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Synthesis of Functionalized Pyridines via a Regioselective Oxazoline Promoted C−H Amidation Reaction

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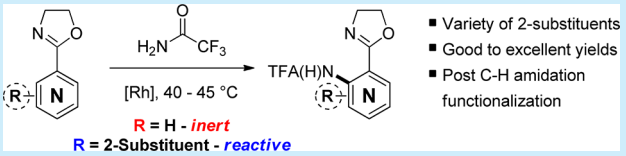
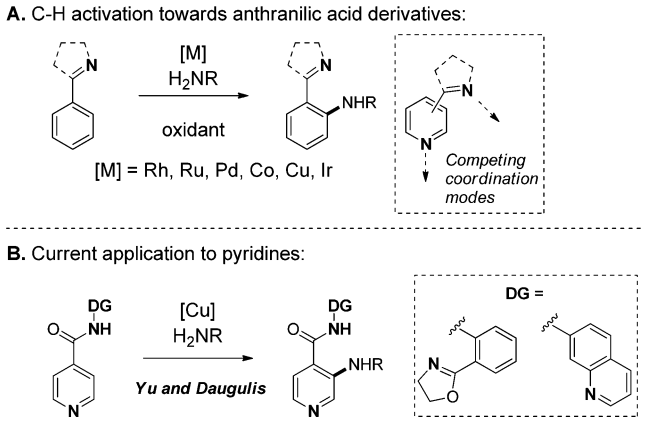
Supporting Information

ABSTRACT: The first Rh-catalyzed C−H amidation of pyridines is reported. The incorporation of a substituent at the C2 position both is crucial to the success of this transformation and provides considerable scope for further elaboration of the resulting products. Among these compounds, 2-chloropyridines allow access to a selection of intermediates including a versatile azaquinazoline scaffold.



Anthranilic acid derivatives are an important class of substrate, particularly for the synthesis of nitrogen-containing heterocycles such as quinazolines, indoles, and quinolines.[1] Despite the broad synthetic utility of anthranilic acids, access to highly functionalized examples of these 1,2-disubstituted aromatic systems remains a significant challenge. Many strategies rely upon multistep and often linear sequences to circumvent the low reactivity of azines toward functionalization via electrophilic aromatic substitution. In this regard, C−H activation has emerged as an effective alternative, offering simpler and more effective approaches to functionalized analogs of this important scaffold.[2] Contributions by Yu, Ackermann, Glorius, and others have allowed for significant advancement in this area (Scheme 1A).[3] Our group has reported a mild Rh-catalyzed oxazoline directed amidation that provides access to highly functionalized quinazolines.[4] Moreover, Ackermann recently demonstrated the applicability of cobalt catalysis to this particular method.[5]

Scheme 1. C−H Amidation of (Hetero)aromatic Compounds



In spite of the successes in sp^2 C−H activation, compatibility with heterocycles remains a significant challenge. While impressive advances have been achieved with heterocycles based on indoles,[3d] pyrroles,[6] furans,[7] and thiophenes,[8] examples of pyridine functionalization are somewhat rare in comparison. The propensity of pyridine itself to function as a directing group in C−H activation chemistry is the likely cause of the relatively slow progress made in the functionalization of this highly important scaffold. Nonetheless, key contributions by Yu and Daugulis have allowed significant advances in this respect with elegant stoichiometric and catalytic copper mediated C−H amidations having been achieved upon pyridine scaffolds by utilizing bidentate directing groups such as the 8-aminoquinoline or oxazoline tethered secondary amides (Scheme 1B).[9] Based on our observations that oxazolines can function as effective promoters of benzene based C−H amidation, we decided to explore their compatibility in the functionalization of pyridines and report herein the successful realization of this strategy.

Our initial studies began by exploring the reactivity of substrates **1a−c** where the directing group was positioned around the parent pyridine ring. As shown in Scheme 2, these substrates were inert to Rh-catalyzed amidation and increasing both reaction temperature and time failed to result in any of the desired amidopyridine products.[10] Based on the hypothesis that the lack of reactivity arises from catalyst deactivation by the Lewis basic pyridine, we considered how this process could be circumvented. In this regard, we were intrigued by a report from Cossy which demonstrated that incorporation of a 2-Cl group on a pyridine could result in efficient Ru-catalyzed cross-metathesis, while the parent pyridine was unreactive in this process.[11] This approach seemed well suited to our C−H amidation conditions, not only to attenuate the Lewis basicity of the heterocycle, but by also offering the opportunity for

