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COMMUNICATION

Regioselective C–H bond functionalizations of acridines using organozinc reagents†‡

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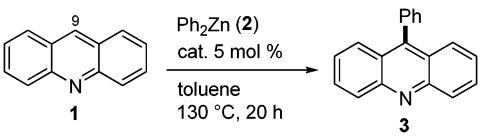
Despite the recent advance in C–H bond functionalization chemistry, the C–H bonds in the acridine ring system, which is an important scaffold in medicinal and material science, have met with limited success, due, in part, to the lack of activated C–H bonds adjacent to the ring nitrogen atom. Herein, several protocols that can effect the regioselective arylation and alkylation of acridines at the C-4 and C-9 positions are described.

The acridine scaffold displays a range of distinctive biological activities, thus serving as kinase inhibitors,[1a] antiviral[1b] and anti-prion[1c] agents, DNA intercalators[1d] and others. In particular, high affinity of the acridine scaffold for DNA and RNA has often rendered it a key component in the field of chemical biology.[2] Despite the broad-spectrum utility of this motif, the synthesis of functionalized acridines greatly depends upon *de novo* ring construction from acyclic components that bear the desired substituents, and only a few catalytic methods exist for the direct functionalization of preformed acridine frameworks.[3] Herein, we report on some methodology that permits the arylation and alkylation of acridine in a regioselective manner.

Remarkable progress made in the catalytic C–H bond functionalization of aromatic and heteroaromatic rings[4] has allowed applications to pyridines, which have been traditionally notorious substrates to deal with.[4e,5–7] However, these methods are not readily translated into acridines, since acridines are lacking in relatively activated C–H bonds, such as those at the 2-position of pyridines.[5] A notable exception to this is Chang's recent work, in which Rh(II)-catalyzed C-4 arylation of acridine is demonstrated.[3] Our approach to this problem involves the use of organozinc reagents,[5g] since we envisioned that their nucleophilic character would direct the carbon–carbon bond formation to proceed at the most electrophilic C-9 position.[8] We initially examined the reaction of acridine (**1**) with diphenylzinc (**2**) in the presence of various metal catalysts (Table 1). As expected, the C-9 arylated acridine **3** was formed when a catalytic amount of copper, iron, and indium salts was added (entries 2–4). Phosphine-ligated palladium (entry 5) and nickel-based (entry 6) catalysts were also found to be active. Interestingly, C-4 phenylated acridine was the major product in the case of the nickel catalyst (*vide infra* for further optimization of this C-4 arylation). Finally, it was found that the use of a $[RhCl(cod)]_2$ catalyst resulted in the cleanest reaction, and the desired product **3** was obtained in 82% yield by increasing the catalyst loading, the amount of **2**, and the reaction temperature (entry 9). Consequently, the conditions shown in entry 9 were identified optimal for further exploration.

Rhodium-catalyzed reactions of several substituted acridine derivatives with diphenylzinc (**2**) afforded the corresponding C-9 arylated product (Table 2). Introduction of strongly electron-donating morpholyl groups into the acridine ring decreased the yield of the C-9 arylated product significantly, indicating that the electrophilicity of C-9 is a determining factor for an efficient reaction, as we envisioned (entry 5). Diarylzinc reagents prepared from Grignard reagents and $Zn(OMe)_2$ were also applicable to this reaction to deliver the corresponding C-9 arylated acridines (entry 6).[9,10]

Table 1 C-9 arylation of acridines: catalyst screen[a]



Entry	Catalyst	Ligand	Yield[b] (%)
1	None	None	0
2	$Cu(OTf)_2$	None	35
3	$FeCl_3$	None	35
4	$InCl_3$	None	35
5	$Pd(OAc)_2$	PCy_3	11
6	$Ni(cod)_2$	PCy_3	10[c]
7	$[RhCl(cod)]_2$	PCy_3	38
8[d]	$[RhCl(cod)]_2$	PCy_3	75
9[e]	$[RhCl(cod)]_2$	PCy_3	85 (82)[f]

[a] Reaction conditions: **1** (0.25 mmol), Ph_2Zn (0.38 mmol), catalyst (0.0125 mmol), PCy_3 (0.025 mmol), when added, and toluene (1 mL) in a screw-capped vial under N_2 at 130 °C for 20 h unless otherwise noted. [b] NMR yields based on **1**. [c] C-4 phenylated acridine was also obtained (30%). [d] Run for 72 h. [e] Run using $[RhCl(cod)]_2$ (0.025 mmol), PCy_3 (0.05 mmol) and **2** (1.0 mmol) at 160 °C. [f] Isolated yield.

