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C–H Activation |*Hot Paper*|

Directing/Protecting-Group-Free Synthesis of Tetraaryl-Substituted Pyrazoles through Four Direct Arylations on an Unsubstituted Pyrazole Scaffold

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Abstract: A directing/protecting-group-free synthesis of 1,3,4,5-tetraaryl-substituted pyrazoles was achieved through four transition metal-catalyzed direct arylations. Various pyrazoles with four different aryl rings were obtained using readily available reagents from an unsubstituted pyrazole. Two aryl-substituted pyrazoles showed intense violet fluorescence, high quantum yields ($\Phi_f = 0.68$, 0.64), and large Stokes shifts (19000, 15200 cm^{-1}).

Introduction

Sequential diversification approaches that are based on heteroaromatic scaffolds with multiple reaction centers are valuable for use in drug discovery and in materials development. These approaches enable the rapid installation of various substituents without extra synthetic steps, such as protection/deprotection and the introduction of activating/directing groups, which do not contribute to structural diversification. From this point of view, a sequential C–H direct arylation approach based on readily available unsubstituted heteroaromatics is an attractive choice. Nakamura[1] and Ohta[2] have conducted pioneering studies on the direct C–H arylation of heteroaromatics, and numerous useful reactions have been reported since.[3] A decade ago, Miura demonstrated the installation of multiple aryl substituents to a thiazole[4] and a thiophene[5] with the aid of a directing and sacrificial carboxanilide group. Fagnou[6] and Itami[7] recently reported sequential C–H direct arylation approaches based on heteroaromatic scaffolds with *N*-oxide and methoxy groups, respectively, which played the role of directing or protecting groups. Although many sequential C–H direct arylation approaches have been reported, the number of directing group/protecting-group-free approaches is surprisingly limited. As far as we could ascertain, only Murai[8] and Itami[9] have demonstrated beautiful sequential direct arylations of unsubstituted 1,3-azoles without the use of a directing or a protecting group. However, directing group/protecting-group-free sequential direct arylation of unsubstituted 1,2-azoles has not yet been achieved, probably due to the lower reactivity of C–H bonds as well as to the smaller reactivity differences among the C–H bonds in 1,2-azoles compared with those of 1,3-azoles. For instance, three C–H bonds in pyrazole were less reactive compared with those of imidazole. Moreover, the reactivity differences among the C–H bonds were smaller compared with those of imidazole.[10]

Multiaryl-substituted pyrazoles make up an important class of compounds, because they are frequently found in pharmaceutical drugs, agricultural chemicals, functional materials, and ligands for transition-metal catalysts.[11] In addition, functional 1,3,4,5-tetraaryl-substituted pyrazoles, such as the ligand in the cannabinoid (CB1) receptor **1**,[12] antimicrobial agent **2**,[13] p38 MAP kinase inhibitor **3**,[14] and electroluminescent compound **4**[15] have been reported (Figure 1). For these reasons, there is a great deal of interest in their synthesis in the academic field as well as in agrochemical, pharmaceutical, and chemical industries.[11] The most conventional approach[11] to the synthesis of multiaryl-substituted pyrazoles—condensation of 1,3-diketone or α,β-unsaturated carbonyl compounds with substituted hydrazines—often suffers from insufficient regioselectivity and/or availability of substrates.[16] Notwithstanding the importance of multiaryl-substituted pyrazoles, direct C–H arylation based on pyrazoles has attracted somewhat less attention. Recently, direct C–H arylation at the C3-, C4-, and C5-positions of pyrazoles[8a,17] and at the C3-position of indazoles[18] have been reported. In particular, Sames achieved a multiaryl-substituted pyrazole synthesis starting from 4-bromopyrazole with the aid of a 2-(trimethylsilyl)ethoxymethyl (SEM) group.[17c] We have developed sequential diversification approaches using Pd-catalyzed cross-coupling based on aromatic scaffolds for drug discovery and materials development.[19] In addition, we recently accomplished a tetraaryl-substituted pyrazole synthesis through a sequence of S_NAr reaction/Suzuki-Miyaura coupling/C–H direct arylations that was based on a 3-iodo-pyrazole scaf-

