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Authors: Hamad H Al Mamari, Diana Al Kiumi, Tamadhir Al Rashdi, Huda Al Quraini, Malak Al Rashdi, and Sumayya Al Sheraiqi

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COMMUNICATION

Ru-Catalyzed C(sp^2)-H bond arylation of benzamides bearing novel design-based 4-aminoantipyrine as a directing group

Hamad H. Al Mamari*, Diana Al Kiumi,Tamadhir Al Rashdi, Huda Al Quraini, Malak Al Rashdi, Sumayya Al Sheraiqi, Mohammed Al Lamki, Ahmed Al Sheidi, Asma Al Zadjali

Dedication ((optional))

Dr. Hamad H. Al Mamari, Ms. Diana Al Kiumi, Ms. Tamadhir Al Rashdi, Ms. Huda Al Quraini, Ms. Malak Al Rashdi, Ms. Sumayya Al Sheraiqi, Mr Mohammed Al Malki, Mr Ahmed Al Sheidi, Ms. Asma Al Zadjali
Department of Chemistry, College of Science
Sultan Qaboos University
PO Box 36, Al Khoudh 123, Muscat, Sultanate of Oman
E-mail: halmamari@squ.edu.om

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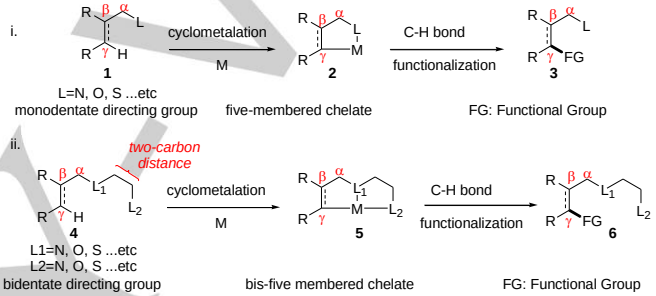
Abstract: A novel design-based removable *N*,*O*-bidentate directing group based on cheap and commercially available 4-aminoantipyrine (**AAP**) is reported herein. Aromatic **AP** amides bearing 4-aminoantipyrine underwent efficient Ru-catalyzed C(sp^2)-H arylation using [$RuCl_2(PPh_3)_3$] as a catalyst and aryl bromides as electrophiles. The novel bidentate directing group enabled the C-H functionalization reaction with good scope, good functional group tolerance and in decent yields.

Functionalization of C-H bonds has emerged as a powerful strategy for formation of chemical bonds. [1] The chemical science allows transformations of otherwise inert nonreactive C-H bonds into functional reactive bonds. Functionalization of C-H bonds could result in rapid access of functionalized molecules from simple nonreactive readily available starting materials. In turn, complex target molecules could be achieved in less steps and shorter reaction times. Thus, C-H bond functionalization is a manifestation of atom and step economies and is a demonstration of environmentally benign green approach. Due to the ubiquitous nature of C-H in organic molecules, functionalization of a specific C-H selectively has been a major issue. Accordingly, regioselectivity and site-selectivity is a pressing challenge. In one approach, such issues have been addressed by using monodentate and bidentate directing groups. Directing groups contain one Lewis basic atom (monodentate directing group) or two Lewis basic atoms (bidentate directing groups) appropriately distanced from the C-H bond to be functionalized. [2] The C(γ)-H bond, with respect to the Lewis basic atom, gets cleaved, *via* chelation-assistance, in C-H functionalization. This carbon distance is driven by the thermodynamic stability of five-membered chelates (Scheme 1, i). [3]



Scheme 1. Monodentate and bidentate directing groups.

Similarly, the two Lewis basic atoms in bidentate directing groups should be two-carbons away from each other to allow formation of a second five-membered chelate. Bis-five-membered chelates are thermodynamically more stable and rigid compared to mono-chelates. Consequently, bidentate directing groups should be able to deliver the C-H functionalization product in a better regio-control (Scheme 1, ii).

