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Ligand controlled orthogonal base-assisted direct C–H bond arylation in oxa(thia)zole-4-carboxylate series. New insights in nCMD mechanism

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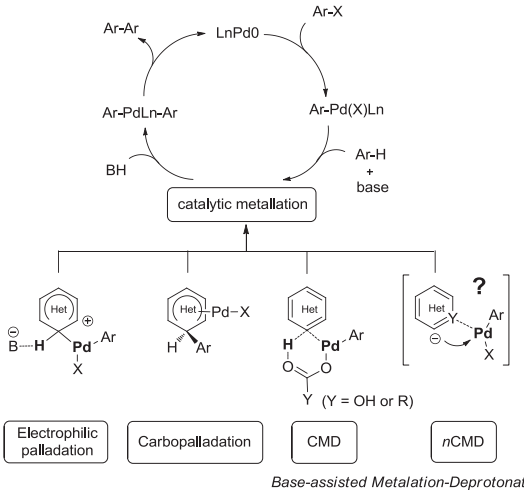
ABSTRACT

Alkyl- and arylphosphines have been screened in competitive C2–H/C5–H direct phenylation of oxa(thia)zole-4-carboxylates using Cs_2CO_3 and Rb_2CO_3 carbonate bases. nCMD-based C2–H selective direct phenylation was highly kinetically reduced (or enhanced) in favor (or to the detriment) of CMD-based direct C5–H phenylation with bromo- and chlorobenzene, respectively, using highly electron-rich ligands. These results gave novel experimental proof in favor of the electrophilic substitution-type mechanism for nCMD process based upon a prior nitrogen-arylpalladium complex interaction that preludes the deprotonation step.

1. Introduction

Over the past decades, researches on direct C–H bond functionalization reactions have grown dramatically.[1] In particular, the base-assisted Pd(0)-catalyzed direct C–H bond arylation of heteroarenes with aryl(pseudo)halides has emerged as an established alternative to commonly employed standard cross-coupling reactions (Scheme 1).[2] In addition to step and atom economies, this method opens innovative routes in diversity and selectivity through an orthogonal control of various catalytic C–H activation modes ranging mainly from electrophilic metalation, carbometalation, and metalation–deprotonation (Scheme 1).[3–6] However, this original site-selectivity approach remains sparsely employed reflecting the need to have constant insights into the controlling-parameters of C–H activation mechanisms including ancillary base, ligand, solvent, chelation and halogen effects.[7] Metalation–deprotonation is currently the most implied mechanism in direct C–H arylation of heterocycles with arylhalides. A first concerted mode (CMD) is based upon a C–Pd interaction concomitant to an internal or external carboxylate and pivalate-assisted abstraction of the proton.[6,8] A second strong base-dependant non-concerted mode (nCMD) stays incompletely evidenced and only few examples have been announced under copper and palladium catalysis.



Scheme 1. Catalytic cycle for Pd(0)-catalyzed direct C–H coupling of (hetero)aromatics with halides and catalytic metalation mechanisms.