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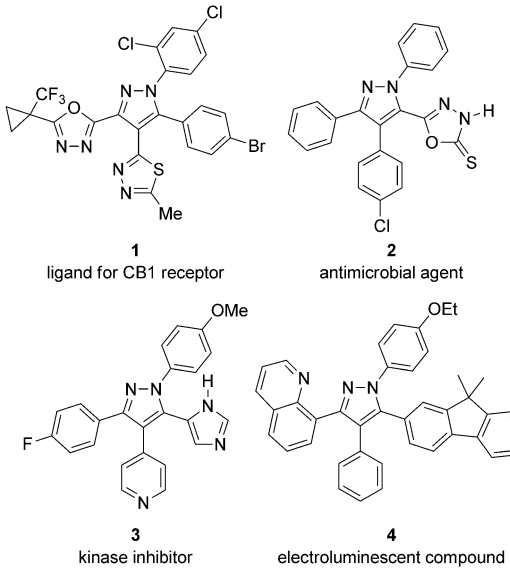


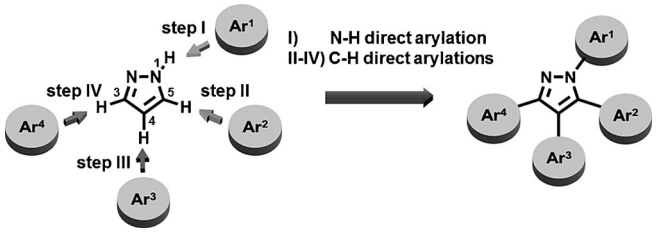
Figure 1. Structures of various useful 1,3,4,5-tetraaryl-substituted pyrazoles.

fold.[20] However, the most ideal approach, namely, installation of four different aryl substituents onto an unsubstituted pyrazole ring by means of four direct arylations, has not been demonstrated.

Herein, we wish to report the four-step synthesis of tetraaryl-substituted pyrazoles based on an unsubstituted pyrazole scaffold without using directing/protecting groups. In order to enable the facile and rapid combinatorial synthesis of a pyrazole library in the future, we only examined readily available reagents that could be handled without using glovebox techniques. In addition, we also report our evaluation of the photophysical properties of synthesized 1,4,5-triaryl- and 1,3,4,5-tetraarylpyrazoles.

Results and Discussion

We planned to introduce Ar^1 at the N1-position based on a Buchwald–Hartwig coupling reaction[21] for the first step (Scheme 1). Sames reported a reactivity trend of three C–H bonds of pyrazole against C–H direct arylation (C5 > C4 ≫ C3).[17c] In accordance with the reported trend, we decided to introduce Ar^2 at the C5-position, Ar^3 at the C4-position, and Ar^4 at the C5-position, in the order indicated in Scheme 1. The key



Scheme 1. Synthetic plan for tetraaryl-substituted pyrazoles via four direct arylations.

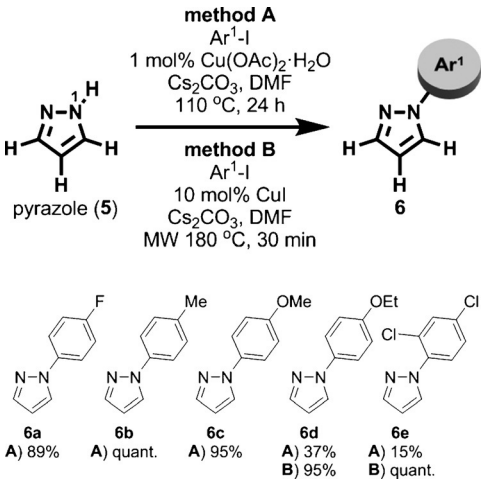


Figure 2. Cu-catalyzed N-arylation of unsubstituted pyrazole (**5**). Ac: acetyl, MW: microwave, DMF: *N*,*N*-dimethylformamide.

to sucess was how to regioselectively activate the C4- and C5-positions without affecting the other reaction centers.

