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Facile Rh(III)-Catalyzed Synthesis of Fluorinated Pyridines

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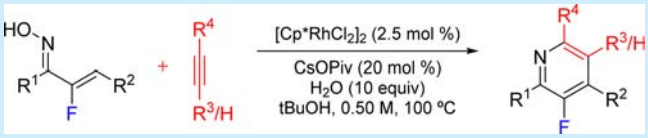
Supporting Information

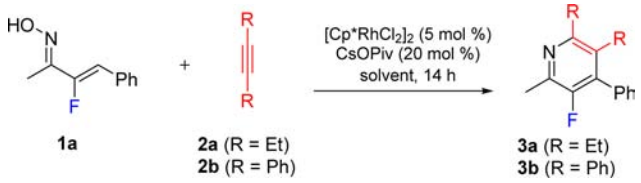
ABSTRACT: A Rh(III)-catalyzed C−H functionalization approach was developed for the preparation of multisubstituted 3-fluoropyridines from α-fluoro-α,β-unsaturated oximes and alkynes. Oximes substituted with aryl, heteroaryl, and alkyl β-substituents were effective coupling partners, as were symmetrical and unsymmetrical alkynes with aryl and alkyl substituents. The first examples of coupling α,β-unsaturated oximes with terminal alkynes was also demonstrated and proceeded with uniformly high regioselectivity to provide single 3-fluoropyridine regioisomers. Reactions were also conveniently set up in air on the benchtop.



Nitrogen heterocycles and their fluorinated analogues are ubiquitous and highly desirable motifs in pharmaceutical compounds.[1−3] While facile new syntheses of fluorinated pyridines have emerged in recent years,[4] current methods of constructing pyridines with fluorine substitution at the 3-position either require functional group transformations upon preinstalled functionality at this site on the pyridine ring[5−9] or rely on heavily functionalized building blocks.[10−13] Herein we describe a new Rh(III)-catalyzed C−H functionalization approach to prepare 3-fluoropyridines bearing multiple substituents from α-fluoro-α,β-unsaturated oximes and alkynes.

Chiba[14] and Rovis[15] have established the utility of $[Cp^*RhCl_2]_2$/metal acetate salt catalyst systems for the synthesis of multisubstituted pyridines from α,β-unsaturated oximes and internal alkynes.[16,17] However, we found that the nucleophilic alcoholic solvents utilized in their protocols, MeOH or 2,2,2-trifluoroethanol (TFE), posed a problem for the construction of fluorinated analogues due to alcohol displacement of the fluorine under the basic reaction conditions (Table 1, entries 1 and 2). To avoid fluoride displacement, we examined a range of nonhydroxylic solvents, and while most proved to be ineffective (see Table S1, Supporting Information), ethyl acetate resulted in complete conversion to fluoropyridine **3a** with minimal byproduct formation as determined by ^{19}F NMR (entry 3). Unfortunately, very low conversion to fluoropyridine **3b** was observed when diphenylacetylene (**2b**) was used as the alkyne partner, both with CsOPiv (entry 4) and the more soluble Bu_4NOAc as the acetate base (entry 5) even at a higher reaction temperature (entry 6). The sterically hindered alcohol solvents *i*-PrOH (entry 7) and *t*-BuOH (entry 8) were explored with the goal of improving reaction rate while minimizing fluoride displacement. *t*-BuOH proved to be the most effective in providing complete conversion with minimal byproduct formation (entry 8). Additionally, the loading of CsOPiv was evaluated, and 20 mol % was determined to be optimal (see Table S2, Supporting Information).

Table 1. Solvent Screen for Rh(III)-Catalyzed Fluoropyridine Formation[a]



1a **2a** (R = Et) **2b** (R = Ph) **3a** (R = Et) **3b** (R = Ph)

entry	R	solvent	temp (°C)	oxime **1a**[b] (%)	pyridine **3**[b] (%)	byprod[b] (%)
1	Et	MeOH	60	0	48	52[c]
2	Ph	TFE	60	36	29	35[c]
3	Et	EtOAc	60	0	88	12
4	Ph	EtOAc	60	95	2	3
5	Ph	EtOAc[d]	60	91	4	5
6	Ph	EtOAc[d]	80	59	22	19
7	Ph	*i*-PrOH	80	18	57	25
8	Ph	*t*-BuOH	80	0	89	11

[a]All reactions were set up in the glovebox and run under nitrogen. [b]Percentages determined by ^{19}F NMR with pentafluorobenzaldehyde as an external standard. [c]Byproduct isolated by column chromatography and determined to be the product of fluoride displacement by the methoxy group. [d]Run with 20 mol % of Bu_4NOAc instead of CsOPiv.