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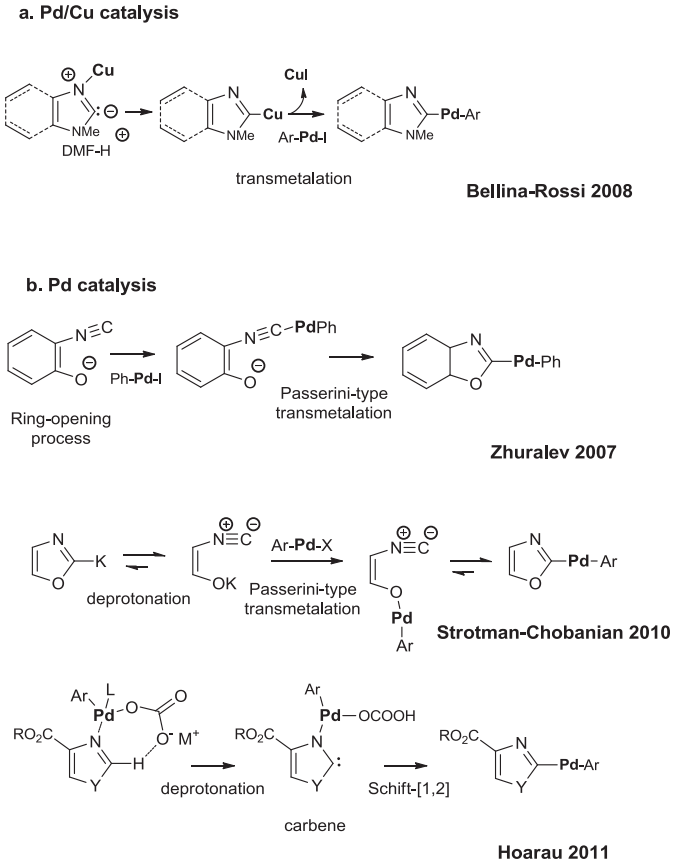
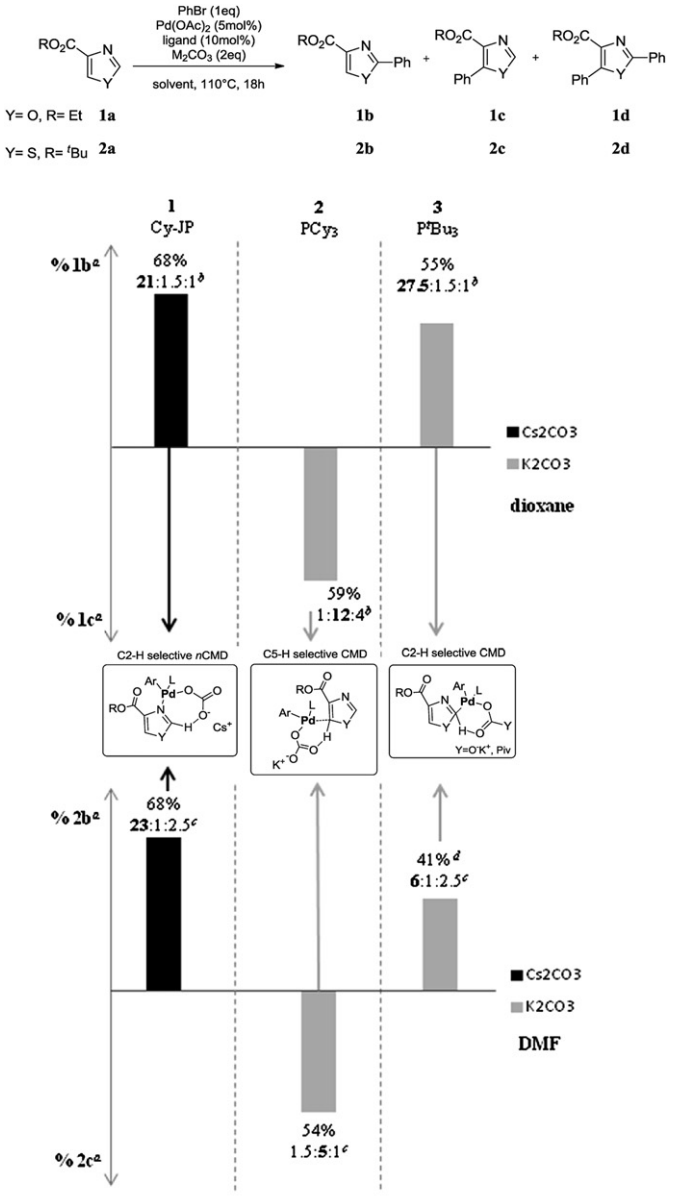
Daugulis Cu(I)-catalyzed direct arylation of azoles under high basic conditions methodology, which is based upon the previous formation of the C2-azolylcuprate, represents one of the earliest examples of nCMD.[9] Bellina and Rossi underlined the fact that the formation of C2-azolylcuprate stays unclear. They suggested a copper-induced reinforcing-acidity effect to facilitate the C2–H deprotonation step, which could be then ensured with a very weak base-like CsF or even DMF solvent for Pd(0)/Cu(I)-catalyzed direct C–H arylation of 1,3-diazoles (Scheme 2a).[10] Zhuralev[11] and then Strotman–Chobanian[3e] proposed also a cross-coupling-type mechanism for direct C2–H arylation of benzoxazole based upon a Passerini-type reaction for the transmetalation step (Scheme 2b). Recently, our group also identified a strong base K_3PO_4, DBU, and Cs_2CO_3-assisted nCMD as operating mechanism for highly selective Pd(0)-catalyzed direct C2–H arylation of oxa(thia)zole-4-carboxylates using Cy-JohnPhos in dioxane and DMF, respectively (Fig. 1, entry 1).[12] Deuterium incorporation experiments led to the production of C2–H and C5–H deuterated oxa(thia)zoles and led us to discard the cross-coupling-type in favor of an electrophilic substitution-type mechanism (Scheme 2c).[13] Considering this hypothesis, we recently focused our attention on the fact that prior nitrogen–arylpalladium complex interaction may reinforce the acidity of C2–H proton and also prevent the formation of the ring-opened tautomer. Indeed, according to Vedej's observations, the previous coordination with triethylborate led to the high stability of the 2-lithiated oxazole.[14] In fact, this prior interaction is supposed to be mainly driven by the electrophilic character of the arylpalladium complex that depends crucially on the electron-donor property of the ligand. Moreover, the electrophilic character of the arylpalladium complex is also dramatically reduced after the energetically-favored and fast displacement of the halogen by the carbonate base.[15]

