JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

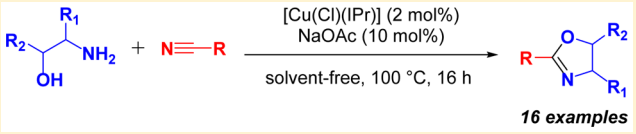
Copper *N*-Heterocyclic Carbene Complexes As Active Catalysts for the Synthesis of 2-Substituted Oxazolines from Nitriles and Aminoalcohols

Michael Trose, Faïma Lazreg, Mathieu Lesieur, and Catherine S. J. Cazin*

EaStCHEM School of Chemistry, University of St. Andrews, St. Andrews, KY16 9ST, U.K.

Supporting Information

ABSTRACT: The reaction between nitriles and aminoalcohols to access 2-substituted oxazolines was investigated. Using copper−NHC complexes, various nitriles were successfully converted into the corresponding oxazolines, under milder and less wasteful conditions than those of previously reported methods.

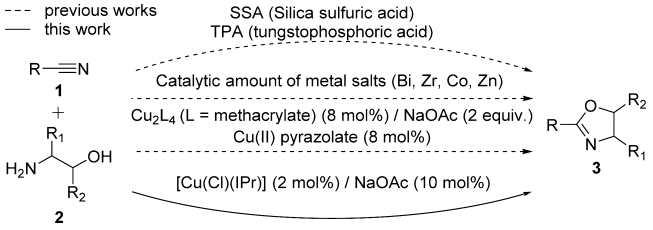


INTRODUCTION

2-Substituted oxazolines constitute the core structure of many biologically active natural compounds and play a major role in medicinal chemistry.[1] Regarding their applications, these molecules are well-known ligands for transition metals in homogeneous catalysis, in particular for the synthesis of chiral products.[2] In organic synthesis, oxazolines are common synthetic intermediates[3] and can also be used as protecting groups for carboxylic acids due to their resistance toward nucleophiles, bases, radicals, and even some acids.[4] Considering their broad applicability, several protocols have been developed to synthesize this important class of compounds.[5] However, the widespread synthetic methodologies leading to this important class of compounds involve cyclodehydration of β-hydroxy amides[6] or the condensation of carbonyls[7] or nitriles with aminoalcohols. Among these options, nitriles have been widely studied because they are readily available and inexpensive starting materials. The common approach requires an electrophile to activate a nitrile (**1**) for a nucleophilic attack by an aminoalcohol (**2**) (Scheme 1). This transformation can be achieved using heterogeneous catalysts such as silica sulfuric acid (SSA)[8] or tungstophosphoric acid (TPA).[9] Different metal salts have also been tested for this purpose. Mohammadpoor-Baltork and co-workers developed two procedures using Bi(III)[10] or Zr(IV)[11] salts; however, despite the good functional group tolerance of these protocols, a large excess of aminoalcohol (up to 8 equiv) is needed to achieve good isolated yields. Recently, Ge and co-workers have used a catalytic amount of $Co(NO_3)_2$ to synthesize 2-subtituted oxazolines,[12] with elemental sulfur added as a nitrile activator. Moreover, Fu and co-workers reported that $Zn(OTf)_2$ in toluene at reflux is an active catalyst for the synthesis of chiral pyridine bis(oxazoline) ligands.[13] Similarly, well-defined organometallic complexes have also been tested as catalysts for this transformation, especially copper, due to its abundance, low toxicity, and affordability with respect to other metals, such as Pd, Pt, or Ru. Li and co-workers developed a methodology using a catalytic amount of a $Cu^{II}_2L_4$ (L = methacrylate) complex.[14] Unfortunately, a relatively high catalyst loading (8 mol %) and an excess of base (2 equiv of NaOAc) were required, as well as the need for the independent preparation of the $Cu^{II}_2L_4$ catalyst. Similar drawbacks were observed with the use of copper(II) pyrazolate complexes, with 4 equiv of aminoalcohol and 8 mol % of catalyst being required.[15]

