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Intramolecular Direct C−H Arylation Approach to Fused Purines. Synthesis of Purino[8,9-*f*]phenanthridines and 5,6-Dihydropurino[8,9-*a*]isoquinolines[§]

Igor Čerňa, Radek Pohl, Blanka Klepetářová, and Michal Hocek*

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, CZ-16610, Prague 6, Czech Republic

hocek@uochb.cas.cz

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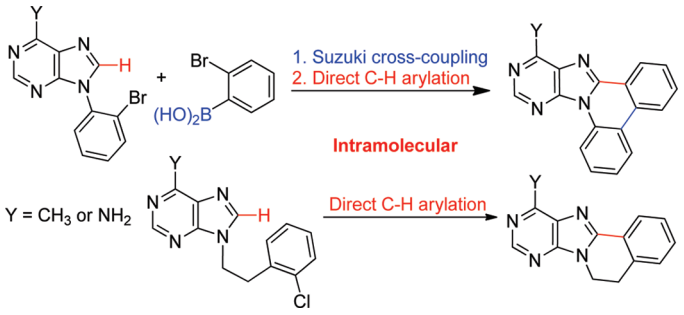

Intramolecular C−H arylations were employed as a key step in the synthesis of hitherto unknown fused purine systems: 13-substituted purino[8,9-*f*]phenanthridines and 11-substituted 5,6-dihydropurino[8,9-*a*]isoquinolines. The purino[8,9-*f*]phenanthridines were prepared in moderate yields by double C−H arylations of 9-phenylpurines with 1,2-diiodobenzene or, more efficiently, by consecutive Suzuki coupling of 9-(2-bromophenyl)purines with 2-bromophenylboronic acid followed by intramolecular C−H arylation. 5,6-Dihydropurino[8,9-*a*]isoquinolines were prepared in quantitative yields by intramolecular C−H arylations of 9-(2-chlorophenethyl)purines.

Purine scaffolds bearing a combination of 2−4 substituents at positions 2, 6, 8, and/or 9 are an important class of pharmacophores and many derivatives display a wide range of biological activities,[1] i.e., inhibition of protein kinases,[2] or tubulin polymerization,[3] antagonist effects to receptors,[4] dedifferentiation of muscle cells to progenitor cells,[5] or induction of polyploidization[6] of cancer cells via inhibition of Aurora kinases. Large combinatorial libraries of several types of tri- and tetrasubstituted purines have been prepared by heterocyclizations[7] or by regioselective nucleophilic substitutions of dihalopurines with amines in combination

[§] Dedicated to the memory of Keith Fagnou.

*To whom correspondence should be addressed. Phone: +420 220183324. Fax: +420 220183559.

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with cross-coupling reactions.[8,9] Fused purine hererocycles have also been extensively studied[10,11] and some of them display biological effects, i.e., antiinflamatory[12] or cytostatic[13] activity or phosphodiesterase inhibition.[14] Unlike N-linked fused purines which are easily available through heterocyclizations of aminopurines,[10−14] synthesis of benzo- and extended benzo-fused purines is much more challenging since, at least when starting from purines, some intramolecular C−C bond forming reaction is needed. Only very scarce examples[15] of saturated *f*- and *e*-dihydro- and tetrahydrobenzo-fused purines prepared by the building-up of the purine ring or by radical cyclizations are known in the literature.

During the last 3 decades, cross-coupling reactions have become the method of first choice for C−C bond formation in purines[16] and were used for attachment of all kind of unfunctionalized or even functionalized C-substituents at positions 2, 6, or 8. Recently, we[17,18] and others[19] have introduced direct C−H arylations[20] as an alternative for C-substitution at position 8 of purine bases and nucleosides and used this reaction in combination with cross-couplings to regioselectively generate[18] small libraries of purines bearing multiple substituents. Intramolecular versions of C−H arylations are often used for the construction of fused heterocycles.[21] To the best of our knowledge, no intramolecular C−H arylation on purine was known until the very recent synthesis of 6*H*-isoindolo[2,1-*f*]purine published[22] during the course of writing up of this paper as a single example within a series of other Cu-catalyzed intramolecular C−H arylations leading to 11*H*-isoindolo[2,1-*a*]benzimidazoles. We report here the use of intramolecular C−H arylations for the synthesis of two novel types of extended *e*-fused purines: purino[8,9-*f*]phenanthridines and 5,6-dihydropurino-[8,9-*a*]isoquinolines. The *e*-fusion (positions 8,9) preserves the base-pairing and major-groove facets of purine ring intact and thus these types of compounds might be able to intercalate to DNA or bind to adenine binding sites of some enzymes. We intended to investigate and compare several approaches based on C−H arylation(s) in the synthesis of *e*-fused derivatives of model 6-methylpurine (containing no interfering functionality) and biologically relevant adenine (containing an amino group that can potentially cause some side reactions[18]).