In addition, CMD is identified as a privileged mechanism using soft K_2CO_3 base. Interestingly, the direct C–H arylation is mainly achieved at the energetically-favored C5–H site identified by DFT calculations.[13,16] As consequence, C2–H site could be only reached under high steric effect using specifically P^tBu_3 ligand under CMD process and notably by using PivOH additive for the thiazole model (Fig. 1). Thus, nCMD and CMD are naturally competitive mechanisms when using hard carbonate bases. In this context, we disclosed herein an additional study of the ligand effect on the behavior of the C2–H/C5–H selectivity under competitive nCMD/CMD direct C–H phenylation of oxa(thia)zole-4-carboxylates. Bromo- and chlorobenzene were used as coupling partners with Rb_2CO_3 and Cs_2CO_3 bases. These experiments gave novel experimental insights in strong base-assisted nCMD process.



Scheme 2. Proposed nCMD mechanism in direct C2–H arylation of 1,3-diazolic systems under different metal catalysis.



[a] isolated yield of major monoarylated product; [b] **1b**:**1c**:**1d** ratio; [c] **2b**:**2c**:**2d** ratio; [d] PivOH used as additive.

Fig. 1. Previously reported Cs_2CO_3-assisted nCMD and K_2CO_3-assisted CMD direct C2–H/C5–H selective arylation procedures.

2. Results and discussions

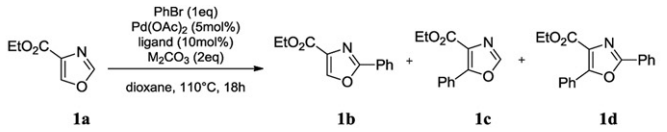
A first set of Cs_2CO_3-assisted competitive nCMD/CMD direct C–H phenylation of ethyl oxazole-4-carboxylate experiments was achieved with various phosphines. Phenyl bromide was selected as optimized coupling partner to ensure the oxidative addition step with various phosphines along with preventing the disruption of the CMD process, which may be encountered by using iodide.[17] The site-selectivity results are ranged from poor to high electron-donor effect of ligand, measured by the NBO charge (Natural Bond Orbital) in the Fig. 2a.[18] As expected, C2–H selectivity is maintained using poor electron-donor ligands such as Cy-JohnPhos and $PnBu_3$ that gave the 2-phenyloxazole **1b** in 68% and 70% yields (Fig. 2a, entries 3 and 4). By contrast, the C5–H selective CMD reaction became kinetically favored using highly sterically hindered and electron-rich ligands such as PCy_3, P^tBu_2Me, CataXium and P^tBu_3 (Fig. 2a, entries 5–8). The comparison of these results with those obtained through K_2CO_3-assisted C5–H selective CMD-based direct C–H phenylation led to three main observations (Fig. 2b).

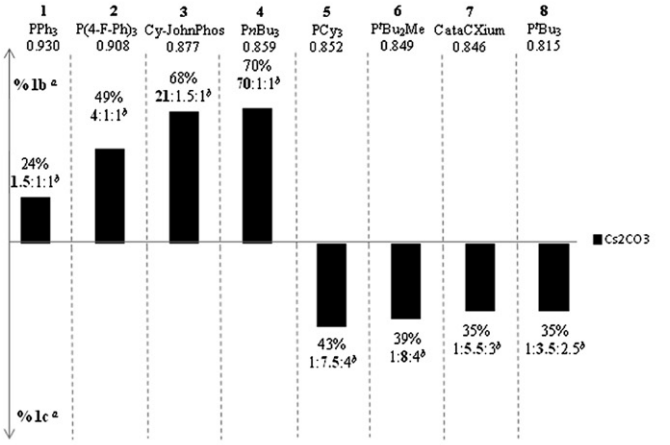
Firstly, nCMD mechanism is clearly selective at C2–H position with electron-poor ligands whereas CMD is selective at C5–H site with electron-rich ligands (Fig. 2a). CMD proved to be also much less effective using Cs_2CO_3 compared to K_2CO_3 pointing out that the steric hindrance of the base-delivering counter-cation penalizes this mechanism.[19] The third important observation is that the CMD process continued to be selective at C5–H site under high steric effect with P^tBu_3 ligand despite of the use of more sterically hindered Cs_2CO_3 versus K_2CO_3 bases (Fig. 2a,b, entry 8). This result could find an explanation on a critical loss of efficiency of the CMD process at C2–H site, so that it is occurring at the most energetically-favored CMD C5–H site, combined necessary, with a strong inhibition of the competitive C2–H selective nCMD process.