The first arylation at the N1-position was examined. A procedure established by Li and Lang[22] (method A) afforded the desired products **6a**–**6c** in high yields, whereas it afforded complex mixtures in the synthesis of **6d** and **6e**. Modifications of a procedure established by You[23] (method B) were useful for the synthesis of **6d** and **6e** (Figure 2). The desired products were obtained in excellent yields.

A regioselective C–H direct arylation at the C5-position of 1-arylpyrazole was examined.[24] Daugulis reported an intermolecular C–H direct phenylation at the C5-position of 1-phenylpyrazole (CuI, 1,10-phenanthloline, *t*BuOLi, in *N*,*N*′-dimethylpropyleneurea, 52% yield).[17b] However, many attempts to obtain **7c** based on the Daugulis conditions resulted only in recovery of the substrate. Greaney reported a C–H direct arylation at the C1-position of 2-phenyl indazole ($[Pd(dppf)Cl_2]\cdot CH_2Cl_2$, PPh_3, Ag_2CO_3 in H_2O, yield: 49–96%). These conditions were applied to the synthesis of **7c**, and the desired product was obtained in a moderate yield (36%). After optimizing the combination of phosphine ligands (PPh_3, $[(Cy_3)PH]BF_4$, $[(tBu_3)PH]BF_4$,[25] cataCXiumA,[26] JohnPhos,[27] DavePhos,[28] SPhos,[29] and XPhos[30]) and solvents (H_2O, H_2O/MeCN, H_2O/1,4-dioxane, H_2O/DMF, and H_2O/DMSO), we found that method D (Figure 3) afforded **7c** in a better yield (46%). However, method D was not effective in the synthesis of either **7f** or **7j** (28 and 26% yields, respectively). Thus, we extensively reinvestigated the reaction conditions using $Pd(OAc)_2$, aryl halides (Ar-I and Ar-Br), phosphine ligands (PPh_3, $[(Cy_3)PH]BF_4$, $[(tBu_3)PH]BF_4$, cataCXium A, and DavePhos), additives (CuI and CuCl), bases (K_2CO_3, Cs_2CO_3, and Ag_2CO_3), solvents (DMA, 1,4-dioxane, and 1,4-dioxane/*t*BuOH), and PivOH. As a result, our originally developed method C afforded the best results. Various Ar^2 groups including electron-donating, electron-withdrawing, and heteroatom-containing aryls were introduced in moderate to good yields (45–72%), as shown in Figure 3. The electronic factor of the Ar^1 group did not greatly influence the yields of this coupling reaction at the C5-position.