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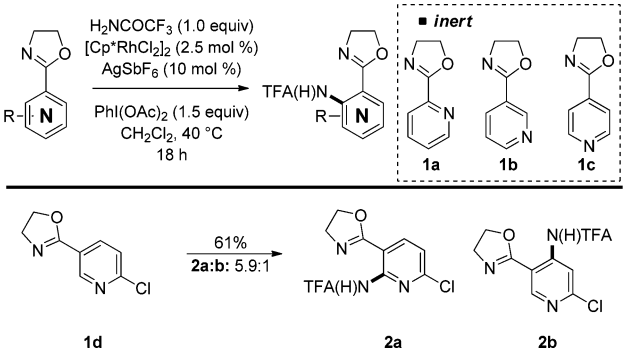
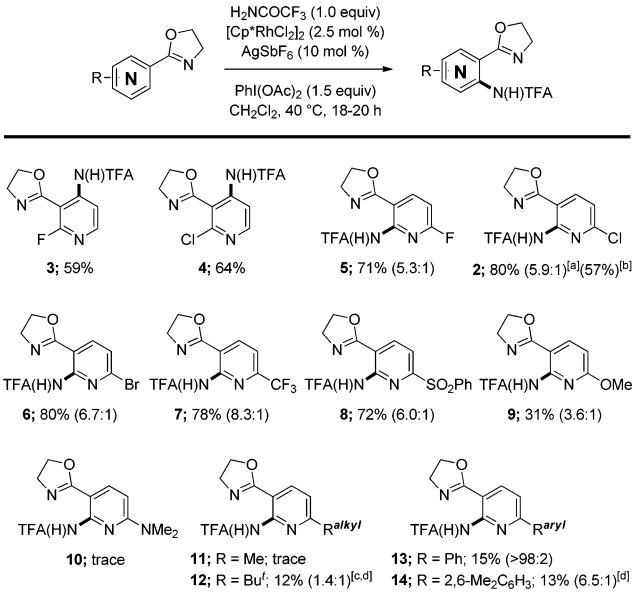
Scheme 2. Oxazoline Directed C−H Amidation of Pyridines



further derivatization. To probe our hypothesis, we prepared substrate **1d** and were delighted to find that amidation proceeded in a promising yield of 61% under mild conditions. Moreover, the reaction demonstrated respectable regioselectivity, with **2a** being the major isomer observed (Scheme 2).

Pleased by the effectiveness of a 3-oxazoline to direct the C−H amidation of 6-chloropyridine, we decided to explore the scope of this process on a range of substrates, subjecting them to the reaction conditions. Notably, we chose to confine our studies to trifluoroacetamide, as the corresponding amidation products can be readily hydrolyzed. As depicted in Scheme 3,

Scheme 3. 3-Oxazoline Directed C−H Amidation of Pyridines

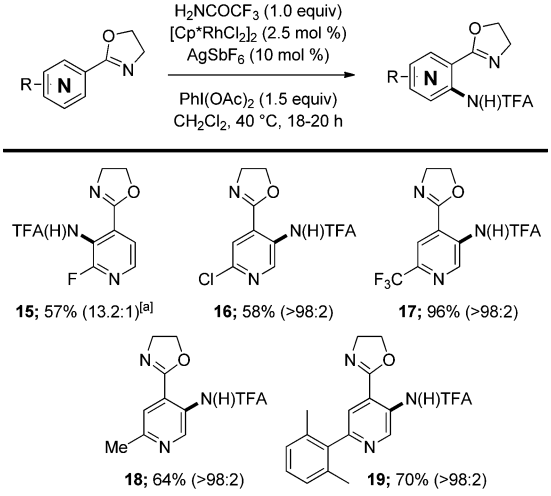


[a]Reaction performed on 4.56 mmol scale. [b]Reaction performed using $[RhCp^*Cl_2]_2$ (1 mol %) and $AgSbF_6$ (4 mol %) for 24 h. [c]Reaction performed at 80 °C. [d]Regioisomers separable by column chromatography.

we observed a variety of functionalities were compatible with these C−H amidation conditions. Both 2- and 6-halopyridines underwent smooth amidation affording the desired products **2a**−**6** in good to excellent yields. Moreover, 3-oxazoline-6-halopyridines underwent regioselective and consistent C−H amidation at the 2-position. Additionally, we were able to lower the Rh-catalyst loading to 1 mol % to deliver **2** with only a modest drop in yield. We could extend this chemistry to trifluoromethyl- and sulfone-substituted analogs **7** and **8**, which afforded the products in good yield with excellent regiocontrol. Notably, the regioselectivity of C−H amidation in these cases complimented that of the Cu-promoted systems developed by Yu and Daugulis.[9a,c] However, switching the 6-substituent to an electron-donating group had a marked effect on reaction efficiency. 2-Methoxy-substituted pyridine afforded **9** in a low yield while the 2-dimethylamino compound only provided a trace amount of compound **10**. Similarly, when alkyl and aryl examples were examined only trace or low reactivity was observed. Overall, although the efficiency of amination strategy was found to be modest in some cases, especially as compared to the analogous reaction of arenes,[4] it represents an effective alternative to traditional methods of pyridine functionalization processes.