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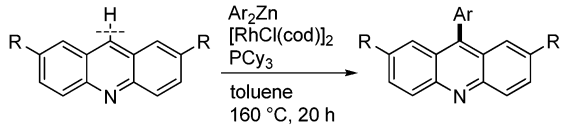
‡ Electronic supplementary information (ESI) available: Preparative and spectroscopic data. See DOI: 10.1039/c1cc16582h

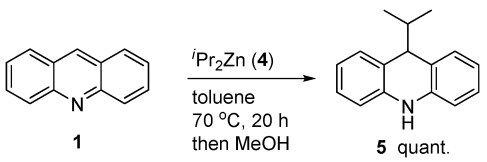
Table 2 Substrate scope for C-9 arylation[a]



Entry	R	Ar	Yield (%)
1	Phenyl	Ph	66
2	4-*n*-Butyl-C_6H_4	Ph	77
3	3,5-Dimethyl-C_6H_4	Ph	54
4	3-Isopropoxy-C_6H_4	Ph	51
5	Morpholyl	Ph	18
6	H	2-Tolyl[b]	54

[a] Reaction conditions: acridine derivative (0.25 mmol), Ar_2Zn (1.0 mmol), $[RhCl(cod)]_2$ (0.025 mmol), PCy_3 (0.05 mmol) and toluene (2 mL) in a screw-capped vial under N_2 at 130 °C for 20 h unless otherwise noted. [b] $(2\text{-Tolyl})_2Zn$ prepared from 2-tolylMgBr and $Zn(OMe)_2$ was used.

On the other hand, the reaction of acridine with diisopropylzinc (**4**) in the presence of a Rh(I) catalyst afforded 9-isopropyl-9,10-dihydroacridine (**5**), an addition product, in quantitative yield. In contrast to the catalytic arylations using diarylzinc, *in situ* aromatization did not proceed.[11] Further investigations revealed that the addition of **4** proceeds, *even in* the absence of transition metal catalyst. (eqn (1)).

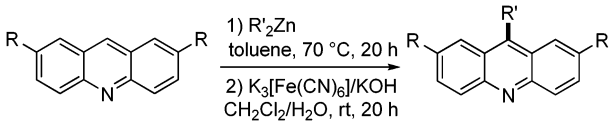


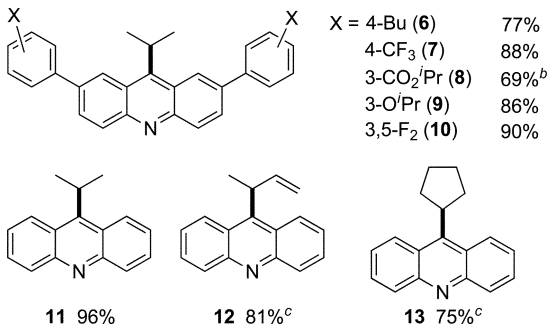
(1)

Although it is well known that strong nucleophiles, such as Grignard and organolithium reagents, add to acridines,[8] the corresponding reaction using organozinc reagents has never been reported, to the best of our knowledge. The subsequent treatment of dihydroacridine **5** with an appropriate oxidant afforded the aromatized product in excellent yield. Thus, the overall transformation can be viewed as the alkylation of acridine at the C-9 position (Table 3). Functional groups including trifluoromethyl (**7**), alkoxy (**9**) and fluoro (**10**) groups were tolerated under these conditions. Importantly, an ester was also compatible with this alkylation reaction, which offers an advantage over the reactions using organolithium and -magnesium reagents.[8] Moreover, dialkylzincs prepared by reacting alkyl Grignard reagents with $ZnCl_2$ can participate in this formal C-9 alkylation reaction. Various secondary alkyl groups can be introduced, as in **12** and **13**. In contrast, primary alkylzinc reagents, such as Me_2Zn, Et_2Zn, and $^nBu_2Zn$, did not form the alkylated products.

As shown in entry 6 of Table 1, the use of a nickel-based catalyst afforded a C-4 phenylated acridine as a major product. Intrigued by the unique selectivity using a nickel catalyst, we attempted to further optimize the C-4 arylation of acridine. 9-Phenylacridine (**3**) was used as a substrate to avoid the competitive C-9 arylation (Table 4). The use of other alkyl phosphines (entries 2 and 3) did not afford any desired product, and the starting material was recovered. While IMes and IPr were ineffective, comparative catalytic activity was

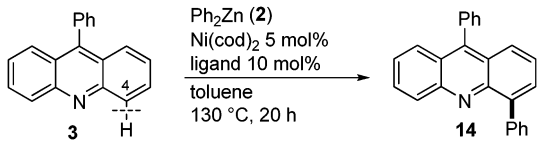
Table 3 Substrate scope of C-9 alkylation of acridines[a]





[a] Reaction conditions: (1) acridine derivative (0.25 mmol), R'_2Zn (0.5 mmol), and toluene (2 mL) in a screw-capped vial under N_2 at 70 °C for 20 h. (2) $K_3[Fe(CN)_6]$ (0.7 mmol), KOH (2.1 mmol), CH_2Cl_2 (5 mL), and H_2O (0.4 mL) in a flask under air at rt for 20 h unless otherwise noted. Isolated yield based on acridine substrate was shown. [b] The first reaction was run at 100 °C. [c] R'_2Zn prepared from R′MgBr (1.0 mmol) and $ZnCl_2$ (0.5 mmol) was used.