Directing groups have allowed a wide range of C-H bond functionalization reactions catalyzed by various transition metals typified by second row-transition metals such as Pd, [4] Rh [5] and Ru. [6] The strategy has extended to the more earth abundant, first row-transition metals [7] such as Ni, [8] Mn, [9] Fe [10] and Co. [11] 8-Aminoquinoline (**7**, Figure 1), is now well-established as a robust *N*,*N*-bidentate directing group in directed metal-catalyzed C-H bond functionalization of its amides (**8**, Figure 1). [12] Intrigued by the strategic design of bidentate directing groups, Ackermann *et. al*. have recently disclosed a novel-triazole-based (**9**, Figure 1) *N*,*N*-directing group (triazolyldimethylmethyl, TAM) (**10**, Figure 1) that has enabled different C-H bond functionalization reactions catalyzed by various transition metals. [13] Despite great advances in the field of directed metal-catalyzed C-H bond functionalization, the discovery of new efficient approaches and protocols for controlling the issue of site-selectivity is always sought. As a one approach, the search for and exploration of novel and efficient directing groups is a constant target.

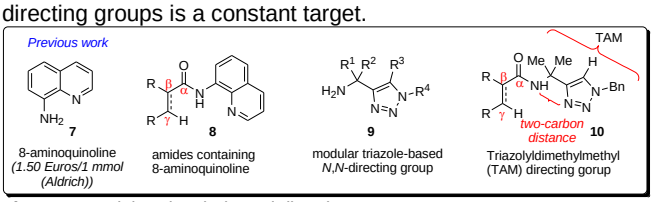


Figure 1. Modular triazole-based directing groups.

4-Aminoantipyrine (**AAP**) (**11**, Figure 2) is known to exhibit biological activity. It has analgesic, anti-inflammatory and antipyretic properties. Studies have shown that derivatives (such as **11DA**, **11DB** and **11DC** (Figure 2)) of 4-aminoantipyrine possess biological activity as well. [14]

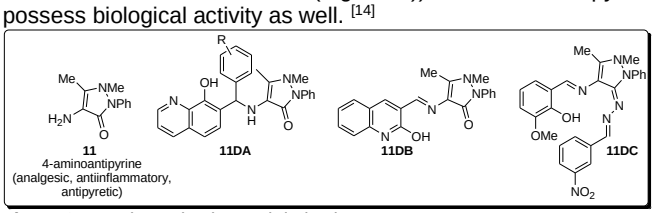


Figure 2. 4-Aminoantipyrine and derivatives.

Structurally, it was envisioned that amides of 4-aminoantipyrine could serve as bidentate directing groups. It was envisaged that the two-distance between the nitrogen on the amino group and the carbonyl oxygen could enable amides bearing 4-aminoantipyrine (**12** & **13**, Figure 3), to function as a *N*,*O*-bidentate directing group (Figure 3).

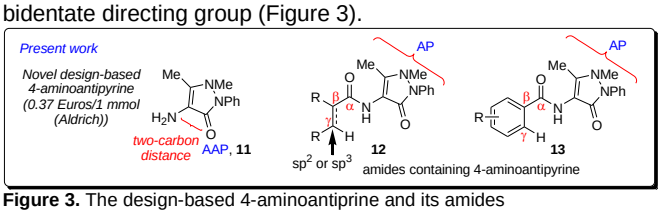
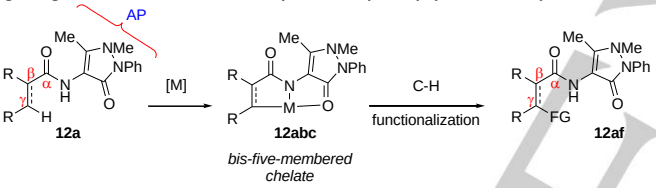


Figure 3. The design-based 4-aminoantiprine and its amides

Hence, it was hypothesized, that upon treatment with a suitable metal, amides of 4-aminoantipyrine (**12a**) could lead to a bis-five-membered chelate (**12abc**) Scheme 2). Accordingly, the C-H bond functionalization was envisaged to take place, after C-H bond cleavage, at C(γ)-H bond with respect to the amino group *N*, giving rise to functionalized product (**12af**) (Scheme 2).

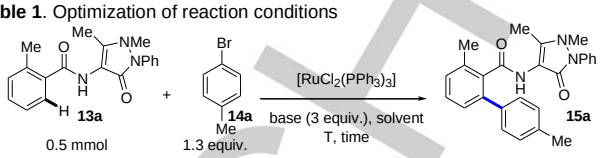


Scheme 2. Potential use of 4-aminoantipyrine amides as bidentate directing groups in C-H bond functionalization.