Results and Discussion

Three possible synthetic pathways were envisaged for the synthesis of 13-substituted purino[8,9-*f*]phenanthridines (Scheme 1): (i) oxidative coupling of 8,9-diphenylpurines, (ii) double C−H arylation of 9-phenylpurines with 1,2-dihalobenzenes, and (iii) the Suzuki coupling of 9-(2-bromophenyl)purines with 2-bromophenylboronic acid followed by intramolecular C−H arylation.

Oxidative coupling of two arenes[23] is the simplest and most straightforward way to form a biaryl since preparation of neither aryl halide nor aryl organometal is needed. On the other hand, such reactions are very challenging in terms of efficiency and selectivity and, therefore, they are mostly

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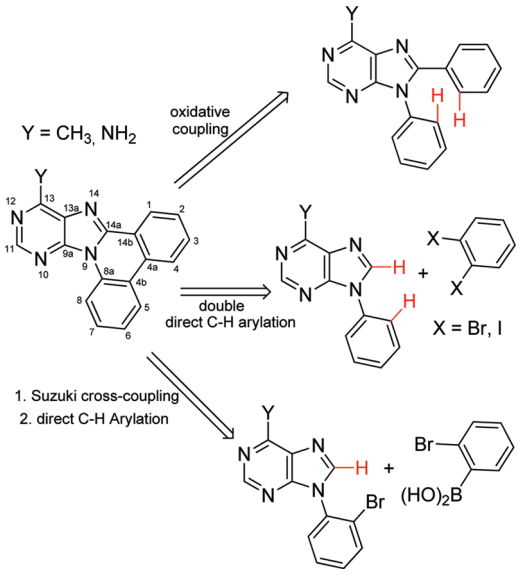
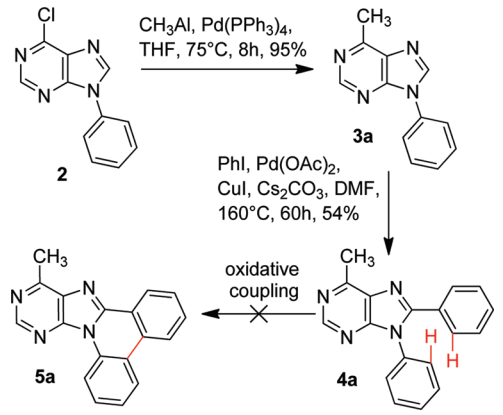
SCHEME 1. Retrosynthetic Analysis of Construction of the Purino[8,9-*f*]phenanthridine Core



SCHEME 2. Synthesis of 4a and Attempted Oxidative Coupling



employed in an intramolecular manner, where the formation of an extended aromatic system is the driving force. We envisaged that in 8,9-diphenylpurines, the two phenyl rings are in perfect orientation to facilitate the ring closure leading to purino[8,9-*f*]phenanthridines. The starting model compound, 6-methyl-6,8,-diphenylpurine (**4a**), was prepared in three steps (Scheme 2). The synthesis started with the N^9-arylation reaction of 6-chloropurine (**1**) with phenylboronic acid,[24] followed by methylation with trimethylaluminum[25] to give 6-methyl-9-phenylpurine (**3a**) in high yield. The final direct arylation[18] of **3a** with phenyl iodide in the presence of CuI and Cs_2CO_3 gave the desired 8,9-diphenyl derivative **4a** in 54% yield. Oxidative coupling of 6-methyl-8,9-diphenyl-9*H*-purine **4a** was attempted with use of several procedures recently published for intra- and intermolecular oxidative couplings of diverse heterocycles, i.e., indoles, benzofurans, etc. ($Pd(OAc)_2$-catalyzed reactions using diverse oxidants—benzoquinone,[26] air,[27] $Cu(OAc)_2$,[28] $Ag(OAc)$[23a]—in the presence or absence of additives—Ag_2CO_3, K_2CO_3 or pivalic acid; or $FeCl_3$-catalyzed reaction in the presence of *m*-CPBA[29]). Unfortunately none of these reactions proceeded to produce even traces of the desired product **5a** and, in all cases, the starting compound **4a** was recovered from the reaction mixture.

The second attempted strategy involved the double C−H arylation of **3a** with 1,2-dihalobenzenes (Scheme 3, Table 1). At first, we tried to employ our conditions previously reported[17] for direct arylation of purines in the reaction of **3a** with 1,2-diiodobenzene **6** (entry 1). This Pd-catalyzed reaction in the presence of CuI and Cs_2CO_3 led to a complex mixture of many products from which we were able to isolate three products. Besides the desired annulated product **5a**, formed in only 10% yield, we isolated also 6-methyl-8,9-diphenyl-9*H*-purine (**4a**, 8%) as a product of C−H arylation at position 8 followed by dehalogenation, and 1,2-bis(6-methyl-9-phenyl-9*H*-purin-8-yl)benzene (**7a**, 25%) as a product of competing intermolecular 2-fold direct C−H arylation of two purines with one diiodobenzene. The structure of this interesting unwanted product was proved by X-ray diffraction (Figure 1). The crystal structure of **7a** showed $\pi-\pi$ stacking of each N(9)-phenyl group with the neighboring purine moiety. Attempts to optimize these conditions (alteration of base and ligands, catalyst loadings, reaction time) as well as the use of 1,2-dibromobenzene did not bring any improvement.

