Rhodium-Catalyzed *ortho*-Arylation of (Hetero)aromatic Acids

B10

Gooßen

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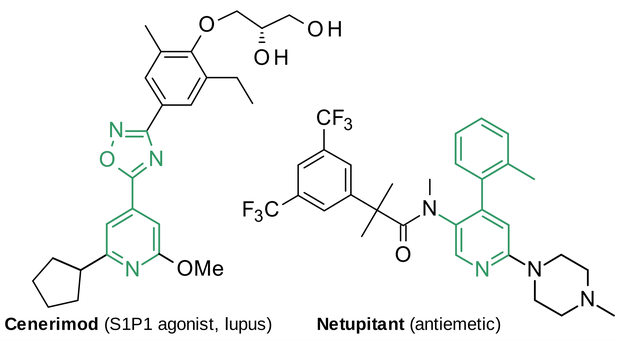
Summary Rhodium acetate effectively promotes the carboxylate-directed *ortho*-arylation of (hetero)aromatic carboxylates with aryl bromides. The main a,dvantage of this phosphine-free, redox-neutral method arises from its efficiency in assembling biologically meaningful electron-rich arylpyridines, which are problematic substrates in known C–H arylations using Pd, Ru, and Ir catalysts.
In **B10**, we elucidate the active species during the initial catalysis cycle utilizing both experimental clues as well as DFT calculations. We conclude that the initially binuclear Rh-species splits up during the cycle but can reform later, or promote another catalytic cycle.

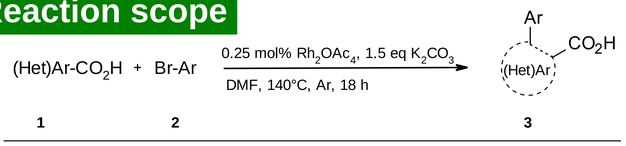
Introduction

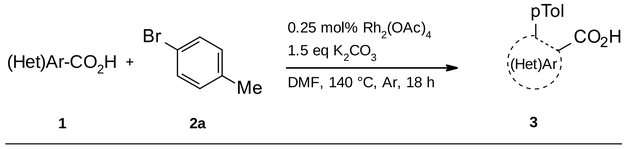
Arylated pyridines represent a key motif in a large number of pharmaceutically active substances. The use of carboxylic acids as directing groups during the construction of large molecules is common, as they often represent leftovers from the construction of heterocycles and can be easily modified or removed from the final product.
Carboxylic acid directed *ortho*-substitution of nicotinic acids have been described previously by *Larossa*, utilizing a sophisticated Pd catalyst. In this research, we utilize simple and readily available $Rh_2(OAc)_4$ as catalyst for *ortho*-arylation of nicotinic acids.

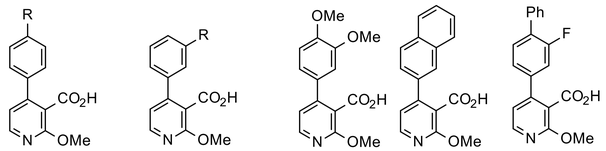


Cenerimod (S1P1 agonist, lupus) **Netupitant** (antiemetic)

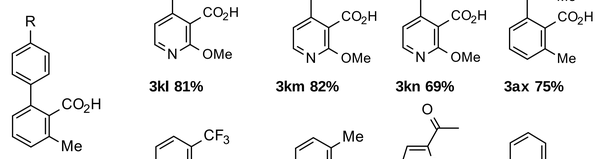
Reaction scope



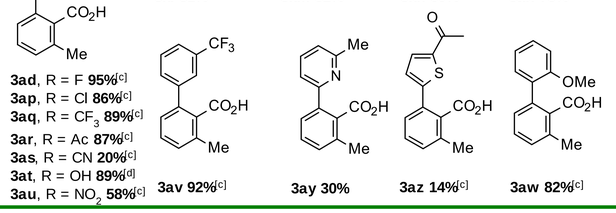




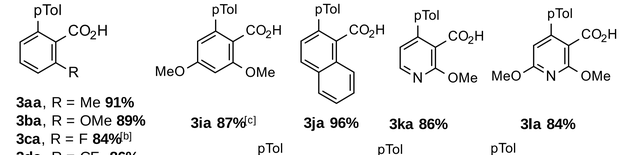
3kb, R = H **85%**
3kc, R = OMe **89%**
3kd, R = F **71%**[b]
3ke, R = CO_2Et **63%**[b]
3kf, R = Ph **87%**
3kg, R = SMe **51%**[b]
3kh, R = OMe **85%**
3ki, R = ^{t}Bu **89%**
3kj 86% **3kk 89%** **3ko 74%**[b]



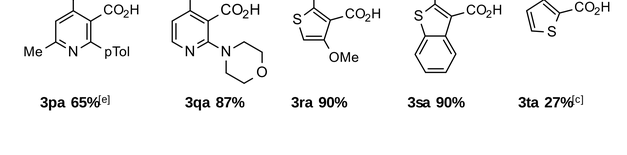
3kl 81% **3km 82%** **3kn 69%** **3ax 75%**



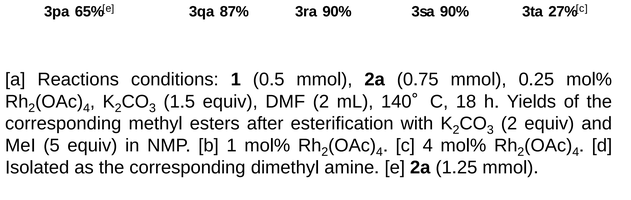
3ad, R = F **95%**[c]
3ap, R = Cl **86%**[c]
3aq, R = CF_3 **89%**[c]
3ar, R = Ac **87%**[c]
3as, R = CN **20%**[c]
3at, R = OH **89%**[d]
3au, R = NO_2 **58%**[c]
3av 92%[c] **3ay 30%** **3az 14%**[c] **3aw 82%**[c]