Inspired by structural features of 4-aminoantipyrine and in continuation of our research program [15] on development and pursuit of novel directing groups capable of promoting C-H bond functionalization, we wish to report herein a novel design-based bidentate directing group based on the cheap commercially available 4-aminoantipyrine (**AAP**). Antipyrinyl (**AP**) benzamides underwent Ru-catalyzed C(sp^2)-H bond arylation with aryl bromides.

At the outset of the work benzamides containing 4-aminoantipyrine were synthesized. Thus aromatic benzamides were prepared using standard protocols, from the corresponding acid chloride and 4-aminoantipyrene (please refer to the SI). In order to test the viability of 4-aminoantipyrine in transition metal-catalyzed C-H bond functionalization, [$RuCl_2(PPh_3)_3$] was chosen as a catalyst. This is based on the relatively lower cost of Ru than Pd or Rh. Toward that end, 2-methylbenzamides containing 4-aminoantipyrine was chosen as a representative arene substrate and [$RuCl_2(PPh_3)_3$] as a Ru catalyst, based on its remarkable efficacy as we reported recently. In addition, [$RuCl_2(PPh_3)_3$] is a cheaper catalyst than [$RuCl_2$(*p*-cymene)]$_2$ precatalyst, which would also require a cocatalyst such as the typical PPh_3 to be added with it. Investigations of C-H functionalization viability mediated by 4-aminoantipyrine began with reacting the representative substrate, 2-methylbenzamides containing 4-aminoantipyrine with 4-bromotoluene (**14**) as an electrophile in the presence of [$RuCl_2(PPh_3)_3$] (20 mol %) as a Ru catalyst, Na_2CO_3 (3 equiv.) as a base, in toluene at 150 °C for 48 h. To our delight, the desired C-H arylation product (**15a**) was obtained in 65% yield. Inspired by this gratifying result, optimization of reaction conditions was performed (Table 1). Thus keeping all conditions as the first successful attempt fixed while reducing the time, resulted in reduction of the yield to 45% (Entry 2).

Table 1. Optimization of reaction conditions

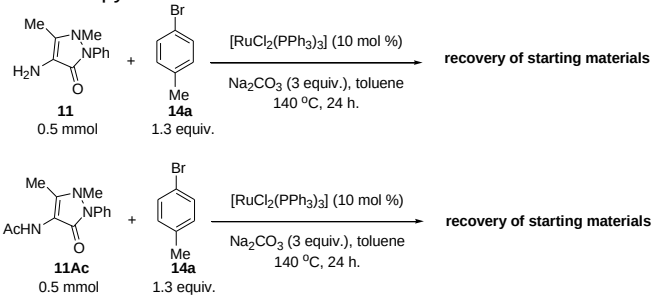


Entry	Catalyst Amount	Base (3 equiv)	Solvent	Temperature	Time	Yield
1	20 mol %	Na_2CO_3	toluene	140 °C	48 h	65%
2	20 mol %	Na_2CO_3	toluene	140 °C	24 h	45%
3	10 mol %	Na_2CO_3	toluene	140 °C	24 h	98%
4	no catalyst	Na_2CO_3	toluene	140 °C	24 h	-
5	10 mol %*	Na_2CO_3	toluene	140 °C	24 h	54%
4	10 mol %	Na_2CO_3	toluene	120 °C	24 h	53%
5	10 mol %	Na_2CO_3	toluene	100 °C	24 h	41%
6	10 mol %	$NaHCO_3$	toluene	140 °C	24 h	36%
7	10 mol %	K_2CO_3	toluene	140 °C	24 h	23%
8	10 mol %	Na_2CO_3	DMF	140 °C	24h	28%
9	10 mol %	Na_2CO_3	H_2O	140 °C	24 h	33%

Reaction conditions: benzamide (**13 a**) (0.5 mmol), aryl bromide (**14**) (1.3 equiv.), catalyst (10 mol %), base (3 equiv.), solvent (3 mL). *: [($RuCl_2$(p-cymene))$_2$ with 40 mol % PPh_3 were used instead of [$RuCl_2(PPh_3)_3$]