Hence, we turned our attention to the recently reported Fagnou's protocol[30] based on the addition of pivalic acid, which acts as a proton shuttle[31] to increase the reactivity of substrates toward the CMD mechanism. Initial experiments employed $Pd(OAc)_2$ with $P(p\text{-}FPh)_3$ in the presence of PivOH (60 mol %) and K_2CO_3 in DMF, at 130 °C for 48 h (Table 1, entry 2). The reaction gave low conversion but cleanly produced the desired product **5a** in 23% yield (no formation of byproducts **4a** and **7a** was observed and most of the starting **3a** was recovered). The conditions were further optimized to increase the conversion. However, the use of $P(F_5Ph)_3$ or $P(Cy)_3 \cdot HBF_4$ ligands or a higher amount of base did not change the conversions significantly (yields 19−25%, entries 3−5). Similar low conversions were also obtained when using 1,2-dibromobenzene (data not shown). The last attempt was based on the protocol of Chattopadhyay et al.[32] that employed $Pd(OAc)_2$ in the presence of tetrabutylammonium bromide (TBAB, Aliquat100) and KOAc, which gave the desired 13-methylpurino[8,9-*f*]phenanthridine (**5a**) in moderate (but improved) 35% yield (entry 6). Application of these conditions to annulation of 9-phenyladenine

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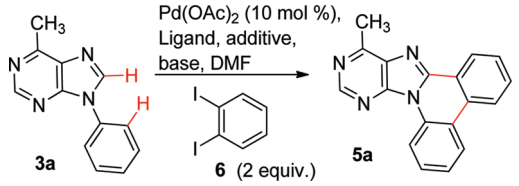
TABLE 1. Double C−H Arylations of 3a with 1,2-Diiodobenzene

entry	ligand (mol %)	additive (equiv)	base (equiv)	temp, °C	time, h	yield, %
1		CuI (3)	Cs_2CO_3 (2.5)	160	60	10[a]
2	P(*p*-FPh)$_3$[b] (10)	PivOH (0.6)	K_2CO_3 (3)	130	48	23
3	P(F_5Ph)$_3$[c] (10)	PivOH (0.6)	K_2CO_3 (3)	130	48	19
4	P(*p*-FPh)$_3$ (20)	PivOH (0.6)	K_2CO_3 (4)	130	43	25
5	P(Cy)$_3$·BF_4 (20)	PivOH (0.6)	K_2CO_3 (4)	130	43	24
6		TBAB (1)	KOAc (4)	140	25	35

[a]Isolated byproducts: **4a** (8%) and **7a** (25%). [b]Tris(4-fluorophenyl)phosphine. [c]Tris(Pentafluorophenyl)Phosphine.

SCHEME 3. Double C−H Arylations of 3a with 1,2-Diiodobenzene



(**3b**) with 1,2-diiodobenzene gave only traces of the desired product **5b**.

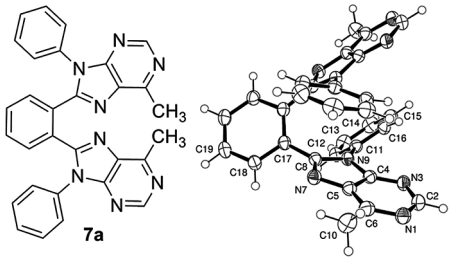
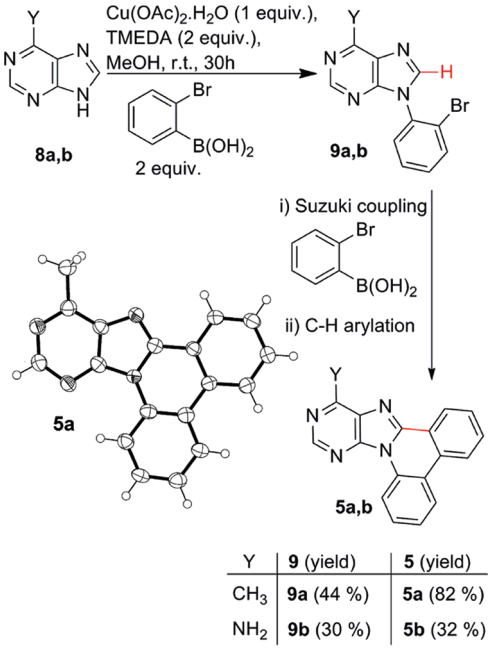


FIGURE 1. Molecular and crystal structure of **7a**. Thermal ellipsoids are drawn at the 50% probability level.