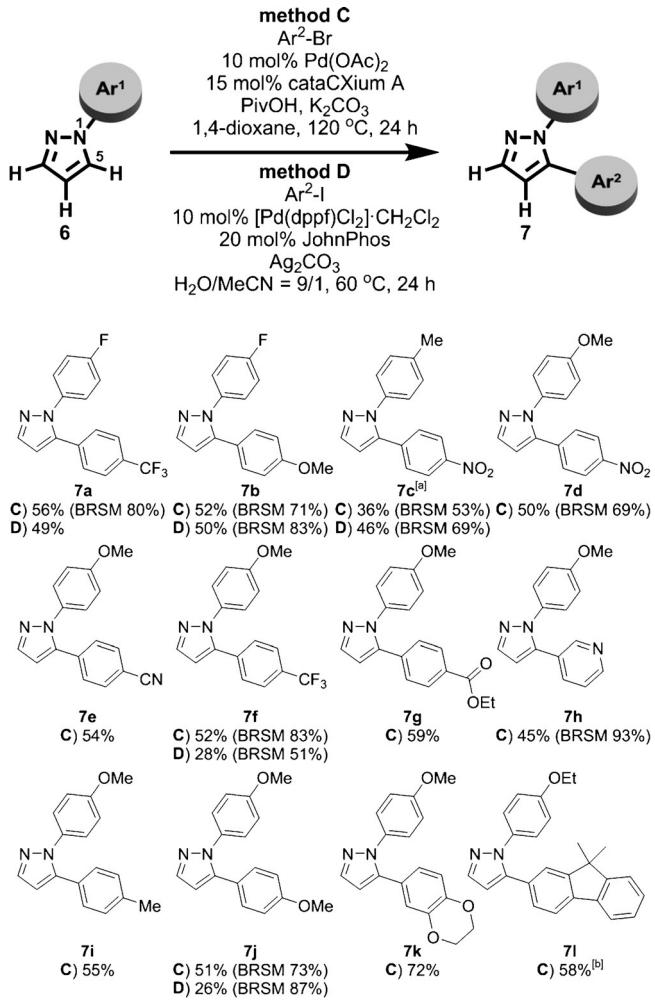


Figure 3. Products of the C–H direct arylation at the C5-position of 1-arylpyrazoles **6**. dppf: 1,1′-bis(diphenylphosphino)ferrocene, Cy: cyclohexyl, JohnPhos: 2-(di-*tert*-butylphosphino)biphenyl, DavePhos: 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, SPhos: 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, cataCXium A: di(1-adamantyl)-*n*-butylphosphine, DMA: *N*,*N*-dimethylacetamide. [a] Overarylation at the C4-position was observed. The ratio of **7c** to the undesired 1,4,5-triaryl product was 7:1 (method C) and 7:2 (method D). The ratio was determined by ^{1}H NMR analysis. [b] The ratio of substrate **6** to Ar-Br was 1.2:1. The yield was calculated based on the Ar-Br.

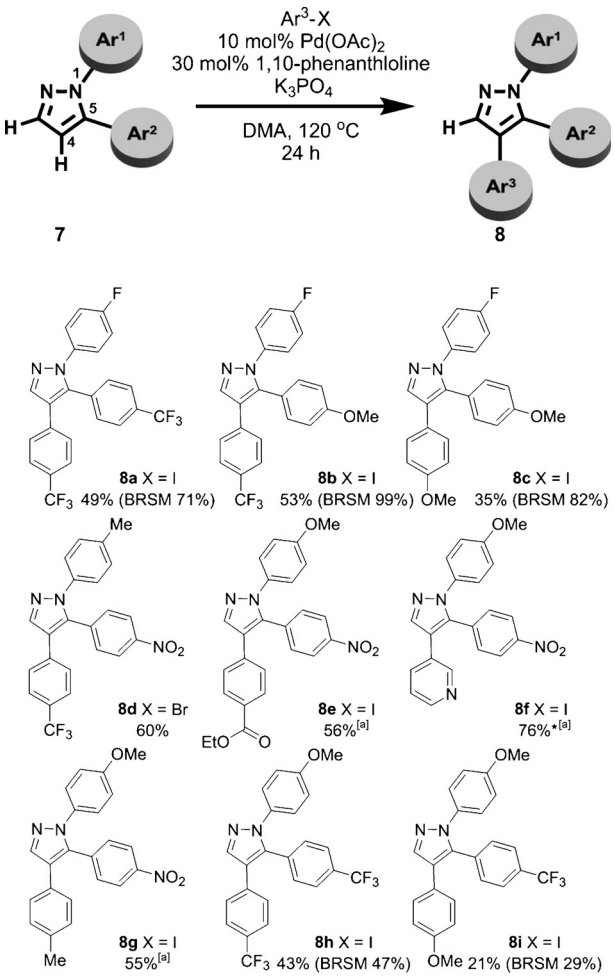
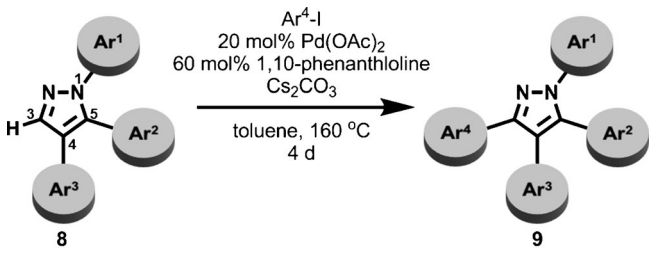


Figure 4. Products of the C–H direct arylation at the C4-position of 1,5-diarylpyrazoles **7**. [a] The ratio of substrate **7** to Ar-I was 2:1. The yields were calculated based on the Ar-I.

