Homogeneous Catalysis

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Palladium-Catalyzed Pyrazole-Directed sp^3 C–H Bond Arylation for the Synthesis of β-Phenethylamines

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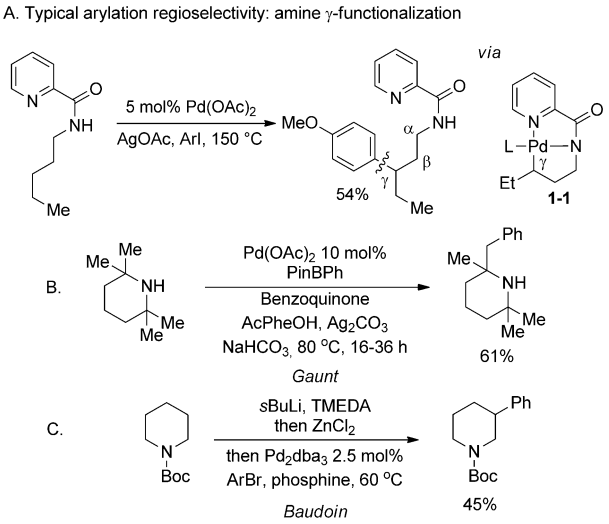
Abstract: *We have developed a method for palladium-catalyzed, pyrazole-directed sp^3 C–H bond arylation by aryl iodides. The reaction employs a $Pd(OAc)_2$ catalyst at 5–10 mol% loading and silver(I) oxide as a halide-removal agent, and it proceeds in acetic acid or acetic acid/hexafluoroisopropanol solvent. Ozonolysis of the pyrazole moiety affords pharmaceutically important β-phenethylamines.*

In recent years, carbon–hydrogen bond functionalization methods have developed from an organometallic curiosity into a useful approach for the synthesis of complex natural products and drug-like molecules.[1,2] The use of C–H bonds as transformable functional groups is advantageous since these moieties are typically the most abundant functionalities in organic molecules. Direct conversion of these bonds into the desired functionality results in economic and ecological benefits since less chemical waste is generated as a result of shortened synthetic pathways.

During the last decade, many examples of directed intermolecular sp^3 C–H bond functionalization reactions have been disclosed.[3,4] However, several key issues are still not solved. Perhaps the most challenging among them is control of the site selectivity of the C–H functionalization. Directing-group strategies allow functionalization at the 4-position from the coordinating heteroatom owing to a preference for five-membered metallacycle formation (Scheme 1A). This results in γ-functionalization of amine and β-functionalization of carboxylic acid derivatives.[3,4] Functionalization of other positions is possible if the 4-position relative to the coordinating heteroatom is blocked or hindered, resulting in a limited reaction scope.[5] Another strategy employs the higher reactivity of methyl relative to methylene groups in non-directed C–H oxygenation, as shown by the Sanford group.[6] Dong and co-workers have reported several examples of the β-oxygenation of amine and alcohol derivatives.[7a,b]

There have been three reported β-arylations of aliphatic amine derivatives (Scheme 1B,C).[7c,d,e] While conceptually important, these methods are limited by the requirement for quaternary centers next to a nitrogen atom or strong base in the deprotonation step. Additionally, relatively few auxiliaries besides bidentate monoanionic directing groups are capable of promoting functionalization at unactivated methylene positions.[4c,d,e,7d,8] Among those, the perfluorinated anilines reported by Yu and co-workers, are notable.[4d,e,8b] Clearly, additional methods are required to achieve convenient and regioselective functionalization of unactivated sp^3 C–H bonds. Especially interesting is the selective and general β-arylation of aliphatic amines, since β-phenethylamines are key structural components in important medicines and natural products.[9] We report herein a method for palladium-catalyzed pyrazole-directed sp^3 C–H bond arylation by aryl iodides. The reaction tolerates a wide range of functional groups and allows removal of the directing group to reveal the pharmaceutically important β-phenethylamine functionality. Furthermore, this is the first example of using a pyrazole moiety as a transformable directing group in sp^3 C–H functionalization.



Scheme 1. Arylation regioselectivity and amine β-functionalization.