CsOPiv is highly hygroscopic as are the other carboxylate salts that have been used with Rh(III) catalysts in pyridine synthesis. For benchtop reactions, we therefore envisaged that it would be important to determine the tolerance of the reaction to moisture. This was investigated by evaluating the

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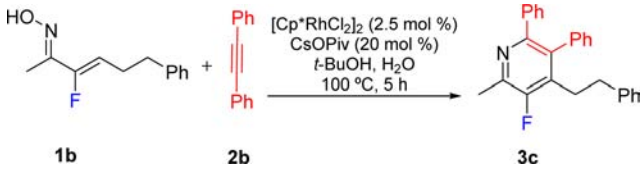
effect of increasing amounts of water upon the reaction of oxime **1b** and alkyne **2b**, which are two of the more challenging coupling partners (Table 2). Significantly, up to stoichiometric

Table 2. Concentration and Added Water Screen for Rh(III)-Catalyzed Fluoropyridine Formation[a]



1b **2b** **3c**

entry	[**1a**] (M)	H_2O (%)	oxime **1b**[b] (%)	pyridine **3c**[b] (%)	byprod[b] (%)
1	0.10	none	50	27	23
2	0.10	10	43	32	25
3	0.10	20	43	33	26
4	0.10	40	43	32	25
5	0.10	100	33	42	25
6	0.10	1000	7	62	31
7	0.10	2000	9	61	28
8	**0.50**	**1000**	**3**	**68**	**29**

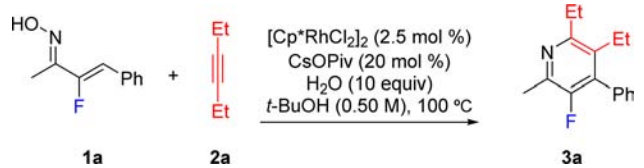
[a]All reactions were set up in a glovebox and run under nitrogen. [b]Percentages were determined by ^{19}F NMR with pentafluorobenzaldehyde as an external standard.

amounts of water had minimal effect on either the yield of **3c** or the formation of byproducts (entries 1−5). Furthermore, at 10 or more equiv of added water, the reaction conversion was actually higher and was accompanied by only a small increase in byproduct formation (entries 6 and 7). Finally, increasing the reaction concentration from 0.1 to 0.5 M, which is desirable for preparative reactions, resulted in a modest increase in conversion and yield (entry 8).

Because the synthesis protocol uses water and a high oxidation state catalyst, we also investigated the feasibility of pyridine synthesis with the reaction set up on the benchtop in air (Table 3). For the coupling of oxime **1a** to alkyne **2a**, no detrimental effect on the reaction rate or selectivity was observed when the reaction was set up in air (see entry 1 vs 2).

With optimized benchtop conditions established, we next explored the scope and generality of fluoropyridine synthesis (Scheme 1). Oximes **1** substituted with phenyl (**3a**, **3b**, **3d**−**g**), alkyl (**3c**, **3h**, **3i**), and the electron-rich furyl (**3j**−**l**) at the *β*-

Table 3. Comparison of Rh(III)-Catalyzed Fluoropyridine Formations Run under Nitrogen and Air[a]

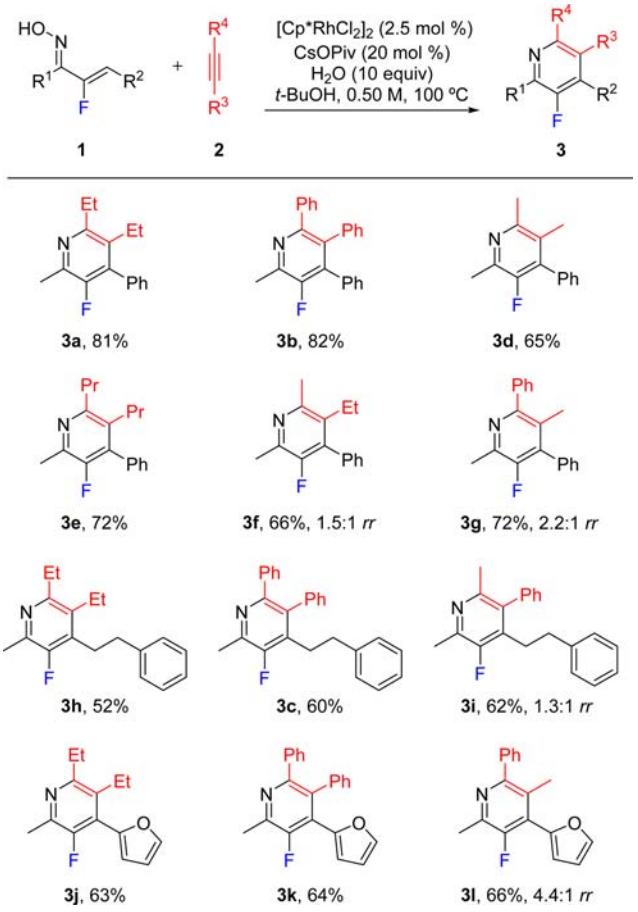


1a **2a** **3a**

entry	time (min)	oxime **1a**[c] (%)	pyridine **3a**[c] (%)	byprod[c] (%)
1[a]	15	28	63	9
	30	9	81	10
2[b]	15	18	74	8
	30	1	91	8

[a]Set up in a glovebox and run under nitrogen. [b]Set up on benchtop in air. [c]Percentages were determined by ^{19}F NMR with pentafluorobenzaldehyde as an external standard.