Regioselective C–H direct arylation at the C4-position of 1,5-diaryl-substituted pyrazole was examined (Figure 4). Method C (Figure 3) was not effective for this coupling reaction, whereas the modified Yu's conditions reported for the C–H direct arylation at the C-3 position of 1,4,5-triphenylpyrazole were useful.[17h] Although the introduction of a strong electron-donating Ar^3 group (methoxyphenyl group) resulted in low yields (**8c**: 35% yield, **8i**: 21% yield), weak electron-donating, electron-withdrawing, and heteroatom-containing Ar^3 groups were introduced in moderate to good yields (43–76%). The electronic factors of the Ar^1 and Ar^2 groups did not greatly influence the yields of this coupling reaction at the C4-position.

A final C–H direct arylation at the most unreactive C3-position of 1,4,5-triarylpyrazoles was investigated based on the use of method C (Figure 3). We extensively examined the addition of various Lewis acids (MX_2; M = Fe, Co, Ni, Cu, Zn, Mn, X = Cl, Br, I, OTf) to enhance the acidity of the proton at the C3-position by metal coordination to the nitrogen atom. However, the desired coupling product could not be obtained in a satisfactory yield. Yu conditions were then examined for the coupling reaction (Figure 5).[17h] In the case of Ar^2 and/or Ar^3 as electron-donating groups (methoxy phenyl group), the coupling yields tended to decrease (**9g**: 62% yield vs. **9j**: 35% yield, **9d**: 68% yield vs. **9k**: 41% yield). In the case of Ar^1 as an electron-withdrawing group (fluorophenyl group), the coupling yields also tended to decrease (**9d**: 68% yield vs. **9a**: 51% yield, **9g**: 62% yield vs. **9b**: 35% yield) probably due to the undesired C–H direct arylation reaction on the Ar^1 ring. In other cases, various Ar^4 groups including electron-donating, electron-withdrawing, and heteroatom-containing aryls were introduced in satisfactory to good yields (57–88%).

The structure of tetraaryl-substituted pyrazole **9c** was unambiguously determined by X-ray crystallographic analysis (Figure 6). All of the four aryl groups were introduced to desired positions. They were distorted from coplanarity by 42.32(9) (4-MePh), 25.58(7) (4-MeOPh), 55.74(10) (4-CF_3Ph), and