Arylpyrazoles can be cyclopalladated, which shows that pyrazole is an efficient directing group.[10] Furthermore, the pyrazole moiety has been extensively used as a directing group for palladium- and ruthenium-catalyzed sp^2 C–H bond arylation.[11] There are only a few isolated reports of pyrazole directing groups in palladium- and iridium-catalyzed sp^3 C–H bond functionalization.[12] In 2006, we showed that 1-phenylpyrazole can be *ortho*-arylated under the conditions that are effective for 2-phenylpyridine functionalization.[11a] Since 2-ethylpyridine is arylated under those conditions, it seemed

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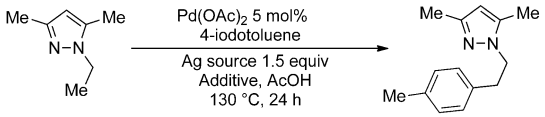
reasonable that 1-ethylpyrazole and other alkylpyrazoles could be reactive as well.

Optimization was carried out with respect to the silver source and additives (Table 1). A reasonable arylation rate was observed at 130 °C in acetic acid, while reactions in other solvents, such as H_2O, DMF, acetonitrile, *t*-butanol, dioxane,

Table 1: Optimization of reaction conditions.[a]

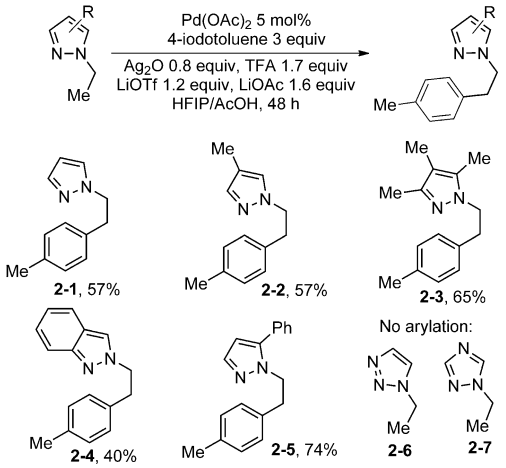


Entry	Ag source	Additive(s)	Yield [%]
1	AgOAc	none	18
2	AgOAc	$NaOCOCF_3$	48
3	AgOAc	NaOTf	63
4	AgOAc	LiOTf	63
5	$AgOCOCF_3$	LiOTf	79
6[b]	AgOAc	LiOTf/TFA	75
7[c]	Ag_2O	LiOTf/TFA	77
8[d]	Ag_2O	LiOTf/TFA	76
9[e]	Ag_2O	LiOTf/TFA/LiOAc	81

[a] Pyrazole 0.2 mmol, 4-iodotoluene 0.6 mmol, AcOH 0.2 mL, additive 0.3 mmol. Yields were determined by GC analysis. [b] Additives: LiOTf 1.2 equiv, trifluoroacetic acid 1.5 equiv. [c] Silver oxide 0.75 equiv, additives: LiOTf 1.2 equiv, trifluoroacetic acid 1.5 equiv. [d] Silver oxide 0.75 equiv, additives: LiOTf 1.2 equiv, trifluoroacetic acid 1.5 equiv, hexafluoropropanol/AcOH solvent (3:1), 120 °C. [e] Silver oxide 0.8 equiv, additives: LiOTf 1.2 equiv, trifluoroacetic acid 1.7 equiv, LiOAc 1.6 equiv, 105 °C, yield of isolated product. OTf = $^-OSO_2CF_3$, TFA = CF_3CO_2H.

dichloroethane, and cyclooctane afforded very low conversions. Entry 1 shows that arylation in acetic acid by using silver acetate as the base and halide-removing agent gives product in only 18% yield. Addition of sodium trifluoroacetate improved the yield to 48% (entry 2). Even higher yields are obtained if sodium triflate is employed as an additive (entry 3). Lithium triflate as an additive gave the same yield as the sodium salt, thus showing that the anion is important in arylation (entry 4). The use of silver trifluoroacetate in combination with lithium triflate further improved the yield to 79% (entry 5). Attempts to replace the expensive silver trifluoroacetate with a cheaper silver source were fruitful, as shown in entries 6 and 7. The use of a silver acetate mixture with trifluoroacetic acid gave a 75% yield of arylation product (entry 6). It is possible to replace AgOAc with Ag_2O, which is one of the cheapest commercially available silver salts (entry 7). An acetic acid/hexafluoroisopropanol solvent mixture gives the same yield as the reaction run in pure acetic acid (entry 8); however, for electron-poor aryl iodides, this is the best solvent combination. Finally, addition of LiOAc slightly increases the yield, allows the reaction to occur at 105 °C, and gives more reproducible reaction yields at larger scale (entry 9). No reaction was observed if $Pd(OAc)_2$ was omitted. The use of bases other than silver salts resulted in very low conversions.