The most frequently encountered drawbacks for all the aforementioned procedures are the large excesses of **2** (4−8 equiv) or additives needed to achieve the desired products. Considering these disadvantages, a methodology that can minimize these amounts of reactants is highly desirable. In the past decade, well-defined copper *N*-heterocyclic carbene (NHC) complexes have emerged as active catalysts in a plethora of reactions that include [3 + 2] cycloaddition,[16] borylation of alkynes,[17] synthesis of phenols,[18] and many others.[19] Up to now, the use of these complexes as catalysts in the formation of oxazoline derivatives has not been reported. Herein, a copper−NHC catalyzed procedure has been developed in which only a substoichiometric amount of base and a small excess of aminoalcohol is used.

Scheme 1. Synthesis of 2-Substituted Oxazolines from Nitriles and Aminoalcohols



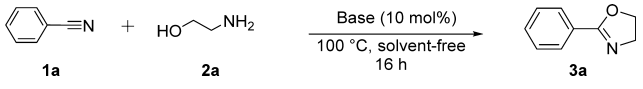
Received: June 17, 2015
Published: October 1, 2015

DOI: 10.1021/acs.joc.5b01382
J. Org. Chem. 2015, 80, 9910−9914

RESULTS AND DISCUSSION

Recently, our group reported a straightforward procedure for the synthesis of 2-substituted thiazolines using only a catalytic amount of NaOH.[20] While trying to expand this base-catalyzed protocol to the synthesis of 2-substituted oxazolines, using benzonitrile **1a** and ethanolamine **2a** as model substrates, we found that a catalytic amount of the base (10 mol %) was solely capable to promote this reaction (Table 1). Strong bases, such as alkali hydroxides (Table 1, entries 2 and 3) and *tert*-butoxides (Table 1, entry 4), gave only poor conversions, whereas slightly better results were obtained using weak bases, especially Na_2CO_3 and NaOAc (Table 1, entries 6 and 9, respectively). This observation is in accordance with previous work using an excess of the same weak bases.[5e,14] Using the base alone as the catalyst, the amount of **2a** was found to be crucial. In the presence of Na_2CO_3, increasing the amount of **2a** leads to a drop in conversion (Table 1, entries 6–8) while an opposite effect is witnessed when using NaOAc (Table 1, entries 9–11).

Table 1. Screening of Bases for the Synthesis of 2-Phenyl-4,5-dihydrooxazole[a]



1a 2a 3a

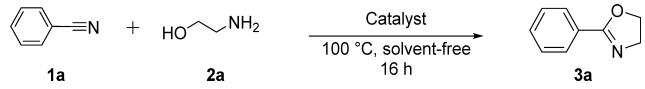
entry	base (10 mol %)	**2a** (equiv)	yield (%)[b]
1	–	2	3
2	NaOH	2	9
3	KOH	2	10
4	KO^{t}Bu	2	11
5	K_2CO_3	2	11
6	Na_2CO_3	2	40
7	Na_2CO_3	4	22
8	Na_2CO_3	10	16
9	NaOAc	2	26
10	NaOAc	4	53
11	NaOAc	10	61

[a]Reaction conditions: **1a** (0.5 mmol), base (0.05 mmol), solvent-free, 100 °C, 16 h, under argon. [b]GC yield based on benzonitrile; *n*-hexadecane used as internal standard; average of two reactions.

Different copper–NHC complexes[21] were then tested in order to activate the nitrile (Table 2). Gratifyingly, these complexes achieved moderate to good conversion depending on the nature of the NHC ligand (Table 2, entries 1–4). Among these, [Cu(Cl)(IPr)] (IPr = *N*,*N*′-bis[(2,6-(di-isopropyl)phenyl)]imidazol-2-ylidene) was chosen for further optimization due to its higher activity. Better conversion was achieved by either increasing the catalyst loading to 2 mol % (Table 2, entry 5) or using 4 equiv of **2a** (Table 2, entry 6). It is worth underlining that [Cu(Cl)(IPr)] showed better activity compared to CuCl, even when 10 mol % of the latter was used (Table 2, entries 7 and 8).