The third approach to the target purino[8,9-*f*]phenanthridines **5** was based on a combination of the Suzuki cross-coupling with direct C−H arylation (Scheme 4). The starting 6-methyl- and 6-amino-9-(2-bromophenyl)purines **9a**,**b** were prepared by Cu(II)-mediated N^9-arylation[33] of 6-methylpurine (**8a**)[34] or adenine (**8b**) with 2-bromobenzeneboronic acid in the presence of TMEDA (Scheme 4). Following exactly the published procedure,[33] the reactions proceeded poorly, giving only 7% and 13% of desired products **9a**,**b**. However, the use of neat MeOH instead of MeOH:H_2O = 4:1, described in the original protocol, improved the yields of products **9a** and **9b** to already acceptable 44% and 30%, respectively. The Suzuki cross-couplings of derivatives **9a** and **9b** with 2-bromobenzeneboronic acid were performed according to published protocol[35] in the presence of Pd(PPh_3)$_4$, Na_2CO_3, and Aliquat 100 in toluene/water. Even after prolonged time (36 h), the conversion was not complete and the biphenylpurine intermediates were not chromatographically separable from starting bromophenylpurines **9**. Therefore, we decided to perform the C−H arylation directly with the reaction mixture after the Suzuki coupling. Thus the reaction mixture was extracted from water to toluene and the

SCHEME 4. Combination of the Suzuki Cross-Coupling with Intramolecular C−H Arylation



Y	9 (yield)	5 (yield)
CH_3	**9a** (44 %)	**5a** (82 %)
NH_2	**9b** (30 %)	**5b** (32 %)

i) Pd(PPh_3)$_4$ (4 mol%), Na_2CO_3 (4 equiv), Aliquat 100 (8 mol%), toluene/H_2O=2:1,110°C, 36h.
ii) Pd(OAc)$_2$ (5 mol %), P(Cy)$_3$·HBF_4 (10 mol %), K_2CO_3 (2.5 equiv), DMF, 150°C, 20h (30h for **9b**).

crude intermediate obtained by evaporation and drying of the organic phase was used in the second step. The intramolecular direct C−H arylation step was performed under conditions (Pd(OAc)$_2$ in the presence of tricyclohexylphosphine (P(Cy)$_3$·HBF_4) and K_2CO_3 in DMF at 150 °C) developed by Fagnou for intramolecular direct arylation with aryl chlorides[36] recently also applied in the synthesis of higher helicenes.[37] The cascade of the two reactions starting from **9a** proceeded smoothly giving the desired annulated product **5a** in excellent 82% yield over the two steps (Scheme 4). The same approach was also successfully used in the synthesis of 13-aminopurino[8,9-*f*]phenanthridine **5b**, though in moderate 32% overall yield due to lower conversions observed for both steps. Apparently, this approach is the most efficient and convenient for the synthesis of 13-substituted purino[8,9-*f*]-phenanthridines. The crystal structure of **5a** by X-ray diffraction (Scheme 4 and the SI) showed a perfectly planar extended aromatic system of the novel purino[8,9-*f*]phenanthridine system.

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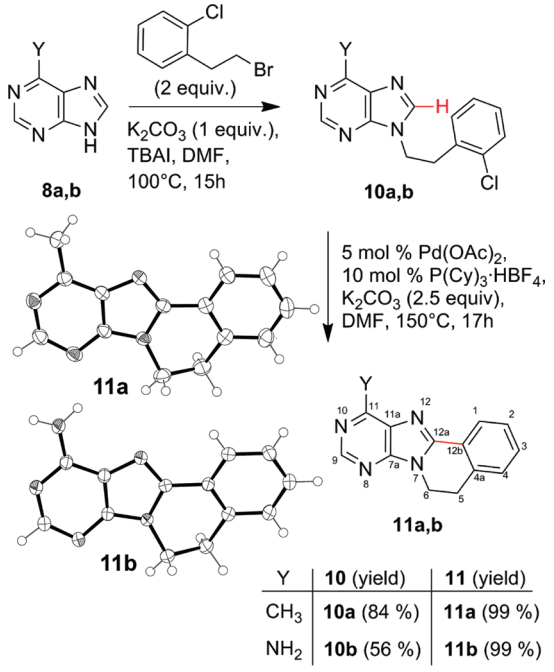
TABLE 2. Absorption and Emission Spectra of Compounds 5 and 11

compd	absorption λ_{max}, nm (ε, L·mol^{-1}·cm^{-1})	Φ	emission λ (nm)
5a	346 (8 200), 330 (10 000), 316 (15 000), 304 (15 000), 263 (43 000)	0.22	358, 375
5b	345 (13 000), 329 (16 000), 315 (15 000), 301 (16 000), 284 (18 000), 268 (25 000), 237(42 000)	0.33	395
11a	333 (22 000), 280 (28 000), 233 (9 500)	0.019	322, 337, 353
11b	309 (25 000), 229 (16 000)	0.45	363, 380