Reducing the amount of the catalyst to 10 mol % resulted, after 24 h, in remarkable yield of 98% of the C-H arylation product (Entry 3). To ascertain the need of the catalyst for the C-H arylation reaction, the reaction was performed in the absence of a catalyst. The reaction resulted in no C-H arylation product with recovery of the starting benzamide and aryl halide (Entry 4). It was concluded that a catalyst is essential for the reaction. In addition, and for comparative purposes, the reaction was carried out using [$RuCl_2$(*p*-cymene)]$_2$ (10 mol %) as a precatalyst, and PPh_3 (40 mol %) as a cocatalyst while keeping other conditions unchanged (Entry 5). The reaction resulted in 54% yield of the arylation product (Entry 5). This reaction proved that [$RuCl_2(PPh_3)_2$] is the better catalyst. Lowering the reaction temperature to 120 °C and 100 °C reduced the yield significantly (Entries 4 & 5). Changing the base to $NaHCO_3$ or K_2CO_3 did not give better results (Entries 6 & 7) than Na_2CO_3. Other solvents were also tested. Thus DMF and water resulted in much lower yield of the C-H arylation product (Entries 8 & 9). As a result, the optimum conditions were found to be in Entry 3 (Table 1).

In a control experiment, and in order to determine whether or not the C-H arylation takes place on the phenyl group of the 4-aminoantipyrine (**11**) moiety rather than the arene part, 4-aminoantipyrine (**11**), was reacted with 4-bromotoluene (**14**) under the optimized reaction reactions (Scheme 3). The test reaction resulted in recovery of the starting materials. In addition, *N*-acetylated **11** (N-antipyrinylacetamide) (**11Ac**, Scheme 3), was subjected to the optimized reaction conditions. The acetylated 4-aminoantipyrine (**11Ac**) did not react either. The result was recovery of the starting amide and 4-bromotoluene. As a result, it was established that the Ru-catalyzed C-H arylation of **AP** benzamides, does, in fact, take place on the arene part of 4-aminoantipyrine amides rather than on the amine itself.



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Scheme 3. Reaction of 4-aminoantipyrine with 4-bromotoluene under optimized reaction conditions.

Under the optimum reaction conditions, the new AAP directing group was compared with the known and commercially available directing groups typified by benzamides of 8-aminoquinoline (**15aa**) and 2-picolylamine (**15aaa**) (Figure 4). Toward that end, the corresponding 2-methylbenzamides bearing 8-aminoquinoline and 2-picolylamine were treated with 4-bromotolunene (**14**) under the optimized reaction conditions. While the AAP benzamide delivered the arylation product in a remarkable 98% yield (Table 1), the analogous 2-methyl 8-aminoquinolyl amide gave the arylation product in modest 53% yield and the 2-picolylbenzamide did not react at all (Figure 4). This result should serve as an evidence for the superiority of the AAP directing group, reported herein, over the existing directing groups.

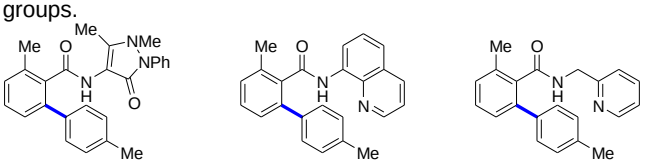
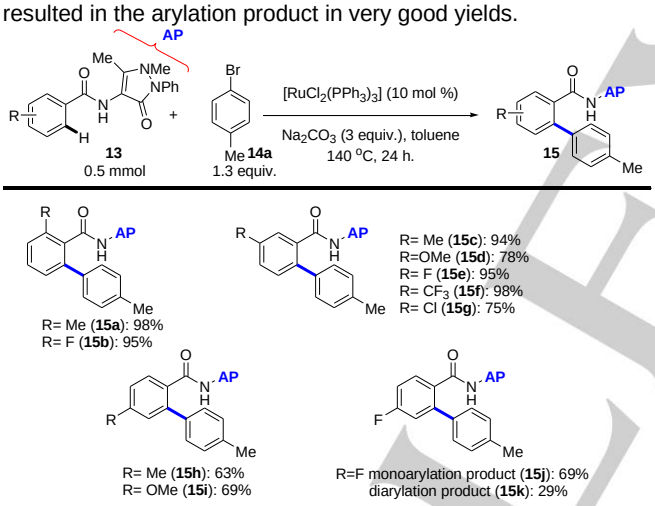


Figure 4. Efficacy of directing groups under optimum reaction conditions.