Considering the good conversion reached when using copper-NHC catalyst and the moderate reactivity of the system when the catalyst is a base, we were interested in exploring the synergic effect of Cu complex and base together. To investigate this possible effect, a catalytic amount of different bases (10 mol %) was tested in the presence of [Cu(Cl)(IPr)] (1 mol %) (Table 3). Among these, only NaOAc was found to be a suitable base (Table 3, entry 3), with a higher conversion obtained compared to the base-free test (Table 2, entry 4). The ideal stoichiometry of **2a** was investigated and an optimal value was found to be 2 equiv (Table 3, entry 3). Satisfyingly, with an increase in Cu loading to 2 mol % (Table 3, entry 6), 95% conversion toward **3a** was observed. The temperature was found to be an important parameter, since any variation from 100 °C caused a significant drop in the conversion (Table 3, entries 7 and 8).

Table 2. Screening of Catalysts for the Synthesis of 2-Phenyl-4,5-dihydrooxazole[a]

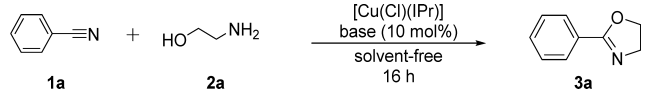


1a 2a 3a

entry	catalyst (mol %)	yield (%)[b]
1	[Cu(Cl)(SIMes)] (1)	50
2	[Cu(Cl)(IMes)] (1)	52
3	[Cu(Cl)(SIPr)] (1)	67
4	[Cu(Cl)(IPr)] (1)	73
5	[Cu(Cl)(IPr)] (2)	83
6[c]	[Cu(Cl)(IPr)] (1)	77
7	CuCl (1)	49
8	CuCl (10)	65

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), catalyst (0.005–0.05 mmol), solvent-free, 100 °C, 16 h, under argon. [b]GC yield based on benzonitrile; *n*-hexadecane used as internal standard; average of two reactions. [c]2 mmol of **2a**.

Table 3. Screening of Bases for the Synthesis of 2-Phenyl-4,5-dihydrooxazole with [Cu(Cl)(IPr)][a]



1a 2a 3a

entry	base	[Cu(Cl)(IPr)] (mol %)	**2a** (equiv)	T (°C)	yield[b] (%)
1	K_2CO_3	1	2	100	11
2	Na_2CO_3	1	2	100	57
3	NaOAc	1	2	100	90
4	NaOAc	1	1.1	100	58
5	NaOAc	1	4	100	88
6	**NaOAc**	**2**	**2**	**100**	**95 (93)**
7	NaOAc	2	2	80	62
8	NaOAc	2	2	120	88

[a]Reaction conditions: **1a** (0.5 mmol), [Cu(Cl)(IPr)] (0.005–0.01 mmol), base (0.05 mmol), solvent-free, 16 h, under argon. [b]GC yield based on benzonitrile; *n*-hexadecane used as internal standard; average of two reactions; isolated yield in parentheses.

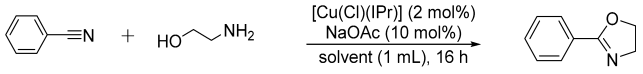
To highlight the superior performance of solvent-free conditions, various solvents were tested using the optimal conditions (Table 4). Among these, the reaction in methanol (Table 4, entry 5) gave a comparable yield to the reaction in the absence of solvent; however, in order to develop a less wasteful procedure, solvent-free conditions were maintained.

With these reaction conditions in hand, the scope of the reaction was investigated with a range of nitrile derivatives (Figure 1).