Other directing groups were tested under the optimized conditions (Scheme 2). Unsubstituted ethylpyrazole and



Scheme 2. Other directing groups.

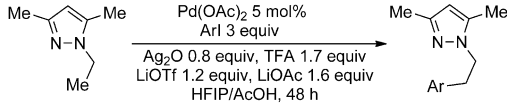
methyl-substituted compounds gave arylation products in yields that are slightly lower than those for 1-ethyl-3,5-dimethylpyrazole (**2-1** to **2-3**). Pyrazoles possessing aryl substituents are also reactive, and products were obtained in fair to good yields (**2-4**, **2-5**). Ethyltriazoles were not arylated under the optimized conditions (**2-6** and **2-7**). This result demonstrates the higher efficiency of bidentate coordination in C–H functionalization, since triazoles possessing an additional chelating group are efficient auxiliaries for C–H functionalization.[4j,13] Overall, 3,5-dimethylpyrazole is the optimal auxiliary for the arylation, based both on reactivity and cost.

The reaction scope with respect to the aryl iodides is presented in Table 2. The reactions were successful with both electron-rich (entries 1–6) and electron-poor (entries 8–13) aryl iodides. Various functionalities, such as methoxy (entries 4, 6), chloro (entries 7, 8), trifluoromethyl (entry 9), ester (entry 10), ketone (entry 11), trifuoromethoxy (entry 12), and fluoro (entry 13) groups are tolerated. The reaction can be scaled to 10 mmol without any loss in yield (entry 7). Typically, the arylations with electron-poor aryl iodides were slower than those with electron-rich substrates. This trend is also often observed for C–H functionalization when employing bidentate auxiliaries.[3b]

The reaction scope with respect to the alkyl on the pyrazoles is presented in Table 3. The isopropyl derivative was arylated in 50% yield (entry 1), while the *s*-butyl-substituted compound reacted at the methyl group to afford product in 60% yield (entry 2). Larger alkyl groups are tolerated as well (entries 3 and 4). Phenethyl and phenylpropylpyrazoles afforded the products in 53 and 56% yields (entries 5 and 6). A compound possessing an ester substitution was arylated in 55% yield (entry 7).

Directed functionalization of secondary, unactivated (not benzylic or α to heteroatom) sp^3 C–H bonds is relatively rare. Besides bidentate monoanionic auxiliaries, which can promote the activation of even some tertiary positions,[14] few directing groups can effect methylene C–H bond functionalization. We were pleased to discover that dimethylpyrazole directs the arylation of some secondary and even tertiary C–

Table 2: Reaction scope with respect to the aryl iodides.[a]