Table 4 Reaction optimization of C-4 arylation[a]



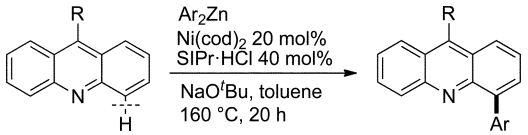
Entry	Ligand	Base[b]	Yield (%)
1	PCy_3	None	16
2	P^tBu_3	None	0
3	PMe_3	None	0
4	IMes·HCl	NaO^tBu	0
5	IPr·HCl	NaO^tBu	0
6	SIPr·HCl	NaO^tBu	21
7[c]	SIPr·HCl	NaO^tBu	45
8[d]	SIPr·HCl	NaO^tBu	68

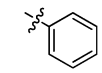
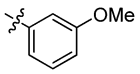
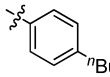
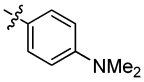
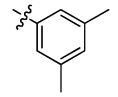
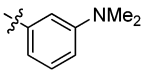
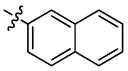
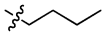
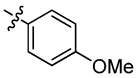
[a] Reaction conditions: **3** (0.25 mmol), **2** (0.38 mmol), $Ni(cod)_2$ (0.0125 mmol), ligand (0.025 mmol), and toluene (1.5 mL) in a screw-capped vial under N_2 at 130 °C for 20 h unless otherwise noted. [b] NaO^tBu (0.025 mmol) was added, when indicated. [c] Run using NaO^tBu (0.50 mmol). [d] Run using $Ni(cod)_2$ (0.050 mmol), SIPr·HCl (0.10 mmol), NaO^tBu (0.50 mmol), and **2** (1.0 mmol) at 160 °C.

observed when SIPr was used as a ligand to furnish 4-phenylated product **14** in 21% yield (entry 6). Finally, the yield of **14** was increased to 68% by using NaO^tBu (2 equiv.), $Ni(cod)_2$ (20 mol%), SIPr (40 mol%), and **2** (4 equiv.).[12]

An array of acridine derivatives can be arylated at the 4-position under these conditions (Table 5). The electronic nature of the C-9 substituent had little impact on the efficiency of the reaction, and the corresponding C-4 arylated product was consistently produced. Although an excess amount of **2** was required for the reaction to proceed, no diarylated product was observed. It should be noted that a methoxy group remained

Table 5 Substrate scope for C-4 arylation[a]



Entry	R	Yield (%)	Entry	R	Yield (%)
1		68	6		55
2		55	7		55
3		63	8		64
4		59	9		52
5		55	10[b]		52

[a] Reaction conditions: 9-substituted acridine (0.25 mmol), **2** (1.0 mmol), $Ni(cod)_2$ (0.050 mmol), SIPr·HCl (0.1 mmol), NaO^{t}Bu (0.5 mmol) and toluene (2 mL) in a screw-capped vial under N_2 at 160 °C for 20 h unless otherwise noted. [b] $(2\text{-Tolyl})_2Zn$ prepared from (2-tolyl)MgBr and $Zn(OMe)_2$ was used.

untouched (entries 5 and 6), while nickel-catalyzed C–O bond cleavage using organozinc reagents has been reported to occur.[13] Similar to the C-9 arylation reaction, Ar_2Zn prepared from ArMgX and $Zn(OMe)_2$ was found to participate in this nickel-catalyzed C-4 arylation reaction (entry 10).

In summary, regioselective functionalizations of acridine derivatives using organozinc reagents are described. With a nickel based catalyst, the reaction proceeded at the 4-position, whereas C-9-selective functionalization took place with a rhodium catalyst. Moreover, the overall C-9 alkylation of acridine can be accomplished by the non-catalytic addition of a dialkylzinc/oxidation sequence. Straightforward synthesis of acridine derivatives can be expected through the present C–H bond functionalization protocols.

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10 The use of diarylzincs prepared by the reaction of ArMgX or ArLi and $ZnCl_2$ afforded only the traces of an arylated product, probably due to the inhibiting effect of residual metal salts. ArZnX was also ineffective.

11 Treatment of **5** with 2 equivalents of **2** at 130 °C for 20 h did not promote an aromatization leading to 9-isopropylacridine (**11**). In contrast, 9-phenyl-9,10-dihydroacridine could be aromatized to afford **3** by the treatment with **2**. From these results, the ease of aromatization of the dearomatized intermediate by an organozinc reagent is likely to determine the course of the reaction.

12 Under these conditions, **1** afforded **3** (10%), 4-phenylacridine (18%) and **14** (15%).

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