SCHEME 5. Synthesis of 5,6-Dihydropurino[8,9-*a*]isoquinolines 11



Similar intramolecular C−H arylation was used for the synthesis of another novel type of fused purines: 5,6-dihydropurino[8,9-*a*]isoquinolines (Scheme 5). The key intermediates, 9-(2-chlorophenethyl)purines **10a**,**b**, were envisaged to be suitable substrates for the intramolecular arylation. They were prepared by alkylation of purines **8a**,**b** with 2-chlorophenethyl bromide in the presence of K_2CO_3 (in analogy to ref 38) in 84% and 56% yield, respectively. Intramolecular direct C−H arylation of methylpurine derivative **10a** was then performed under the aforementioned Fagnou conditions.[36] The reaction proceeded smoothly within 17 h to afford the desired 11-methyl-5,6-dihydropurino[8,9-*a*]-isoquinoline **11a** in quantitative yield. Similarly, the same intramolecular cyclization of adenine derivative **10b** gave quantitative conversion to 11-amino-5,6-dihydropurino[8,9-*a*]-isoquinoline **11b**. The higher yields of this intramolecular C−H arylation compared to the synthesis of purino[8,9-*f*]-phenanthridines are probably due to the flexible saturated linker in intermediates **10** that makes the C−H arylation more efficient even for ethylene-tethered chlorobenzene compared to *o*-phenylene-tethered bromobenzene. Attempts to oxidize 5,6-dihydropurino[8,9-*a*]isoquinolines **11** to fully aromatic purino[8,9-*a*]isoquinolines with use of diverse oxidants (MnO_2,[39] Pd/C,[40] DDQ[41]) failed. Crystal structures of both 5,6-dihydropurino[8,9-*a*]isoquinolines **11a**,**b** (Scheme 5 and the SI) revealed a small distortion of the planarity caused by the saturated ethylene bridge (torsion angles of purine and benzene rings were ca. 8° or 12° for **11a** and **11b**, respectively). Crystal packings of both compounds show head-to-tail $\pi-\pi$ stacking of the heteroaromatic systems (see the SI).

Electronic absorption and emission spectra of the novel fused aromatic systems **5** and **11** were also studied (Table 2 and the SI). The purino[8,9-*f*]phenanthridines **5** showed a very complex pattern of absorption with 5−7 distinct bands of similar absorbance in the UV region, while the 5,6-dihydropurino[8,9-*a*]isoquinolines **11** revealed standard 2−3 absorption bands. All compounds were shown to be luminescent. Adenine derivative **5b** and **11b** possess higher quantum yields and longer wavelengths of emission compared to the 6-methylpurines **5a** and **11a**.

In conclusion, three approaches relying on Pd-catalyzed C−H arylations have been investigated in the quest for synthesis of purino[8,9-*f*]phenanthridines. While oxidative couplings of 8,9-diphenylpurines did not work, double C−H arylations of 9-phenylpurines with 1,2-diiodobenzene gave moderate yields of the desired products (up to 35%) and, in some cases, side products were detected. The most efficient approach was based on consecutive Suzuki coupling of 9-(2-bromophenyl)purines with 2-bromophenylboronic acid followed by intramolecular C−H arylation. Analogous intramolecular C−H arylation was used in a simple two-step synthesis of 5,6-dihydropurino[8,9-*a*]isoquinolines from purines. The cyclizations of 9-(2-chlorophenethyl)-purines proceeded quantitatively. The novel fused heterocyclic systems of purino[8,9-*f*]phenanthridines **5** and 5,6-dihydropurino[8,9-*a*]isoquinolines **11** showed interesting absorption spectra and luminescence. Compounds **5a**,**b**, **7a**, and **11a**,**b** did not show any considerable cytostatic activity in several tested cancer and leukemia cell lines (CCRF-CEM, HL60, HeLaS3, HCT116, HS578, DU145, and H23)[42] most probably due to very limited solubility in water. However, this synthetic approach may find applications in straightforward preparation of other novel extended heterocyclic systems.

Experimental Section

Double Direct Arylation of 3a with 1,2-Diiodobenzene 6. Method A (Table 1, entry 1): DMF (6 mL) was added through

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a septum to an argon-purged vial containing 6-methyl-9-phenyl-9*H*-purine **3a** (210 mg, 1 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol %), CuI (571 mg, 3 mmol), 1,2-diiodobenzene (260 μL, 2 equiv), and Cs_2CO_3 (814 mg, 2.5 mmol). The reaction mixture was heated to 160 °C for 60 h. The solvent was evaporated under reduced pressure. Products **5a** (10% yield), **4a** (8% yield), and **7a** (25% yield) were isolated by flash column chromatography (gradient elution THF/hexanes 1:9 → THF/hexanes 4:6).

Method B (Table 1, entry 2): DMF (3 mL) was added through a septum to an argon-purged vial containing 6-methyl-9-phenyl-9*H*-purine **3a** (105 mg, 0.5 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), P(*p*-FPh)$_3$ (15.8 mg, 0.05 mmol), PivOH (30.6 mg, 0.3 mmol), 1,2-iodobenzene (130 μL, 1 mmol), and K_2CO_3 (207 mg, 1.5 mmol). The reaction mixture was heated to 130 °C for 48 h. The solvent was evaporated under reduced pressure. Product **5a** (23% yield) was isolated by flash column chromatography (gradient elution hexanes → ethyl acetate/hexanes 2:8).