Competitive Rb_2CO_3-assisted nCMD/CMD direct C–H phenylation of **1a** with phenyl bromide was further executed (Fig. 2c). Immediately, the nCMD process appeared to be highly penalized under these less basic conditions. Indeed, a poor C2–H selectivity (30%) was only observed with Cy-JohnPhos ligand mainly due to the poor performance of this ligand for the CMD process (Fig. 2c, entry 3). In addition, an improved CMD reactivity is recovered in accordance with the use of a less sterically hindered base-delivering counter-ion. Indeed, CMD proved to be more kinetically favored than the nCMD process with electron-poor ligand such as $P(4\text{-F–Ph})_3$ as well as several electron-rich phosphines (Fig. 2c, entries 1, 5–8). Therefore, unexpectedly, the selectivity is remained at C5–H site under high steric hindrance using P^tBu_3 and despite the significant best performance of the CMD process (Fig. 2c, entry 8). This last result brings additional experimental evidences that high electron-donor ligands dramatically penalize the nCMD reaction, the optimal inhibiting effect being obtained with P^tBu_3 ligand (Fig. 2a,c, entry 8).

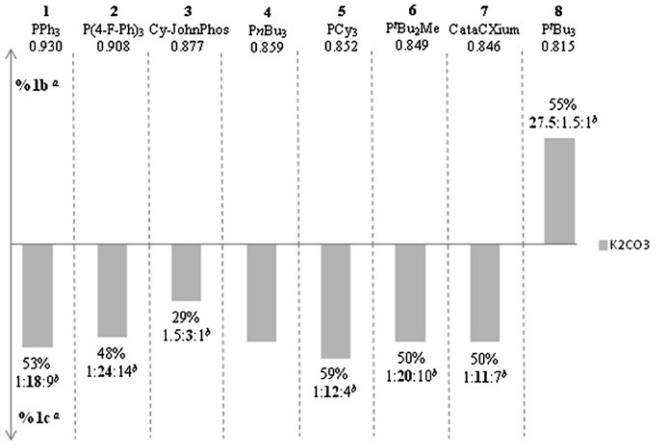
Same conclusions were then made by achieving identical competitive Rb_2CO_3- and Cs_2CO_3-assisted nCMD/CMD direct C–H phenylation of *tert*-butyl thiazole-4-carboxylate with phenyl bromide in DMF solvent (Fig. 3). Indeed, the additional screening of phosphines showed clearly an inversion of selectivity from C2–H to C5–H site with the most electron-rich P^tBu_3 with both Rb_2CO_3 and Cs_2CO_3 bases (Fig. 3, entry 7). The phenomenon is even more significant than one observed in oxazole-4-carboxylate series since the *tert*-butyl protection displays an additional external steric hindrance effect. Moreover due to the enhancement of the basicity in a high polar DMF solvent, the C2–H selective nCMD reaction becomes more competitive toward the C5–H CMD process over a more important range of phosphines under Cs_2CO_3 as well as Rb_2CO_3 base-assistance.

Having highlighting through ligand-controlled nCMD/CMD competitive reaction experiments that nCMD implies a prior

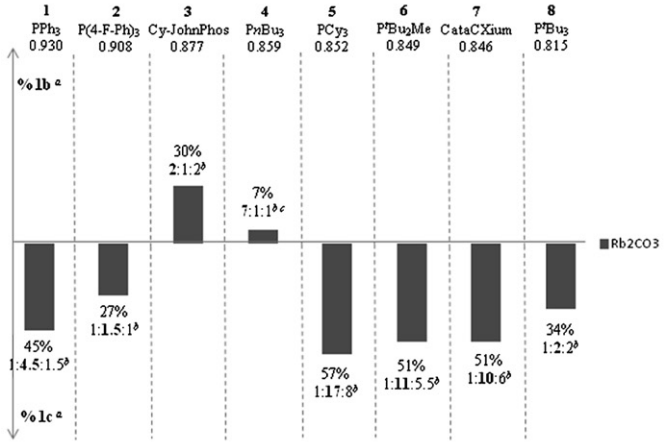




(a) Ligand control through Cs_2CO_3-assisted competitive nCMD/CMD reactions.



(b) Ligand control through K_2CO_3-assisted competitive nCMD/CMD reactions.



(c) Ligand control through Rb_2CO_3-assisted competitive nCMD/CMD reactions.