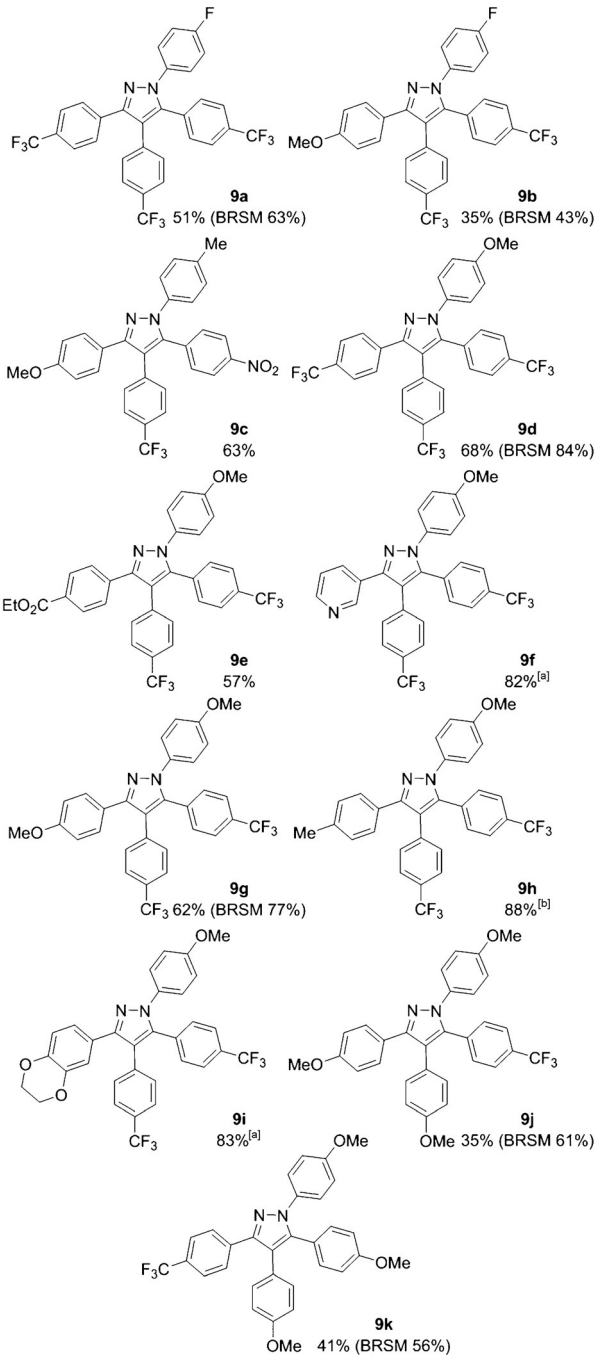


Figure 5. Products of the C–H direct arylation at the C3-position of 1,4,5-triarylpyrazoles **8**. [a] The ratio of substrate **8** to Ar-I was 2:1. The yields were calculated based on the Ar-I. [b] The ratio of substrate **8** to Ar-I was 1.5:1. The yield was calculated based on the Ar-I.

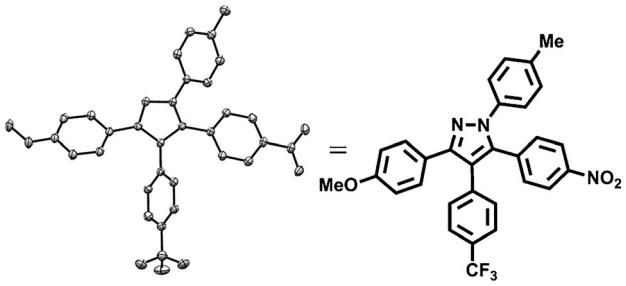


Figure 6. X-ray crystallographic analysis of **9c**. Hydrogen atoms are omitted for clarity.

42.29(12)° (4-NO_2Ph) with respect to the central pyrazole ring, probably due to the steric repulsion among the aryl rings.

There are previous reports detailing interesting photophysical properties (large Stokes shifts) of 3,4-diaryl-[31] and 3,5-diaryl-substituted pyrazoles[32] (6100–13600 cm^{-1}) and 1,3,5-[32a] and 3,4,5-triaryl-substituted pyrazoles[31] (4200–15800 cm^{-1}) that make them potentially useful for functional fluorescent dyes.[32b] Therefore, we were interested in the photophysical properties of the synthesized 1,4,5-triaryl-substituted pyrazoles **8** and 1,3,4,5- tetraaryl-substituted pyrazoles **9**, as shown in Table 1 (for the absorption/emission spectra, see the Supporting Information).

Pyrazoles **8** and **9**, with the exceptions of **8d**–**8g** and **9c** that all had nitro groups,[33] exerted violet emissions and large Stokes shifts (**8**: 11000–19000 cm^{-1}; **9**: 14100–17900 cm^{-1}). In particular, 1,3,5-triaryl-substituted pyrazole **8i** and 1,3,4,5-tetraaryl-substituted pyrazole **9e** showed near UV absorption (**8i**: $\lambda_{max,abs}=237$ nm, $\varepsilon=24100\ L\,mol^{-1}\,cm^{-1}$; **9e**: $\lambda_{max,abs}=263$ nm,

Table 1. Photophysical properties of triaryl- and tetraaryl-substituted pyrazoles.