Method C (Table 1, entry 6): A mixture of Aliquat 100 (158 mg, 0.5 mmol) and KOAc (184 mg, 2 mmol) in dry degassed DMF (20 mL) was stirred for 20 min. This solution was added through a septum to an argon-purged vial containing 6-methyl-9-phenyl-9*H*-purine **3a** (105 mg, 0.5 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), and 1,2-iodobenzene (130 μL, 1 mmol). The reaction mixture was heated to 140 °C for 25 h. The solvent was evaporated under reduced pressure. Product **5a**, 50.3 mg (35% yield), was isolated by flash column chromatography (gradient elution hexanes → ethyl acetate/hexanes 2:8).

13-Methylpurino[8,9-*f*]phenanthridine (5a): brownish crystals from $CHCl_3$/*t*BuOMe, mp 252−255 °C; ^{1}H NMR (600.1 MHz, $CDCl_3$) δ 3.04 (s, 3H, CH_3), 7.51 (ddd, 1H, $J_{6,5}$ = 8.2 Hz, $J_{6,7}$ = 7.1 Hz, $J_{6,8}$ = 1.2 Hz, H-6), 7.64 (ddd, 1H, $J_{2,1}$ = 7.9 Hz, $J_{2,3}$ = 7.2 Hz, $J_{2,4}$ = 1.0 Hz, H-2), 7.66 (ddd, 1H, $J_{7,8}$ = 8.4 Hz, $J_{7,6}$ = 7.1 Hz, $J_{7,5}$ = 1.3 Hz, H-7), 7.76 (ddd, 1H, $J_{3,4}$ = 8.1 Hz, $J_{3,2}$ = 7.2 Hz, $J_{3,1}$ = 1.4 Hz, H-3), 8.30 (d, 1H, $J_{4,3}$ = 8.1 Hz, H-4), 8.33 (dd, 1H, $J_{5,6}$ = 8.2 Hz, $J_{5,7}$ = 1.3 Hz, H-5), 8.74 (ddd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{1,3}$ = 1.4 Hz, $J_{1,4}$ = 0.4 Hz, H-1), 8.99 (s, 1H, H-11), 9.64 (dd, 1H, $J_{8,7}$ = 8.4 Hz, $J_{8,6}$ = 1.2 Hz, H-8); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 19.2 (CH-3), 118.6 (CH-8), 121.3 (C-4b), 122.2 (C-14b), 122.5 (CH-4), 123.4 (CH-5), 125.9 (CH-6), 126.1 (CH-1), 128.8 (CH-2), 129.6 (CH-7), 130.3 (C-4a), 131.8 (CH-3), 132.8 (C-8a), 133.6 (C-13a), 147.7 (C-14a), 149.6 (CH-11), 149.8 (C-9a), 158.1 (C-13); MS (ESI), *m*/*z* (% rel intensity) 224 (2), 257 (3), 267 (3), 285 (MH^+, 100); HR MS (MH^+) 285.1135 (calcd for $C_{18}H_{13}N_4$ 285.1135). Anal. Calcd for $C_{18}H_{12}N_4 \cdot 0.25H_2O$: C, 74.85; H, 4.36; N, 19.4. Found: C, 74.95; H, 4.24; N, 19.16.

General Procedure for Combination of Suzuki Cross-Coupling Reaction with Intramolecular Direct C−H Arylation: Method D. Toluene (2 mL) and water (1 mL) were added through a septum to an argon-purged vial containing **9a** or **9b** (0.5 mmol), 2-bromobenzeneboronic acid (150 mg, 0.75 mmol), $Pd(PPh_3)_4$ (23.5 mg, 0.02 mmol), Aliquat 100 (25 mg, 0.08 mmol), and Na_2CO_3 (212 mg, 1.5 mmol). The reaction mixture was heated to 110 °C for 36 h. After being cooled to room temperature the resulting reaction mixture was diluted with water (10 mL) and extracted with toluene (3 × 10 mL). Combined organic extracts were dried over $MgSO_4$ and filtered, then solvent was evaporated and residue was dried at room temperature in vacuo for 14 h. The crude residue was then dissolved in DMF (4 mL) and transferred through a septum to an argon-purged vial containing $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $P(Cy)_3 \cdot HBF_4$ (18.4 mg, 0.05 mmol), and K_2CO_3 (173 mg, 1.25 mmol). The reaction mixture was heated to 150 °C for 20 h (30 h for **9b**). The crude mixture was diluted with $CHCl_3$ (20 mL) and the solvents were evaporated under reduced pressure. Products **5a** (116 mg, 82% overall yield starting from **9a**) and **5b** (45 mg, 32% overall yield starting from **9b**) were isolated by flash column chromatography (gradient elution hexanes → ethyl acetate/hexanes 2:8).