Considering *para*-substituted benzonitriles, in which the steric effects are negligible, the outcome of the reaction depends mainly on the electronic nature of the substituents. Benzonitriles bearing electron-withdrawing groups (EWGs), such as trifluoromethyl- (**3b**) and chloro- (**3c**) substituents, gave excellent isolated yields. Moderate results were obtained

DOI: 10.1021/acs.joc.5b01382
J. Org. Chem. 2015, 80, 9910–9914

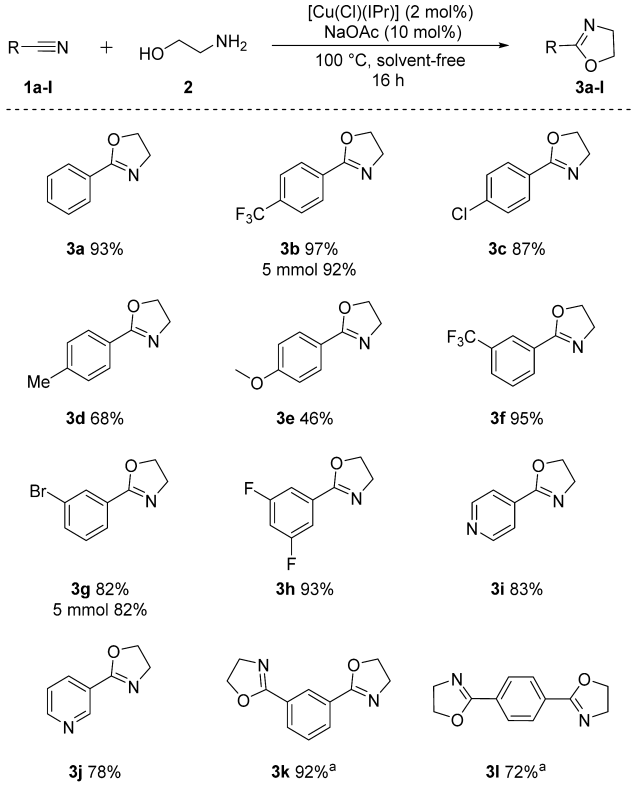
Table 4. Screening of Solvents for the Synthesis of 2-Phenyl-4,5-dihydrooxazoles[a]



1a 2a 3a

entry	solvent	T (°C)	yield (%)[b]
1	toluene	100	15
2	benzene	100	15
3	1,4-dioxane	100	3
4	H_2O	100	0
5	MeOH	100	92
6	MeOH	80	77
7	EtOH	80	16
8	*i*PrOH	80	3

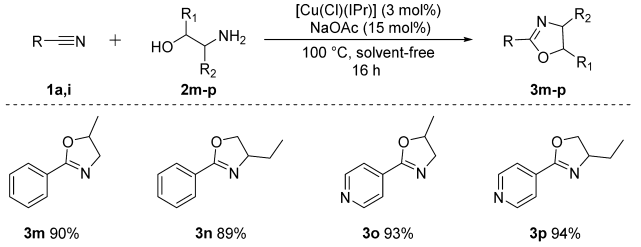
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), [Cu(Cl)(IPr)] (0.01 mmol), NaOAc (0.05 mmol), solvent (1 mL), 100 °C, 16 h, under argon. [b]GC yield based on benzonitrile; *n*-hexadecane used as internal standard; average of two reactions.



Reaction conditions: **1** (1 mmol), **2a** (2 mmol), [Cu(Cl)(IPr)] (0.02 mmol), NaOAc (0.1 mmol), 100 °C, solvent-free, 16 h, under argon; isolated yields, average of two reactions. [a] 4 mmol of **2a**.