Under the optimized reaction conditions found, the arene substrate scope of **AP** benzamides was carried out (Scheme 4). Thus differently substituted and electronically different **AP** aromatic benzamides were subjected to the optimum Ru-catalyzed C-H arylation conditions (Scheme 4). The Ru-catalyzed C-H arylation tolerated a wide range of functional groups and resulted in the arylation product in very good yields.

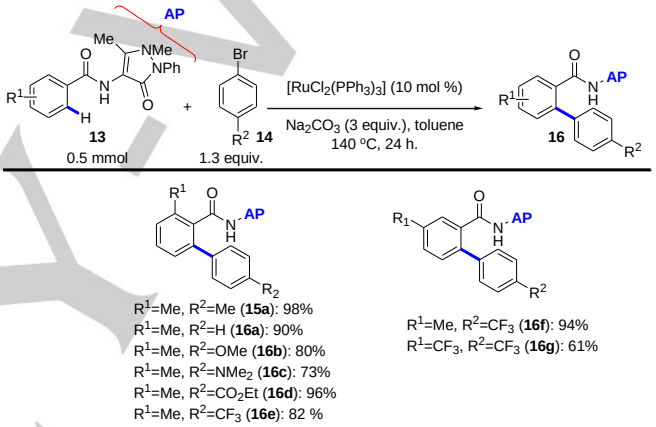


Scheme 4. Substrate scope of the Ru-catalyzed arylation.

Electron-donating groups represented by a methyl group at C2 (**15a**), C3 (**15c**) and C4 (**15h**) delivered the C-H arylation product un 98%, 94% and 63% yields respectively. Electron-rich AP benzamides substituted with methoxy (OMe) groups such as 3-OMe and 4-OMe reacted efficiently giving rise to the corresponding arylation products **15d** and **15i** in 78% and 69% yields respectively. Electron-withdrawing groups as a fluoro (F) group on C2 (**15b**), C3 (**15e**) and C4 (**15j**) were also tolerated successfully to give the product in excellent 95%, 95%, and 69% yields respectively. It was observed, that 4-F AP benzamides not only gave a monoarylation product (**15j**, 69%) but also a yielded a dirylation product (**15k**) in 29% yield. An AP benzamide substituted with an electron-withdrawing trifluoromethyl (CF_3) group at C3 participated in the Ru-catalyzed arylation reaction giving rise to the desired arylation product **15f** in excellent 98% yield. Another halogen (Cl) at C3 was also tolerated under the optimum reaction conditions to give rise to the desired arylation product **15g** in decent 75% yield.

The substrate scope results suggest that differently substituted and electronically different benzamides bearing 4-aminoantipyrine as a directing group successfully underwent Ru-catalyzed C-H arylation, in decent yields and with good functional group tolerance.

In addition to the substrate scope above, an electrophilic aryl bromide scope was also explored (Scheme 5). As indicated in the optimization table (Table 1), 4-Bromotoluene was established to be a model aryl bromide electrophile giving rise to the desired arylated product (**15a**) in 98% yield. When AP benzamide **13a** was reacted with bromobenzene as the aryl bromide under the optimized reaction conditions, the arylation product **16a** was obtained in 90% yield (Scheme 5). 4-Bromoanisole, as an example of an electro-rich aryl bromide gave the desired arylation product (**16b**) in 80% yield. Another electron-rich aryl bromide, 4-bromo-(*N*,*N*-dimethylamino)aniline, worked successfully to give the desired product (**16c**) in 73% yield. An electron-poor electrophile, ethyl 4-bromobenzoate, gave the arylation product (**16d**) in 96% yield. Reaction of the AP benzamide **13a** with another electron-poor electrophile, 4-bromobenzotrifluoride, gave the desired arylation product (**16e**) in 82% yield (Scheme 5).

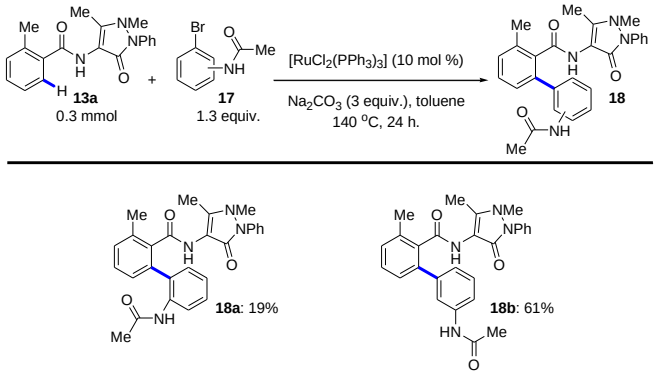


Scheme 5. Electrophile scope of the Ru-catalyzed arylation.

