. H. Babu, J. B. Nanubolu, S. Suresh, *J. Org. Chem.* **2017**, *82*, 2926-2934.

[16] For recent development and applications see: C. D. Mboyi, C. Testa, S. Reeb, S. Genc, H. Cattey, P. Fleurat-Lessard, J. Roger, J.-C. Hierso, *ACS Catal*. **2017**, *7*, 8493−8501.

[17] W. Hagui, H. Doucet, J.-F. Soulé, *Chem* **2019**, *5*, 2006-2078.

[18] D. L. Davies, S. A. Macgregor, C. L. McMullin, *Chem. Rev.* **2017**, *117*, 8649-8709.

[19] M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570-14571.

[20] S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848-10849.

[21] D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066-1067.

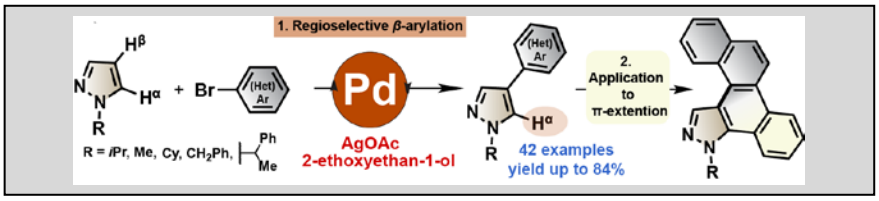
[22] D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880-6886.

[23] M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754-8756.

[24] a) M. D. Lotz, N. M. Camasso, A. J. Canty, M. S. Sanford, *Organometallics* **2017**, *36*, 165-171; b) K. L. Bay, Y. F. Yang, K. N. Houk, *J. Organomet. Chem.* **2018**, *864*, 19-25; c) B. Bhaskararao, S. Singh, M. Anand, P. Verma, P. Prakash, C. Athira, S. Malakar, H. F. Schaefer, R. B. Sunoj, *Chem. Sci.* **2020**, *11*, 208-216.

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By using a very simple ligand-free palladium-catalyst and without directing group installation, the less-acidic β-C–H of pyrazoles is regioselectively arylated (up to 98%) conserving untouched α-C–H bonds.

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