[a] isolated yield of major monoarylated product; [b] **1b**:**1c**:**1d** ratio; [c] conversion: 21%

Fig. 2. Ligand control on the C2–H/C5–H direct phenylation selectivity of ethyl oxazole-4-carboxylate depending on nature of carbonate bases in dioxane.

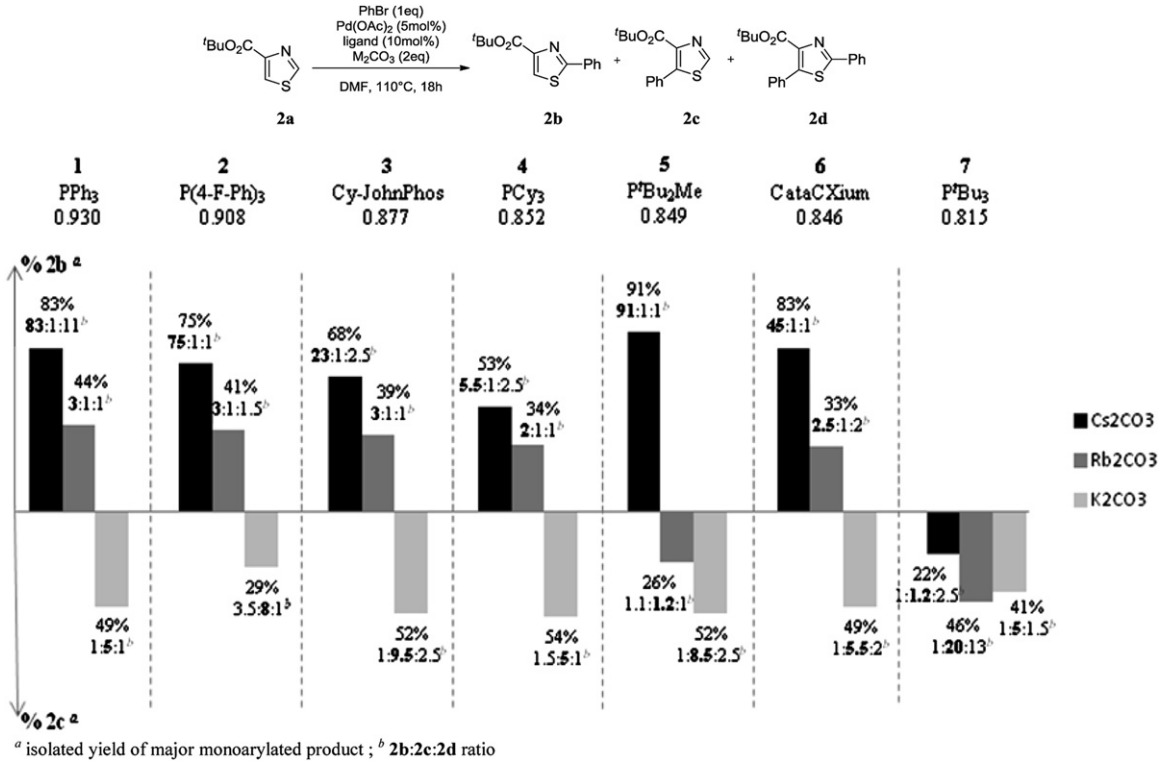


Fig. 3. Ligand control on the C2–H/C5–H directs phenylation selectivity of *tert*-butyl thiazole-4-carboxylate depending on nature of carbonate bases in DMF.

carbonate coordinated arylpalladium complex–nitrogen interaction, we then reasoned that the halogenoarylpalladium complex immediately generated after the oxidative step should be a better candidate for the nCMD process. Nevertheless the behavior of the halogenoarylpalladium complex depends mainly on the efficiency of the energetically favored halogen-substitution reaction achieves by the carbonate base.[20,3e] Clot and Baudoin recently proposed an associative S_N2-type pathway on tricoordinated palladium(II) center for this halogen-substitution reaction.[15] Nevertheless, it is highly kinetically reduced through highly electron-donor ligand effect. On the basis of this observation, we decided to examine the evolution of the C2–H/C5–H selectivity in Cs_2CO_3- and Rb_2CO_3-assisted competitive nCMD/CMD direct C–H phenylation of oxa(thia)zole-4-carboxylate with poor to high electron-rich phosphines using chlorobenzene as coupling partner. Two main reasons led to this choice (i) The Pd–Cl bond is stronger than Pd–Br bond and the chloride is then harder to substitute from palladium than bromide through a S_N2-type substitution;[21] (ii) the chloroarylpalladium(II) complex, generated beyond oxidative addition step, displays a more important electrophilic character than its brominated complex and may interact more strongly with the substrate. The results are depicted in Figs. 4 and 5 and are directly compared to those obtained with phenyl bromide under the same catalysis. As expected, the C2–H selective nCMD reaction was found to be immediately more predominant with the chloride partner when high electron-rich ligands were employed, interestingly, in both oxazole and thiazole series (Fig. 4, entries 3–5 and Fig. 5, entries 3 and 5). Herein, the ligand acts as an inhibitor of the halogen-substitution reaction to increase the life-time of the chloroarylpalladium complex. This latter complex proved to be reactive in the nCMD process.