	$\lambda_{max,abs}$[a] [nm]	ε[b] [$L\,mol^{-1}\,cm^{-1}$]	$\lambda_{max,em}$[c] [nm]	Stokes shift[d] [cm^{-1}]
8a	249	17300	390	14600
8b	272	18600	387	11000
8c	235	23200	389	16800
8d	262	23100	–[e]	–[e]
8e	277	30000	–[e]	–[e]
8f	253	18900	–[e]	–[e]
8g	254	20600	–[e]	–[e]
8h	273	20900	436	13700
8i	237	24100	432	19000
9a	252	21800	395	14300
9b	256	22500	429	15700
9c	267	22700	–[e]	–[e]
9d	253	15400	435	16500
9e	263	24300	436	15200
9f	247	23000	438	17700
9g	251	21100	436	16900
9h	247	25500	439	17700
9i	270	11100	436	14100
9j	243	23200	428	17900
9k	236	15900	410	17900

[a] Absorption maxima in MeCN at $c=10^{-4}$ M. [b] Emission maxima in MeCN at $c=10^{-5}$ M. [c] Molar absorption coefficients in MeCN. [d] $\lambda_{max,abs}-\lambda_{max,em}$. [e] Fluorescence too weak to be determined.

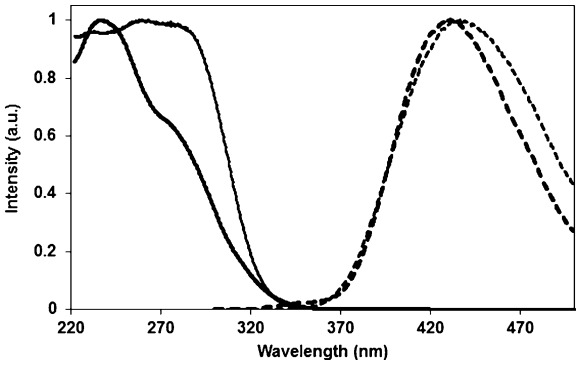


Figure 7. Normalized absorption (solid line) and emission (dotted line) spectra of **8i** (bold line) and **9e** (plain line) recorded in MeCN, 293 K and at *c* (**8i** and **9e**) = 10^{-4} M (absorption) and *c* (**8i** and **9e**) = 10^{-5} M (emission).

$\varepsilon = 24\,300\ L\,mol^{-1}\,cm^{-1}$) and intense violet emission (**8i**: $\lambda_{max,em} = 432$ nm, $\Phi_f = 0.68$; **9e**: $\lambda_{max,em} = 436$ nm, $\Phi_f = 0.64$). It should be noted that the both compounds **8i** and **9e** exerted particularly large Stokes shifts (**8i**: 19 000 cm^{-1}; **9e**: 15 200 cm^{-1}). Thus, there was almost no overlap between the absorption and emission bands (Figure 7). As far as we could ascertain, there are few violet-emitting ($\lambda_{max,em}$ = 400-450 nm) compounds with good quantum yields and large Stokes shifts.[34]

Conclusion

In summary, we demonstrated the rapid and divergent synthesis of 1,3,4,5-tetraaryl-substituted pyrazoles through four transition-metal-catalyzed direct arylations. Various pyrazoles with four different aryl rings were obtained using readily available reagents that can be treated, without using glovebox techniques, based on an unsubstituted pyrazole scaffold. This is the first synthesis of fully substituted 1,2-azoles by menas of sequential direct arylation reactions. In addition, the absorption/emission spectra of synthesized 1,4,5-triaryl-substituted pyrazoles **8** and 1,3,4,5-tetraaryl-substituted pyrazoles **9** were measured. Two aryl-substituted pyrazoles, **8i** and **9e**, showed intense violet fluorescence, high quantum yields ($\Phi_f = 0.68$, 0.64), and large Stokes shifts (19 000, 15 200 cm^{-1}). These properties make them potentially useful for functional fluorescent dyes. The developed synthetic approach would be a valuable aid in drug discovery and in materials development based on multiaryl-substituted pyrazoles.

Experimental Section

Experimental details are given in the Supporting Information. These include synthetic procedures, full spectroscopic and analytical data for all new compounds.

Keywords: C–H activation · cross-coupling · fluorescence · heterocycles · palladium

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