Having thoroughly explored the scope of 3-oxazoline substituted pyridines, we turned our attention to the scope of 4-oxazoline substituted pyridines and our results are summarized in Scheme 4. Interestingly, we found that 2-F

Scheme 4. 4-Oxazoline Directed C−H Amidation of Pyridines[a]



[a]Regioisomers separable by column chromatography.

and 2-Cl pyridines underwent dichotomous regiochemical insertion processes to afford isomeric major products **15** and **16**. The trifluoromethyl substituted pyridine afforded **17** in excellent yield and selectivity. Surprisingly, however, both 2-methyl- and 2-aryl-substituted pyridines were also well tolerated in this case, producing **18** and **19** in good yield. These results are notable in light of the observations described earlier (Scheme 3, compounds **11**−**14**) and highlight that the position of the directing group can have a profound effect on substrate reactivity.

We turned our attention to the 6-oxazoline substituted pyridines in order to complete the scope of our studies. Disappointingly, however, subjection of 2-halo-6-oxazoline-substituted pyridines to the standard reaction conditions failed to deliver the corresponding products, regardless of the reaction temperature/time (Scheme 5). We suspect the lack of reactivity arises from the ability of these substrates to act as strong ligands, thereby deactivating the Rh-catalyst.[12]

Having confirmed the importance of the 2-substituent for catalyst reactivity, we wanted to highlight the potential of these groups as valuable functional handles (Scheme 6). Hydrolysis

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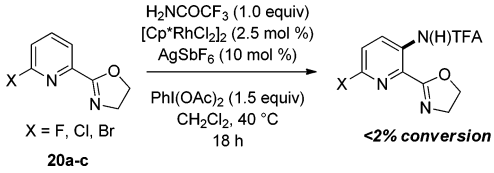
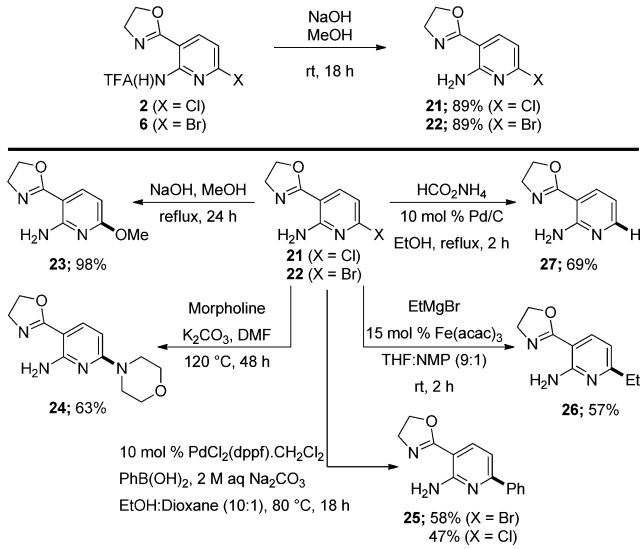
Scheme 5. 2-Oxazoline Substituted Pyridines



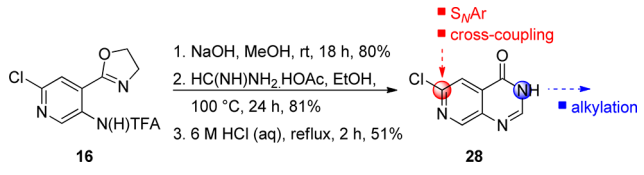
Scheme 6. Post C−H Amidation Functionalization



of the trifluoroacetamide to the corresponding aniline was achieved successfully on both 2-Cl and 2-Br substrates **2** and **6** in excellent yield. Most pleasingly, S_NAr reactions were found to be successful with both alcohol and amine based nucleophiles, affording **23** and **24** in good to excellent yields.[13] Despite the potential of these compounds to form strong complexes with transition metal catalysts, we were delighted that both Suzuki and Fe-catalyzed cross-coupling pathways were viable affording aryl and alkyl substituted pyridines **25** and **26**.[14] Moreover, removal of the 2-Cl substituent could be readily achieved affording the parent unsubstituted pyridine **27** in 69% yield.[15] Overall and importantly, the transformation of 2-halo pyridines **21**−**22** to products **23**−**27** allows us to circumvent some of the limitations associated with 3-oxazoline directed C−H amidations shown in Scheme 3.