3. Conclusion

This present ligand- and/or halogen-controlled competitive nCMD/CMD direct C–H phenylation of oxa(thia)zole-4-carboxylate

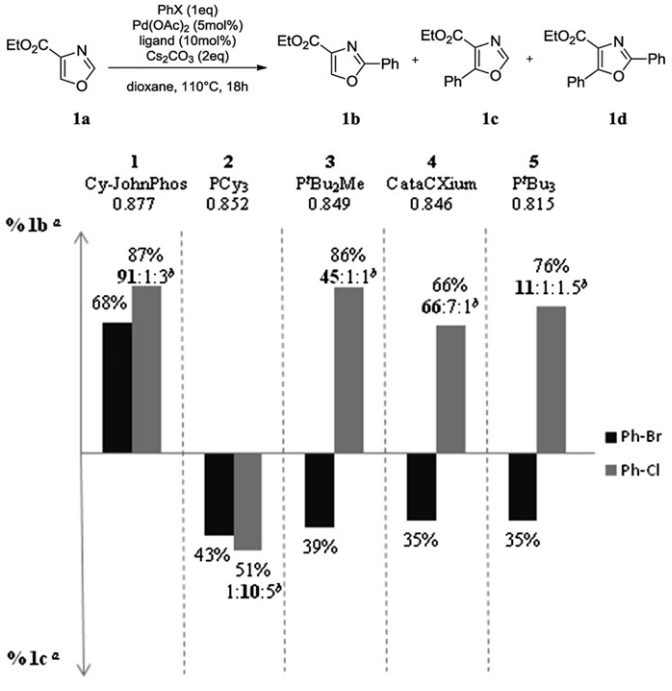
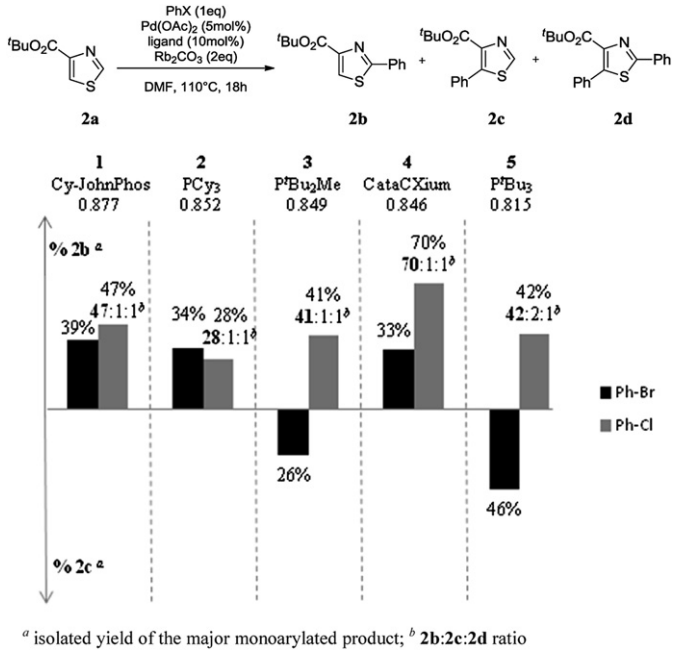


Fig. 4. Halide control on the Cs_2CO_3-assisted C2–H/C5–H direct phenylation selectivity of ethyl oxazole-4-carboxylate in dioxane.