13-Aminopurino[8,9-*f*]phenanthridine (5b): white solid, from $CHCl_3$/heptane, mp > 300 °C; ^{1}H NMR (600.1 MHz, DMSO-d_6) δ 7.62 (ddd, 1H, $J_{6,5}$ = 8.4 Hz, $J_{6,7}$ = 7.1 Hz, $J_{6,8}$ = 1.3 Hz, H-6), 7.63 (br s, 2H, NH_2), 7.78 (ddd, 1H, $J_{2,1}$ = 7.9 Hz, $J_{2,3}$ = 7.0 Hz, $J_{2,4}$ = 1.0 Hz, H-2), 7.81 (ddd, 1H, $J_{7,8}$ = 8.3 Hz, $J_{7,6}$ = 7. Hz1, $J_{7,5}$ = 1.2 Hz, H-7), 7.84 (ddd, 1H, $J_{3,4}$ = 8.3 Hz, $J_{3,2}$ = 7.0 Hz, $J_{3,1}$ = 1.3 Hz, H-3), 8.42 (s, 1H, H-11), 8.67 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{1,3}$ = 1.3 Hz, H-1), 8.68 (br d, 1H, $J_{4,3}$ = 8.3 Hz, H-4), 8.71 (dd, 1H, $J_{5,6}$ = 8.4 Hz, $J_{5,7}$ = 1.2 Hz, H-5), 9.76 (dd, 1H, $J_{8,7}$ = 8.3 Hz, $J_{8,6}$ = 1.3 Hz, H-8); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 118.2 (CH-8), 120.3 (C-13a), 121.2 (C-4b), 123.0 (C-14b), 123.7 (CH-4), 124.5 (CH-5), 124.8 (CH-1), 125.9 (CH-6), 129.3 (CH-2), 129.4 (C-4a), 129.8 (CH-7), 131.0 (CH-3), 133.3 (C-8a), 143.1 (C-14a), 148.7 (C-9a), 152.4 (CH-11), 156.7 (C-13); TOF MS (EI^+), *m*/*z* (% rel intensity) 151 (6), 178 (19), 214 (20), 258 (29), 285 (M, 100); HR MS (EI^+) 285.1024 (calcd for $C_{17}H_{11}N_5$ 285.1014). Anal. Calcd for $C_{17}H_{11}N_5 \cdot 0.4H_2O$: C, 69.8; H, 4.07; N, 23.94. Found: C, 70.0; H, 3.89; N, 23.77.

General Procedure for Intramolecular Direct Arylation of 10a and 10b. DMF (3 mL) was added through a septum to an argon-purged vial containing purine (**10a** or **10b**, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $P(Cy)_3 \cdot HBF_4$ (18.4 mg, 0.05 mmol), and K_2CO_3 (172 mg, 1.25 mmol). The reaction mixture was heated to 150 °C for 17 h. The crude mixture was diluted with $CHCl_3$ (20 mL) and the solvents were evaporated under reduced pressure. Products **11a** and **11b** were isolated by flash column chromatography (gradient elution $CHCl_3$ → 10% of MeOH in $CHCl_3$).

5,6-Dihydro-11-methylpurino[8,9-*a*]isoquinoline (11a): yield 99%, colorless crystals from $CHCl_3$/heptane, mp 156−157 °C; ^{1}H NMR (600.1 MHz, $CDCl_3$) δ 2.91 (s, 3H, CH_3), 3.30 (t, 2H, $J_{5,6}$ = 6.9 Hz, H-5), 4.47 (t, 2H, $J_{6,5}$ = 6.9 Hz, H-6), 7.37 (ddq, 1H, $J_{4,3}$ = 7.4 Hz, $J_{4,2}$ = 1.6 Hz, $J_{4,1}$ = $J_{4,5}$ = 0.8 Hz, H-4), 7.45 (tdt, 1H, $J_{2,1}$ = $J_{2,3}$ = 7.4 Hz, $J_{2,4}$ = 1.6 Hz, $J_{2,5}$ = 0.7 Hz, H-2), 7.48 (td, 1H, $J_{3,2}$ = $J_{3,4}$ = 7.4 Hz, $J_{3,1}$ = 1.6 Hz, H-3), 8.32 (ddd, 1H, $J_{1,2}$ = 7.4 Hz, $J_{1,3}$ = 1.6 Hz, $J_{1,4}$ = 0.8 Hz, H-1), 8.81 (s, 1H, H-9); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 19.6 (CH_3), 27.9 (CH_2-5), 39.3 (CH_2-6), 125.6 (C-12b), 126.0 (CH-1), 127.9 (CH-2), 128.4 (CH-4), 131.4 (CH-3), 133.9 (C-11a), 135.4 (C-4a), 150.0 (C-12a), 151.0 (C-7a), 151.7 (CH-9), 157.9 (C-11); MS (ESI), *m*/*z* (% rel intensity) 195 (4), 237 (MH^+, 100); HR MS (MH^+) 237.1134 (calcd for $C_{14}H_{13}N_4$ 237.1135). Anal. Calcd for $C_{14}H_{12}N_4 \cdot 1.5H_2O$: C, 63.86; H, 5.74; N, 21.28. Found: C, 63.85; H, 5.6; N, 21.14.