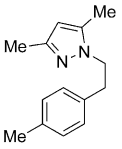
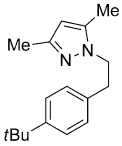
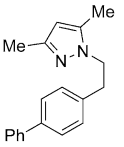
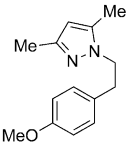
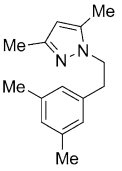
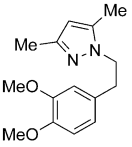
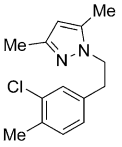
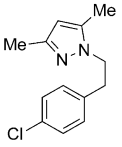
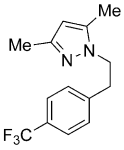
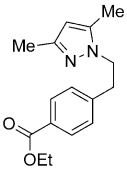
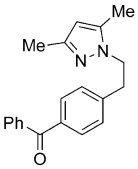
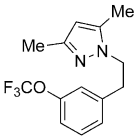
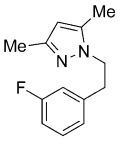
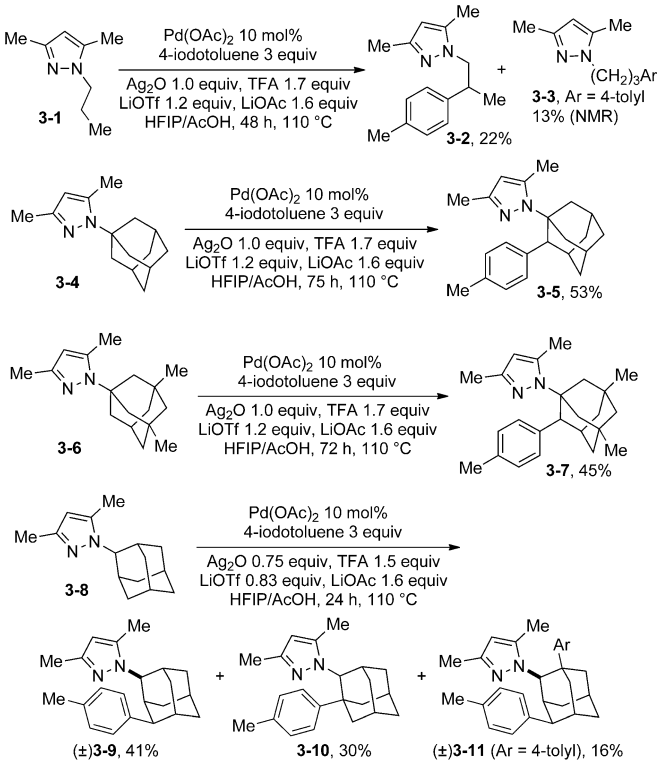
Entry	Ar	Product	Yield [%]
1[b]	4-MeC_6H_4		81
2[b]	4-$tBuC_6H_4$		68
3[c]	4-PhC_6H_4		63
4[d]	4-$MeOC_6H_4$		76
5[b]	3,5-$Me_2C_6H_3$		71
6[d]	3,4-$(MeO)_2C_6H_3$		70
7[c]	3-Cl-4-MeC_6H_3		78 80[e]
8[c]	4-ClC_6H_4		76
9[c]	4-$CF_3C_6H_4$		69
10[c]	4-$EtO_2CC_6H_4$		64

Table 2: (Continued)

Entry	Ar	Product	Yield [%]
11[c]	4-$PhCOC_6H_4$		65
12[c]	3-$CF_3OC_6H_4$		67
13[c]	3-FC_6H_4		75

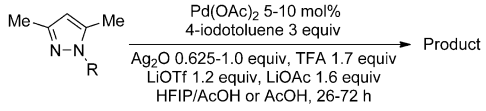
[a] Pyrazole 1 mmol, hexafluoroisopropanol 0.75 mL, AcOH 0.25 mL. Yields of isolated product are given. See the Supporting information for details. [b] Temperature: 105 °C. [c] Temperature: 120 °C. [d] Temperature: 110 °C. [e] Scale: 10 mmol.

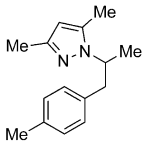
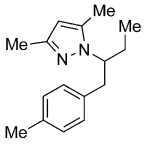
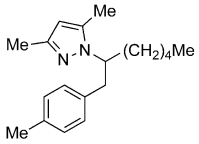
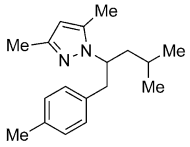
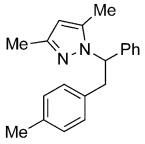
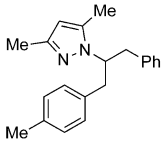
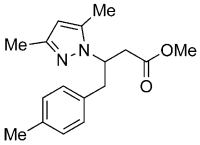
H bonds (Scheme 3). Propylpyrazole gave a mixture of products resulting from arylation of both the methylene and methyl groups (**3-2** and **3-3**). Pyrazolyladamantane **3-4** was arylated in 53% yield to give product **3-5**. Compound **3-6**, which contains the dimethyladamantane moiety present in memantine,[15] reacted well to give arylation product **3-7** in 45% yield. Interestingly, 2-adamantyl-substituted pyrazole **3-8** was reactive and afforded three compounds. The major one



Scheme 3. Arylation of secondary and tertiary C–H bonds.