Figure 1. Formation of 2-substituted oxazolines from nitriles and ethanolamine.

when electron-donating groups (EDGs), such as methyl- (**3d**) and methoxy- (**3e**) moieties, are present. Likewise, substitution in the *meta*-position with EWGs gave good to excellent yields (**3f**–**3h**). *Ortho*-substituted benzonitriles do not react under these conditions, possibly due to steric hindrance in the proximity of the nitrile moiety. Heteroaromatic nitriles were converted to the corresponding oxazolines in good yields (**3i**–**3j**). When 1,3-dicyano- and 1,4-dicyanobenzene were used, the selective double functionalization was achieved by simply increasing the amount of **2a** to 4 equiv (**3k**–**3l**).[22] When alkyl nitriles were tested, no conversion was observed. Moreover, scaling-up reactions with two selected substrates (**3b** and **3g**) to 5 mmol gave comparable isolated yields with respect to the small scale experiments (1 mmol), allowing the synthesis of these important compounds in gram quantities. Gratifyingly, substitutions in the aliphatic chain of the aminoalcohol were well tolerated by this catalytic system (Figure 2), yielding the corresponding products in excellent yields (**3m**–**3p**).



Reaction conditions: nitrile (1 mmol), **2** (3 mmol), [Cu(Cl)(IPr)] (0.03 mmol), NaOAc (0.15 mmol), 100 °C, solvent-free, 16 h, under argon; isolated yields, average of two reactions.

Figure 2. Formation of 2-substitued oxazolines from nitriles and aminoalcohols.

CONCLUSION

The copper–NHC complex [Cu(Cl)(IPr)] was found to be an active catalyst in the presence of a base cocatalyst for the conversion of different nitriles into the corresponding 2-substituted oxazolines. Gratifyingly, good to excellent isolated yields of the final products were achieved using a minimum excess of aminoalcohols and only a substoichiometric amount of base (10 mol % of NaOAc) under solvent-free conditions.

EXPERIMENTAL SECTION

General Information. ^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} Nuclear Magnetic Resonance (NMR) spectra were recorded at 298 K using the residual solvent peak for ^{13}C{^{1}H} NMR ($CDCl_3$: δC = 77.36 ppm) and TMS as a reference for ^{1}H NMR. Gas chromatography (GC) analyses were performed on an apparatus equipped with a flame ionization detector and a (5%-phenyl)-methylpolysiloxane column (30 m, 320 μm, film: 0.25 μm). The reaction's efficiency did not seem to be affected when carried out outside the glovebox, using Schlenk techniques, under air-free conditions; however, all reactions reported here have been conducted in a glovebox for more convenience.

Materials. All commercially available reagents were used without further purification. Analytical thin layer chromatography was performed on 0.20 mm silica gel plates. Flash chromatography was performed using silica gel (200–300 mesh).

General Procedure for the Synthesis of 2-Substituted Oxazolines with Ethanolamine. In a glovebox, a vial was charged with [Cu(Cl)(IPr)] (0.02 mmol), NaOAc (0.1 mmol), the nitrile (1 mmol), and ethanolamine (2 mmol). The reaction was stirred at 100 °C for 16 h under solvent-free conditions. The conversion was determined by GC analysis or by ^{1}H NMR. The crude mixture was purified by column chromatography to give the desired compound.

2-Phenyl-4,5-dihydrooxazole (3a).[14] The general procedure yielded after flash chromatography (SiO_2, CH_2Cl_2/ethyl acetate, 1:1) the title compound as a colorless oil (136.9 mg, 93%). The general procedure repeated using standard Schlenk techniques yielded after flash chromatography (SiO_2, CH_2Cl_2/ethyl acetate, 1:1) the title compound as a colorless oil (135.4 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98–7.95 (m, 2H), 7.51–7.40 (m, 3H), 4.44 (t, 2H, J = 9.8 Hz), 4.07 (t, 2H, J = 9.8 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.7, 131.3, 128.3, 128.1, 127.8, 67.6, 54.9.