3aa, R = Me **91%**
3ba, R = OMe **89%**
3ca, R = F **84%**[b]
3da, R = CF_3 **86%**
3ea, R = CN **50%**[c]
3fa, R = Ac **55%**
3ga, R = NHAc **63%**[b]
3ha, R = NH_2 **63%**[d]
3ia 87%[c] **3ja 96%** **3ka 86%** **3la 84%**



3ma 51% **3na 80%** **3oa 63%**

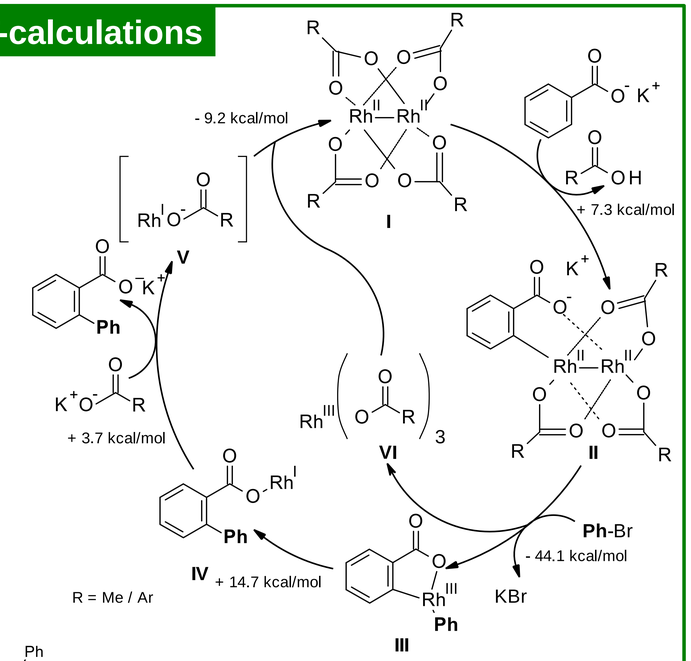


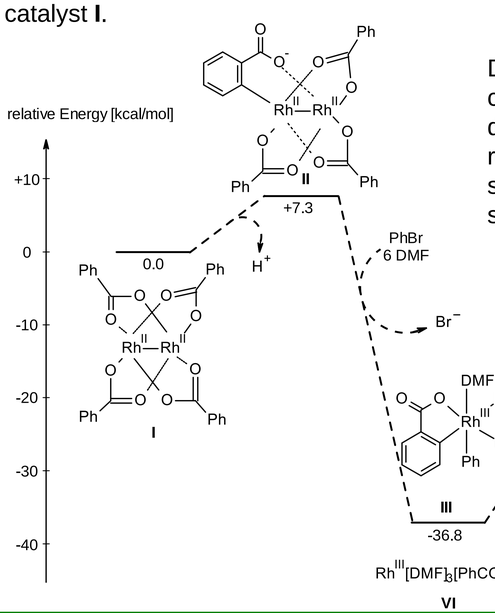
3pa 65%[e] **3qa 87%** **3ra 90%** **3sa 90%** **3ta 27%**[c]

[a] Reactions conditions: **1** (0.5 mmol), **2a** (0.75 mmol), 0.25 mol% $Rh_2(OAc)_4$, K_2CO_3 (1.5 equiv), DMF (2 mL), 140° C, 18 h. Yields of the corresponding methyl esters after esterification with K_2CO_3 (2 equiv) and MeI (5 equiv) in NMP. [b] 1 mol% $Rh_2(OAc)_4$. [c] 4 mol% $Rh_2(OAc)_4$. [d] Isolated as the corresponding dimethyl amine. [e] **2a** (1.25 mmol).

Mechanism and DFT-calculations

The catalytic cycle starts with the dirhodium-tetraacetate **I** exchanging one ligand for the carboxylic acid substrate in a base-assisted cyclo-metallation deprotonation (CMD) step, analogous to the observations with aryl phosphines. This resulting intermediate **II** reacts with the aryl bromide, resulting in the diaryl rhodium complex **III** and Rh^{III} acetate **VI**. The product is formed by reductive elimination from **III** to **IV** and salt metathesis, yielding intermediate Rh^{I}-salt **V**. Comproportionation of **V** and **VI** regenerate the catalyst **I**.





DFT-calculations support the suggested catalytic cycle. The critical dissociation of the dimeric species **II** into **III** and **VI** drive the reaction. The final comproportionation is supported by the experimentally observed stability of the Rh_2-carboxylate **I**.

References

[1] P. Weber, C. Rank, E. Yalcinkaya, M. Dyga, T. van Lingen, R. Schmid, F. W. Patureau, L. Gooßen, *Adv. Synth. Catal.* **2019**, *361*, 3925 – 3929.
[2] G. Zhang, Z. Hu, F. Belitz, Y. Ou, N. Pirkl, L. Gooßen, *Angew. Chem.* **2019**, *131*, 6501-6505; *Angew. Chem. Int. Ed.* **2019**, *58*, 6435-6439.
[3] M. Pichette Drapeau, L. J. Gooßen, *Chem. Eur. J.* **2016**, *22*, 18654.