In addition, *meta*-substituted AP benzamide with Me and CF_3 were reacted with electron-poor electrophile, 4-bromobenzotrifluoride, to give the corresponding arylated products **16f** and **16g** in 94% and 61% yields respectively.

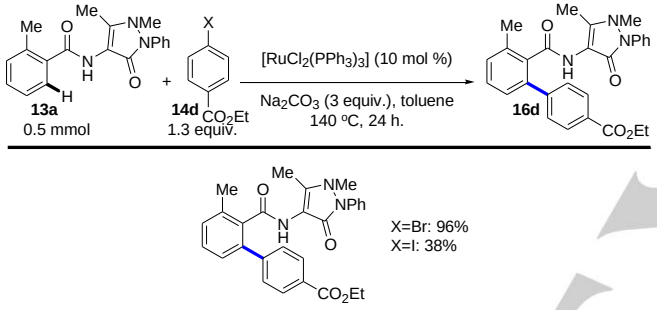
Based on the electrophile scope above, the results suggest that electron-rich and electron-poor aryl bromide electrophiles participate in the Ru-catalyzed C-H arylation of **AP** benzamides bearing 4-aminoantipyrine as a directing group.

To prove that Ru-catalyzed C-H arylation of AP benzamides works with 2- and 3-substituted aryl bromides, the standard 2-methyl AP benzamide (**13a**) was reacted with *N*-acetyl 2-bromoaniline (**17a**) and *N*-acetyl 3-bromoaniline (**17b**) under the optimum reaction conditions (Scheme 6). The reaction with *N*-acetyl 2-bromoaniline (**17a**) gave the corresponding arylated product (**18a**) in modest 19%. The reaction was judged incomplete after 24 h by TLC. The sterically hindered aryl bromide was sluggish to effectively react in the given reaction time. Thus the modest performance of **17a** in the reaction was attributed to the steric hindrance of aryl bromide. On the other hand, the reaction was *N*-acetyl 3-bromoaniline (**17b**) was of a better outcome. The reaction went to completion after 24 h giving rise to the corresponding arylated product (**18b**) in decent 61% yield (Scheme 6) after multiple purifications by chromatography and preparative TLC. As a result, it was concluded that steric hindrance of the aryl bromide plays an important role in the reaction.



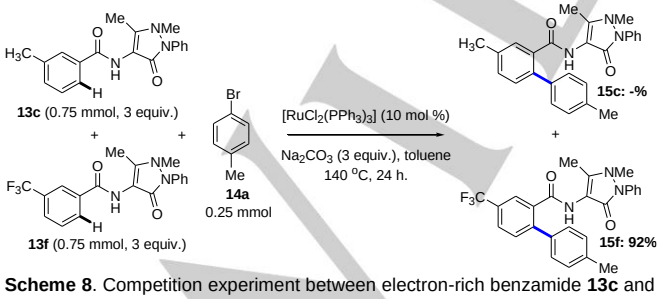
Scheme 6. Ru-catalyzed C-H arylation of 2-methyl AP benzamide with *N*-acetyl 2-bromoaniline (**17a**) and *N*-acetyl 3-bromoaniline (**17b**).

In order to ascertain that aryl bromides were indeed the most suitable for the Ru-catalyzed C-H arylation reaction, the representative AP amide **13a** was allowed to react with each of ethyl 4-bromobenzoate and 4-iodobenzoate under the optimized reaction conditions (Scheme 7). The former gave the arylation product in 96% yield while the latter gave the product in 38% (Scheme 6). Aryl bromides were then confirmed to be more effective in the reaction.