2-(4-Trifluoromethylphenyl)-4,5-dihydrooxazole (3b). The general procedure yielded after flash chromatography (SiO_2, CH_2Cl_2,

DOI: 10.1021/acs.joc.5b01382
J. Org. Chem. 2015, 80, 9910–9914

ethyl acetate, 8:2) the title compound as a colorless solid (208.6 mg, 97%). Mp 104−106 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, 2H, J = 8.2 Hz), 7.70 (d, 2H, J = 8.2 Hz), 4.50 (t, 2H, J = 9.4 Hz), 4.12 (t, 2H, J = 9.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.4, 132.8 (q, J_{C-F} = 33.2 Hz), 131.1, 128.5, 125.3 (q, J_{C-F} = 3.6 Hz), 123.8 (q, J_{C-F} = 272.4 Hz), 67.9, 55.1. ^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz): δ −62.19. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{10}H_8F_3NO$ 216.0631; Found 216.0632.

2-(4-Chlorophenyl)-4,5-dihydrooxazole (3c).[14] The general procedure yielded after flash chromatography (SiO_2, hexane, ethyl acetate, 2:8) the title compound as a colorless solid (157.5 mg, 87%). Mp 77−79 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90−7.86 (m, 2H), 7.40−7.37 (m, 2H), 4.44 (t, 2H, J = 9.4 Hz), 4.06 (t, 2H, J = 9.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.9, 137.6, 129.6, 128.8, 126.4, 67.9, 55.1.

2-*p*-Tolyl-4,5-dihydrooxazole (3d).[14] The general procedure yielded after flash chromatography (SiO_2, hexane, ethyl acetate, 3:7) the title compound as a colorless solid (109.5 mg, 68%). Mp 69−71 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86−7.83 (m, 2H), 7.24−7.21 (m, 2H), 4.42 (t, 2H, J = 9.4 Hz), 4.05 (t, 2H, J = 9.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.7, 141.6, 129.0, 128.1, 125.5, 67.5, 54.9, 21.6.

2-(4-Methoxyphenyl)-4,5-dihydrooxazole (3e).[6a] The general procedure yielded after flash chromatography (SiO_2, hexane, ethyl acetate, 1:9) the title compound as a colorless solid (81.5 mg, 46%). Mp 60−62 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89−7.85 (m, 2H), 6.91−6.87 (m, 2H), 4.37 (t, 2H, J = 9.4 Hz), 4.00 (t, 2H, J = 9.4 Hz), 3.81 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.4, 162.0, 129.9, 120.3, 113.7, 67.5, 55.3, 54.9.

2-(3-Trifluoromethylphenyl)-4,5-dihydrooxazole (3f). The general procedure yielded after flash chromatography (SiO_2, CH_2Cl_2, ethyl acetate, 8:2) the title compound as a colorless oil (204.3 mg, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25 (s, 1H), 8.15 (d, 1H, J = 7.7 Hz), 7.75 (d, 1H, J = 7.7 Hz), 7.57 (t, 1H, J = 7.7 Hz), 4.50 (t, 2H, J = 9.5 Hz), 4.12 (t, 2H, J = 9.5 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.4, 131.9, 130.9 (q, J_{C-F} = 32.9 Hz), 128.9, 128.6, 127.7 (q, J_{C-F} = 3.4 Hz), 125.1 (q, J_{C-F} = 3.7 Hz), 123.8 (q, J_{C-F} = 272.4 Hz), 67.9, 55.0. ^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz): δ −62.83. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{10}H_8F_3NO$ 216.0631; Found 216.0632.

2-(3-Bromophenyl)-4,5-dihydrooxazole (3g).[5e] The general procedure yielded after flash chromatography (SiO_2, hexane, ethyl acetate, 1:1) the title compound as a colorless oil (184.5 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (t, 1H, J = 1.8 Hz), 7.87 (dt, 1H, J = 8.0 Hz, J = 1.3), 7.59 (dq, 1H, J = 8.0 Hz, J = 1.3), 7.27 (t, 1H, J = 8.0 Hz), 4.43 (t, 2H, J = 9.6 Hz), 4.06 (t, 2H, J = 9.6 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.4, 134.3, 131.2, 130.0, 129.8, 126.8, 122.4, 67.9, 55.0.