11-Amino-5,6-dihydropurino[8,9-*a*]isoquinoline (11b): yield 99%, colorless crystals from $CHCl_3$/heptane, mp > 300 °C; ^{1}H NMR (600.1 MHz, DMSO-d_6) δ 3.24 (t, 2H, $J_{5,6}$ = 6.9 Hz, H-11), 4.30 (t, 2H, $J_{6,5}$ = 6.9 Hz, H-10), 7.27 (br s, 2H, NH_2), 7.41−7.47 (m, 3H, H-2,3,4), 8.05 (m, 1H, H-1), 8.14 (s, 1H, H-9); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 27.4 (CH_2-5), 39.1 (CH_2-6), 119.7 (C-11a), 124.4 (CH-1), 126.3 (C-12b), 127.6 (CH-2), 128.8 (CH-4), 130.4 (CH-3), 135.60 (C-4a), 145.7 (C-12a), 150.0 (C-7a), 152.5 (CH-9), 155.8 (C-11); HR MS (ESI, MH^+) 238.1088 (calcd for $C_{13}H_{12}N_5$ 238.1087). Anal. Calcd for $C_{13}H_{11}N_5$: C, 65.81; H, 4.67; N, 29.52. Found: C, 65.50; H, 4.69; N, 29.32.

Single Crystal X-ray Structure Analysis. The diffraction data of single crystals of **5a** (colorless, 0.01 × 0.09 × 0.60 mm^3), **7a** (colorless, 0.11 × 0.20 × 0.42 mm^3), **11a** (colorless, 0.07 × 0.32 × 0.60 mm^3), and **11b** (colorless, 0.02 × 0.29 × 0.60 mm^3) were collected on Xcalibur X-ray diffractometer with Cu Kα (λ = 1.54180 Å). All three structures were solved by direct methods with SIR92[43] and refined by full-matrix least-squares on F with CRYSTALS.[44] All hydrogen atoms were located in a difference map, but those attached to carbon atoms were repositioned

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geometrically and then refined with riding constraints, while all other atoms were refined anisotropically in all cases.

Crystal data for 5a: $C_{18}H_{12}N_4$, orthorhombic, space group *Pnn*2, $a = 17.463(3)$ Å, $b = 18.850(4)$ Å, $c = 3.9169(10)$ Å, $V = 1289.4(5)$ Å^3, $Z = 4$, $M = 284.32$, 11932 reflections measured, 1561 independent reflections. Final $R = 0.057$, $wR = 0.068$, GoF = 1.090 for 1199 reflections with $I > 1.5\sigma(I)$ and 199 parameters. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 762123.

Crystal data for 7a: $C_{30}H_{22}N_8$, monoclinic, space group *C*2/*c*, $a = 15.3485(11)$ Å, $b = 9.7269(4)$ Å, $c = 18.4269(13)$ Å, $\beta = 119.133(9)°$, $V = 2403.0(3)$ Å^3, $Z = 4$, $M = 247.28$, 27606 reflections measured, 2530 independent reflections. Final $R = 0.048$, $wR = 0.056$, GoF = 1.099 for 2009 reflections with $I > 2\sigma(I)$ and 172 parameters. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 762121.

Crystal data for 11a: $C_{14}H_{15}N_4O_{1.5}$, triclinic, space group $P\bar{1}$, $a = 10.2023(13)$ Å, $b = 11.7179(15)$ Å, $c = 11.9757(16)$ Å, $\alpha = 84.147(11)°$, $\beta = 65.064(13)°$, $\gamma = 82.177(11)°$, $V = 1284.6(3)$ Å^3, $Z = 4$, $M = 263.30$, 27466 reflections measured, 5385 independent reflections. Final $R = 0.051$, $wR = 0.063$, GoF = 0.940 for 4003 reflections with $I > 2\sigma(I)$ and 353 parameters. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 767124.

Crystal data for 11b: $C_{13}H_{11}N_5$, triclinic, space group $P\bar{1}$, $a = 7.3513(6)$ Å, $b = 10.8273(10)$ Å, $c = 13.9340(10)$ Å, $\alpha = 103.269(7)°$, $\beta = 93.029(6)°$, $\gamma = 91.387(7)°$, $V = 1077.20(16)$ Å^3, $Z = 4$, $M = 237.26$, 35870 reflections measured, 4541 independent reflections. Final $R = 0.050$, $wR = 0.056$, GoF = 1.079 for 3288 reflections with $I > 2\sigma(I)$ and 326 parameters. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 762122.

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Supporting Information Available: Complete experimental details and characterization of all compounds, copies of all NMR spectra, UV and fluorescence spectra, additional figures of ORTEPs and crystal packing, and CIF files for **7a**, **5a**, **10a**, and **10b**. This material is available free of charge via the Internet at http://pubs.acs.org.