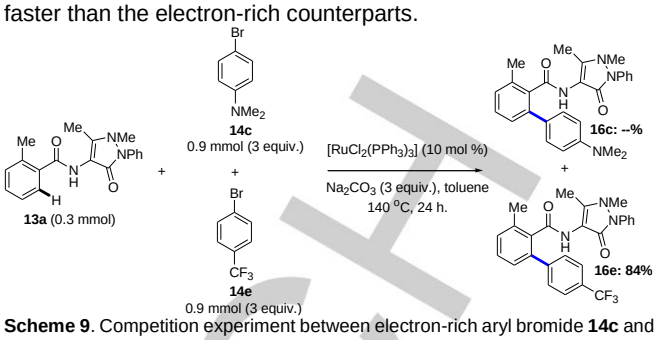
Scheme 7. Effect of halogen of the aryl halide in the C-H arylation reaction.

In order to gain insights into the rate of the reaction of an electron-rich and an electro-poor benzamide substrates, were allowed to compete with each other under the optimized reaction conditions. Thus, electron-rich benzamide substituted with Me group, benzamide **13c** and electron-poor benzamide substituted with a **CF_3** group, benzamide **13f** were mixed with 4-bromotoluene **14** under the optimized reaction conditions (Scheme 8). Only arylation product **15f** was obtained and isolated and in 92% yield. This competition experiment suggests that the electron-poor benzamide **13f** reacted faster than the electron-rich counterpart **13c**.



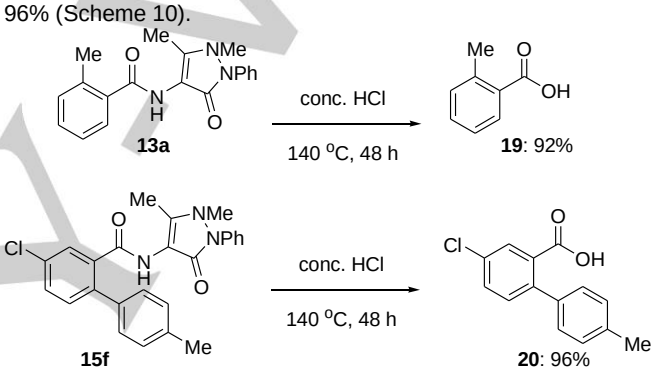
Scheme 8. Competition experiment between electron-rich benzamide **13c** and electron-poor benzamide **13e**.

In another competition experiment designed to determine suitable electronic nature of the electrophile, the representative AP benzamide **13a** was mixed with electron-rich **14c** and electron-poor **14e** under the optimum reaction conditions (Scheme 9). The reaction took place only between benazamide **13a** and electron-poor **14e** to give the corresponding arylation product in 84% yield (Scheme 8). Electron-rich **14c** did not react at all and thus arylation product **16c** was not obtained. This competition experiment suggests that the electron-poor aryl bromides react faster than the electron-rich counterparts.



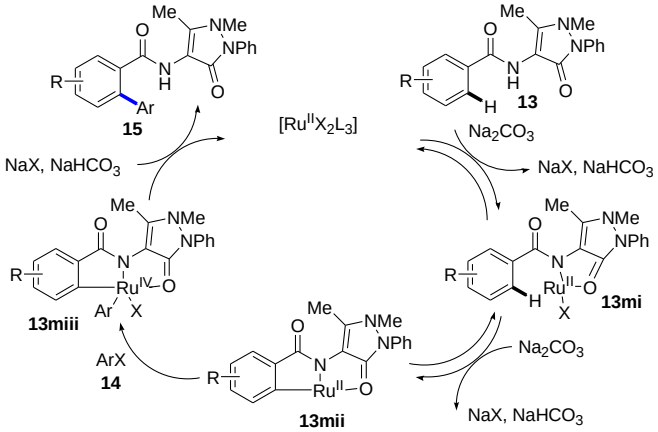
Scheme 9. Competition experiment between electron-rich aryl bromide **14c** and electron-poor aryl bromide **14e**.

It was of strategic importance to investigate the removability of the 4-aminoantiupyrine directing group. Thus 2-methylbenzamide bearing the directing group **13a** was treated with concentrated HCl to deliver the arylation carboxylic acid **19** in 92% (Scheme 9). In addition, the arylated product of the 3-Cl benzamide bearing the AAP directing group **15f** was subjected to the same acidic cleavage conditions to deliver the arylation carboxylic acid **20** in 96% (Scheme 10).



Scheme 10. Cleavage of the 4-aminoantipyrine directing group.