Table 3: Reaction scope with respect to the alkylpyrazoles.[a]



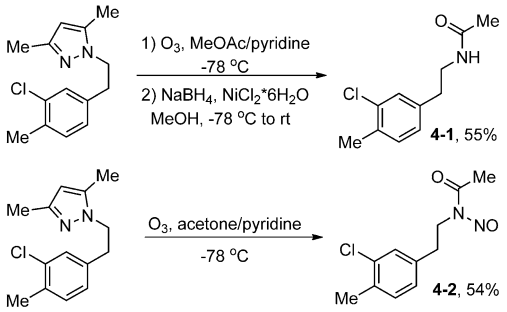
Entry	R	Product	Yield [%]
1	isopropyl		50
2	*s*-butyl		60
3	2-hexyl		57
4	4-Me-2-pentyl		53
5[b]	1-phenethyl		53
6	1-phenyl-2-propyl		56
7	1-methoxy-carbonyl-2-propyl		55

[a] Pyrazole 1 mmol, solvent: 1–2 mL of hexafluoroisopropanol/AcOH or AcOH, temperature: 80–130°C. Yields of isolated product are shown. See the Supporting information for details. [b] Purity: 91%.

was the γ-functionalizaton product **3-9**, which was isolated in 41% yield. Monoarylation at the tertiary β-position was also observed, giving **3-10** in 30% yield. Diarylation product **3-11** was isolated in 16% yield. This is a rare example of a directed arylation of a non-activated tertiary sp^3 C–H bond.

The advantage of pyrazole directing groups lies in the possibility of their removal to afford useful β-arylamines (Scheme 4). Ozonolysis of arylated pyrazole[16] (Table 2, entry 7) affords phenethylamine **4-1** in 55% yield. If reductive workup is omitted, 54% of the *N*-nitroso derivative **4-2** is obtained.

In conclusion, we have shown that pyrazoles can direct the palladium-catalyzed functionalization of unactivated sp^3 C–H bonds. The reaction employs $Pd(OAc)_2$ as the catalyst at 5–10 mol% loading and silver(I) oxide as a halide-removal agent and base precursor, and it proceeds in either acetic acid or acetic acid/hexafluoroisopropanol solvent. Ozonolysis of the pyrazole moiety affords pharmaceutically significant β-phenethylamines. Since *N*-substituted pyrazoles can be obtained from alkylamines,[17] their arylation can be thought of as β-funtionalization of aliphatic amines, which are revealed after ozonolysis. The chemistry described here is a rare example of formal amine sp^3 C–H bond β-arylation.



Scheme 4. Directing-group removal.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arenes · C–C coupling · C–H activation · homogeneous catalysis · palladium

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Communications

Homogeneous Catalysis

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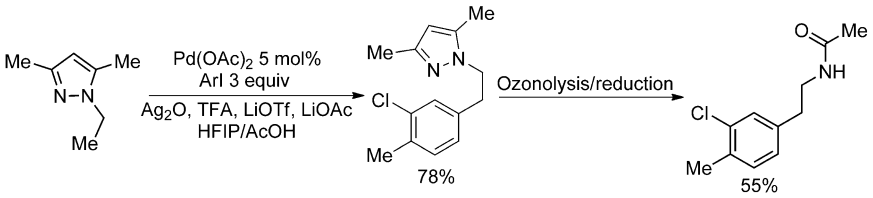
Palladium-Catalyzed Pyrazole-Directed sp^3 C–H Bond Arylation for the Synthesis of β-Phenethylamines



Palladium-catalyzed, pyrazole-directed sp^3 C–H bond arylation by aryl iodides is reported. The reaction employs a Pd-$(OAc)_2$ catalyst and silver(I) oxide as a halide-removal agent and base precursor, and it proceeds in either acetic acid or acetic acid/hexafluoroisopropanol solvent. Ozonolysis of the pyrazole moiety affords pharmaceutically important β-phenethylamines.