Finally, we were able to prepare functionalized quinazolinone **28** in good yield, utilizing our previously reported conditions on substrate **16** (Scheme 7).[4] This highlights the ability to

Scheme 7. Azaquinazolinone Synthesis



exploit this chemistry to successfully prepare otherwise difficult to access heterocyclic scaffolds that bear versatile functionality for further derivatization.[16]

In summary, we have reported on the first example of rhodium-catalyzed C−H amidation of pyridines that allows valuable scaffolds to be generated with high regioselectivities. The mild and efficient reaction conditions allow for the introduction of a readily deprotectable amino source on a range of pyridine scaffolds. Furthermore, the synthetic value of 2-halo substituted pyridines is demonstrated by their successful late stage derivatization into a variety of highly functionalized scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01612.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For representative examples of *N*-heterocycle synthesis from anthranilic acid derivatives, see: (a) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469−6480. (b) Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. *RSC Adv.* **2014**, *4*, 24463−24476. (c) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153−10202.

(2) For representative reviews on C−H activation, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115. (b) De Sarkar, S. D.; Liu, W.; Kozhushkov, I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461−1479. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678. (d) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053−1064. (e) Lyons, T. W.; Sanford, M. *Chem. Rev.* **2010**, *110*, 1147−1169. (f) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814−825.

(3) For C−H activation approaches to anthranilic acid derivative synthesis, see: (a) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862−12864. (b) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466−1474. (c) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 9904−9908. (d) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2013**, *15*, 3014−3017. (e) Kim, J.; Chang, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 2203−2207. (f) Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686−693.

(4) Maiden, T. M. M.; Swanson, S.; Procopiou, P. A.; Harrity, J. P. A. *Chem. - Eur. J.* **2015**, *21*, 14342−14346.

(5) Mei, R.; Loup, J.; Ackermann, L. *ACS Catal.* **2016**, *6*, 793−797.

(6) Qin, Q.; Yu, S. *Org. Lett.* **2014**, *16*, 3504−3507.

(7) Shang, M.; Zeng, S.-H.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 5286−5289.

(8) Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 646−649.

(9) For reported C−H amidation upon pyridines, see: (a) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354−3357. (b) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043−6046. (c) Roane, J.; Daugulis, O. *J. Am. Chem. Soc.* **2016**, *138*, 4601−46−47.

(10) For further details, see Supporting Information.

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Org. Lett. XXXX, XXX, XXX−XXX

(11) Lafaye, K.; Nicolas, L.; Guérinot, A.; Reymond, S.; Cossy, J. *Org. Lett.* **2014**, *16*, 4972−4975.
(12) Subjecting these substrates to reaction conditions in CD_3OD failed to return deuterated substrate; see Supporting Information for details. For the use of related compounds as ligands for transition metal catalysis, see: Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K. *Tetrahedron: Asymmetry* **1993**, *4*, 143−150.
(13) Chang, L.; Lee, S.-Y.; Leonczak, P.; Rozenski, J.; De Jonghe, S.; Hanck, T.; Muller, C. E.; Herdewijn, P. *J. Med. Chem.* **2014**, *57*, 10080−10100.
(14) (a) Chai, Y.; Paul, Y.; Rettig, M.; Wilson, W. D.; Boykin, D. W. *J. Org. Chem.* **2014**, *79*, 852−866. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856−13863. (c) Petersen, J. G.; Sørensen, T.; Damgaard, M.; Nielsen, B.; Jensen, A. A.; Balle, T.; Bergmann, R.; Frølund, B. *Eur. J. Med. Chem.* **2014**, *84*, 404−416.
(15) Sadler, S. A.; Tajuddin, H.; Mkhalid, I. A. I.; Batsanov, A. S.; Albesa-Jove, D.; Cheung, M. S.; Maxwell, A. C.; Shukla, L.; Roberts, B.; Blakemore, D. C.; Lin, Z.; Marder, T. B.; Steel, P. G. *Org. Biomol. Chem.* **2014**, *12*, 7318−7327.
(16) Crawford, T. D.; Ndubaku, C. O.; Chen, H.; Boggs, J. W.; Bravo, B. J.; DeLaTorre, K.; Giannetti, A. M.; Gould, S. E.; Harris, S. F.; Magnuson, S. R.; McNamara, E.; Murray, L. J.; Nonomiya, J.; Sambrone, A.; Schmidt, S.; Smyczek, T.; Stanley, M.; Vitorino, P.; Wang, L.; West, K.; Wu, P.; Ye, W. *J. Med. Chem.* **2014**, *57*, 3484−3493.

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