The Ru-catalyzed C-H bond arylation presented is proposed to proceed *via* base-assisted cyclometalation of benzamide **13** with $[RuCl_2(PPh_3)_3]$ to give cyclometalated complex **13mi** (Scheme 11).[16] Base-assisted C-H bond cleavage should result in formation of double five-membered chelate **13mii**. Oxidative addition of the aryl halide should allow formation of cyclometalated complex **13miii**. Subsequent reductive elimination furnishes the arylation product **15** with regeneration of the Ru catalyst. As noted previously, electron-deficient **AP** benzamides competed effectively with electron-rich **AP** benzamides for 4-bromotoluene under the optimum reaction conditions (Scheme 8). In addition, it was observed that electron-deficient aryl bromides competed effectively with its electron-rich counterpart for the 2-methyl **AP** benzamide (Scheme 9). Electron-deficient amide substrates and electron-deficient aryl bromide electrophiles facilitate the C-H arylation reaction. As a result, the Ru-catalyzed C-H arylation reaction is dominated by the electronic natures of the **AP** benzamide substrates and the aryl bromide electrophiles as well. Since electron-deficient aryl bromides accelerate the oxidative addition step, it can tentatively be suggested that oxidative addition could be the rate-determining step in the present Ru-catalyzed C(sp^2)-H arylation reaction.



Scheme 11. Proposed mechanism for the Ru-catalyzed C-H bond arylation of benzamides bearing 4-aminoantipyrine.

In summary, a novel design-based *N*,*O*-bidentate directing group based on the cheap and commercially available material 4-aminoantipyrine (**AAP**) is reported herein. Aromatic benzamides bearing 4-aminoantipyrine (**AP** benzamides) underwent Ru-catalyzed C(sp^2)-H bond arylation that employed amongst other optimum reaction conditions; [$RuCl_2(PPh_3)_3$] (10 mol %) as a catalyst, an aryl bromide as an electrophile and Na_2CO_3 as a base. Differently substituted and electronically different **AP** benzamides underwent efficient Ru-catalyzed C(sp^2)-H arylation reaction in decent yields and with good functional group tolerance. This development of the novel bidentate directing group based on 4-aminoantiprine presented herein, should contribute to the advances in the field of directed C-H bond functionalization catalyzed by transition metals. The present report should set stage for potentially different C-H bond functionalization reactions catalyzed by other transition metals, particularly the cheaper and more earth-abundant second-row transition metals.

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Keywords: 4-Aminoantipyrine • Directing group • C-H Functionalization • Ru-Catalysis• Chelation Assistance

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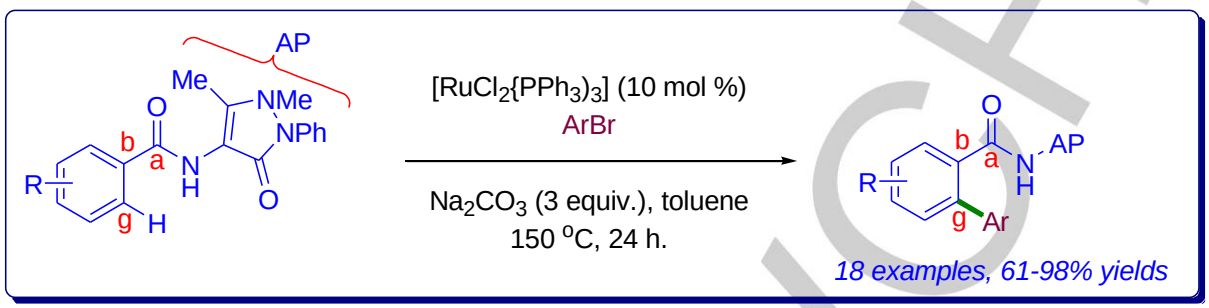

Herein, a novel design-based removable *N*,*O*-bidentate directing group based on commercially available 4-aminoantipyrine (**AAP**) is reported. Aromatic benzamides bearing the **AAP** directing group underwent efficient Ru-catalyzed C(sp^2)-H bond arylation reactions under mild reaction conditions. The C-H bond arylation employed amongst other reaction conditions; [$RuCl_2(PPh_3)_3$]. Various differently substituted and electronically different antipyrinyl (**AP**) benzamides participated in the Ru-catalyzed C(sp^2)-H arylation reaction and in decent yields and with good functional group tolerance.