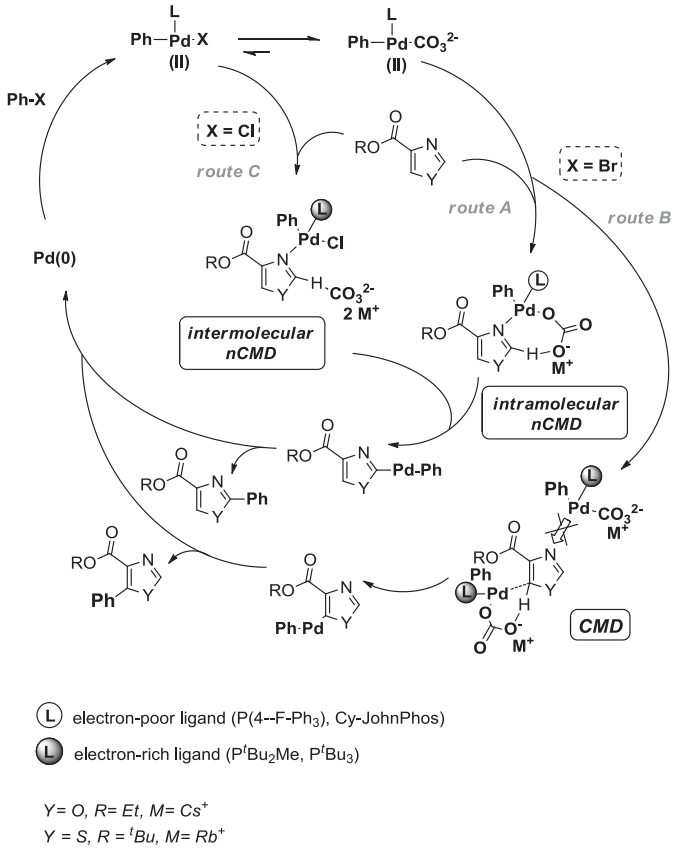
pointed out our previously proposed nCMD mechanism (Scheme 2b), based upon a prior arylpalladium complex-nitrogen interaction to prelude the deprotonation step. This study allows also to refine the nCMD mechanism as depicted in Scheme 3. As standard route, the halogenoarylpalladium complex delivered by oxidative addition of halides to Pd(0) is subsequently engaged in



[a] isolated yield of the major monoarylated product; [b] **2b**:**2c**:**2d** ratio

Fig. 5. Halide control on the Rb_2CO_3-assisted C2–H/C5–H direct phenylation selectivity of *tert*-butyl thiazole-4-carboxylate in DMF.

energetically favored halogen-substitution reaction leading to the carbonate coordinated arylpalladium complex in which an intramolecular abstraction of the C2–H proton takes place (Scheme 3, route A). This standard route could be confirmed indirectly by two main observations.



Scheme 3. Ligand and halide control for orthogonal C2–H/C5–H selective direct phenylation of oxa(thia)zole-4-carboxylate series through intramolecular nCMD (route A), intermolecular nCMD (route C) or CMD (route B).

First, intramolecular nCMD reaction could be highly kinetically reduced by using highly electron-donor ligands, notably P^tBu_3, in favor of the C5–H selective CMD reaction (Scheme 3, route B). Moreover, the chloride-substitution reaction could be kinetically reduced through the use of high electron-rich ligands to allow the nCMD reaction with a high electrophilic chloroarylpalladium complex through an intermolecular deprotonation process (Scheme 3, route C).

4. Experimental section

4.1. General

All experiments were carried out under a nitrogen atmosphere in oven-dried screw-caped sealed tubs. The ethyl oxazole-4-carboxylate 1a and *tert*-butyl thiazole-4-carboxylate **2a** were prepared according to our previously reported procedure.[12] Palladium acetate, phosphonium salts ligands, phosphine ligands, and halides were purchased from major chemical suppliers and were used as received. Palladium acetate and ligands were stored in desiccators as well as cesium, rubidium and potassium carbonate bases after drying over P_2O_5. Extra dry dioxane and DMF, stored on Acroseal® microsieves, were purchased from Acros. Chromatography columns were performed using silica gel (mesh size 60–80 mesh). ^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz (Brüker). Chemical shifts (δ) are given as parts per million relative to the residual solvent peak. Melting points are uncorrected. IR spectra were obtained with Bomen MB-100 or Perkin–Elmer Spectrum 100 FT IR spectrometers. Microanalyses were carried out at the analytical laboratory of our Department (IRCOF).

4.2. General procedure for the direct arylation of oxa(thia)zole-4-carboxylate derivatives with halogenoarenes through carbonate-assisted nCMD/CMD reaction competition

Oxazole or thiazole-4-carboxylate derivative (0.35 mmol or 0.27 mmol) was placed in a dried-oven sealed tub (10 ml) containing a magnetic stir bar with $Pd(OAc)_2$ (5 mol %), ligand (10 mol %) and carbonate base (2 equiv). A solution of halide (1 equiv) in dry dioxane or DMF (1 ml) was added. The resulting mixture was purged with nitrogen and stirred at 110 °C for 18 h. After filtration on Celite® and concentration under vacuo, the crude product was purified by flash column chromatography on silica gel using a mixture of petroleum ether–Ethyl acetate as eluent to give pure arylated products **1b**–**d** and **2b**–**d**.