Scheme 1. Scope of Rh(III)-Catalyzed Fluoropyridine Formation from Oximes and Internal Alkynes[a]



[a]All reactions were set up in air on the benchtop. Yields are based upon the mass balance of pure material after column chromatography.

position each provided 3-fluoropyridines in moderate to excellent yields (Scheme 1). Symmetrical dialkyl- and diaryl-alkynes coupled in comparable yields for the different oxime coupling partners, as exemplified by 3-fluoropyridine **3a** versus **3b**, **3h** versus **3c**, and **3j** versus **3k**. Unsymmetrical internal alkynes also provided 3-fluoropyridines **3f**, **3g**, **3i**, and **3l** in good yields, but with variable regioselectivities as has been previously reported for the preparation of nonfluorinated pyridines.[14,15] Attempts to incorporate internal alkynes with bulky *tert*-butyl or TMS substituents were not successful.

To the best of our knowledge, terminal alkynes have not previously been demonstrated to be viable partners for Rh(III)-catalyzed pyridine formation.[18] Moreover, while we had reported conditions for the Rh(I)-catalyzed synthesis of pyridines from *α*,*β*-unsaturated oximes and terminal alkynes, the regioselectivities were generally modest.[19] In the current study, a range of terminal alkynes **2** coupled efficiently with oximes **1** to give single regioisomers of the 3-fluoropyridines **3** (Scheme 2). Straight-chain alkyl (**3m**,**r**,**s**) and branched alkyl (**3n**,**p**−**q**) terminal alkynes, and even neohexyne (**3o**), were effective coupling partners. The complete selectivity for the formation of the 5-substituted 3-fluoropyridines **3** is consistent with the regioselectivity observed by Fagnou et al. for terminal alkyne insertion in their Rh(III)-catalyzed synthesis of isoquinolones.[20] Coupling of phenylacetylene with oxime **1a**

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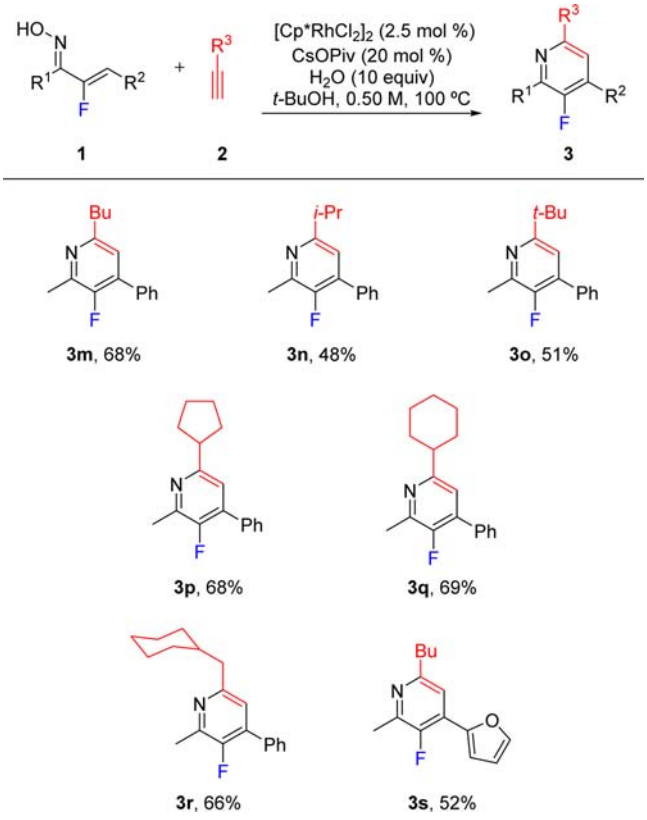
Scheme 2. Scope of Rh(III)-Catalyzed Fluoropyridine Formation from Oximes and Terminal Alkynes[a]



[a]All reactions were set up in air on the benchtop. Yields are based upon the mass balance of pure material after column chromatography.

was also attempted but did not yield any of the desired 3-fluoropyridine.

In conclusion, we have developed a one-step method for the preparation of 3-fluoropyridines from α-fluoro-α,β-unsaturated oximes and alkynes by Rh(III)-catalyzed C−H functionalization. The method is straightforward with the reaction set up on the benchtop. α-Fluoro-α,β-unsaturated oximes and alkynes with a variety of alkyl, aryl, and heteroaryl substituents are effective coupling partners. Moreover, the first examples of coupling terminal alkynes with α,β-unsaturated oximes with uniformly high selectivity provides an efficient approach to obtain single isomers of the 3-fluoropyridine products with predictable regioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, ^{1}H, ^{13}C, and ^{19}F NMR spectra of 3-fluoropyridines and intermediates. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00979.

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Notes

The authors declare no competing financial interest.

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