*4.2.1. Ethyl 2-phenyloxazole-4-carboxylate (**1b**).* Following the general procedure using **1a** (50 mg, 0.35 mmol) with bromobenzene (37 μl, 0.35 mmol), P*n*Bu_3 (7 μl, 0.035 mmol), cesium carbonate (228 mg, 0.70 mmol) in dioxane (0.35 M). Standard workup followed by flash chromatography (petroleum ether–EtOAc/8:2, R_f=0.4) afforded the title compound (52 mg, 70%) as a white solid (mp=66–67 °C). ^1H NMR ($CDCl_3$, 300 MHz) δ=1.38 (t, 3H, J=7.2 Hz), 4.40 (q, 2H, J=7.2 Hz), 7.44–7.46 (m, 3H), 8.07–8.11 (m, 2H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.4, 61.4, 126.5, 126.9, 128.9, 131.2, 134.8, 143.7, 161.4, 162.5. IR (KBr) ν 3136, 3080, 2962, 900, 1727, 1610, 1563 cm^{-1}; Anal. Calcd for $C_{12}H_{11}NO_3$ (217.2): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.54; H, 5.35; N, 6.38.

*4.2.2. Ethyl 5-phenyloxazole-4-carboxylate (**1c**).* Following the general procedure using **1a** (50 mg, 0.35 mmol) with bromobenzene (37 μl, 0.35 mmol), $PCy_3 \cdot HBF_4$ (12.9 mg, 0.035 mmol), potassium carbonate (96 mg, 0.70 mmol) in dioxane (0.35 M). Standard workup followed by flash chromatography (petroleum ether–EtOAc/8:2, R_f=0.2) afforded the title product (44 mg, 59%) as a white solid (mp<50 °C). ^1H NMR ($CDCl_3$, 300 MHz) δ=1.39 (t, 3H,

J=7.2 Hz), 4.41 (q, 2H, J=7.2 Hz), 7.45–7.47 (m, 3H), 7.90 (s, 1H), 8.04–8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.3, 61.5, 126.7, 126.8, 128.5, 130.5, 149.1, 155.6, 162.0; IR (KBr) ν 3109, 2977, 1719, 1583, 1495, 1370, 1226, 1189, 1066, 762, 686, 643 cm^{-1}; Anal. Calcd for $C_{12}H_{11}NO_3$ (217.2): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.27; H, 5.04; N, 6.58.

*4.2.3. tert-Butyl 2-phenylthiazole-4-carboxylate (**2b**).* Following the general procedure using **2a** (50 mg, 0.27 mmol) with bromobenzene (28 μl, 0.27 mmol), P^{t}Bu$_2$Me·HBF$_4$ (6.7 mg, 0.027 mmol), cesium carbonate (175 mg, 0.54 mmol) in DMF (0.27 M). Standard workup followed by flash chromatography (petroleum ether–EtOAc/9:1, R_f=0.2) afforded the title product (64 mg, 91%) as a white solid (mp=78 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.62 (s, 9H), 7.42–7.45 (m, 3H), 7.99–8.03 (m, 2H), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=28.3, 82.1, 126.4, 127.0, 129.0, 130.7, 133.0, 149.5, 160.6, 168.6; IR (KBr) ν 3112, 2993, 2976, 2932, 1714 cm^{-1}; Anal. Calcd for $C_{12}H_{11}NO_3$ (261.34): C, 64.34; H, 5.79; N, 5.36; S, 12.27 Found: C, 64.38; H, 5.86; N, 5.31; S, 12.25.

*4.2.4. tert-Butyl 5-phenylthiazole-4-carboxylate (**2c**).* Following the general procedure using **2a** (50 mg, 0.27 mmol) with bromobenzene (28 μl, 0.27 mmol), PCy$_3$·HBF$_4$ (10 mg, 0.027 mmol), potassium carbonate (75 mg, 0.54 mmol) in DMF (0.27 M). Standard workup followed by flash chromatography (petroleum ether–Et$_2$O/8:2, R_f=0.1) afforded the title product (41 mg, 59%) as a white solid (mp=52–54 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.39 (s, 9H), 7.41–7.44 (m, 5H), 8.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ=27.9, 82.2, 128.3, 129.1, 130.1, 130.9, 143.4, 144.9, 151.3, 161.3; IR (KBr) ν 3073, 2972, 1715, 1139 cm^{-1}; Anal. Calcd for $C_{12}H_{11}NO_3$ (261.34): C, 64.34; H, 5.79; N, 5.36; S, 12.27 Found: C, 64.60; H, 5.82; N, 5.38; S, 12.33.

Acknowledgements

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.01.073.

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