2-(3,5-Difluorophenyl)-4,5-dihydrooxazole (3h). The general procedure yielded after flash chromatography (SiO_2, hexane, ethyl acetate, 6:4) the title compound as a colorless solid (170.2 mg, 93%). Mp 74−76 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50−7.44 (m, 2H), 6.92 (tt, 1H, J = 8.8 Hz, 2.4 Hz), 4.45 (t, 2H, J = 9.4 Hz), 4.08 (t, 2H, J = 9.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.7, 162.6 (dd, J_{C-F} = 235.7 Hz, J_{C-F} = 12.5 Hz), 130.9 (t, J_{C-F} = 10.4 Hz), 111.3 (dd, J_{C-F} = 19.6 Hz, J_{C-F} = 7.8 Hz), 106.6 (t, J_{C-F} = 25.5 Hz), 68.0, 55.0. ^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz): δ −109.05. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_9H_8F_2NO$ 184.0568; Found 184.0565.

2-(Pyridin-4-yl)-4,5-dihydrooxazole (3i).[14] The general procedure yielded after flash chromatography (SiO_2, ethyl acetate) the title compound as a white solid (122.9 mg, 83%). Mp 109−111 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.72 (s, 2H), 7.78 (s, 2H), 4.47 (t, 2H, J = 9.7 Hz), 4.10 (t, 2H, J = 9.7 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.0, 150.3, 135.0, 122.0, 68.0, 55.1.

2-(Pyridin-3-yl)-4,5-dihydrooxazole (3j).[14] The general procedure yielded after flash chromatography (SiO_2, ethyl acetate) the title compound as a white solid (115.5 mg, 78%). Mp 68−70 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.15 (s, 2H), 8.71−8.69 (m, 1H), 8.21 (dt, 1H, J = 8.0 Hz, J = 1.9 Hz), 7.36−7.34 (m, 1H), 4.46 (t, 2H, J = 9.7 Hz), 4.08 (t, 2H, J = 9.7 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.7, 152.0, 149.4, 135.5, 123.9, 123.2, 67.8, 55.0.

1,3-Bis(4,5-dihydrooxazol-2-yl)benzene (3k).[14] The general procedure yielded after flash chromatography (SiO_2, CH_2Cl_2, ethyl acetate, 1:1) the title compound as a white solid (198.8 mg, 92%). Mp 137−139 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49−8.48 (m, 1H), 8.07 (dd, 2H, J = 7.8 Hz, 1.7 Hz), 8.07 (t, 1H, J = 7.8 Hz), 4.44 (t, 4H, J = 9.4 Hz), 4.07 (t, 4H, J = 9.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.1, 130.9, 128.5, 128.2, 128.0, 67.8, 55.1.

1,4-Bis(4,5-dihydrooxazol-2-yl)benzene (3l).[14] The general procedure yielded after flash chromatography (SiO_2, CH_2Cl_2, ethyl acetate, 1:1) the title compound as a white solid (156.3 mg, 72%). Mp 238−240 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99 (s, 4H), 4.45 (t, 4H, J = 9.6 Hz), 4.08 (t, 4H, J = 9.6 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.2, 130.3, 128.2, 67.8, 55.1.

General Procedure for the Synthesis of 2-Substituted Oxazolines with Substituted Aminoalcohols. In a glovebox, a vial was charged with [Cu(Cl)(IPr)] (0.03 mmol), NaOAc (0.15 mmol), the nitrile (1 mmol), and aminoalcohol (3 mmol). The reaction was stirred at 100 °C for 16 h under solvent-free conditions. The conversion was determined by ^{1}H NMR. The crude mixture was purified by column chromatography to give the desired compound.

5-Methyl-2-phenyl-4,5-dihydrooxazole (3m).[6c] The general procedure yielded after flash chromatography (SiO_2, CH_2Cl_2, ethyl acetate, 8:2) the title compound as a colorless oil (145 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, 2H, J = 7.4 Hz), 7.51−7.47 (m, 1H), 7.42 (t, 2H, J = 7.4 Hz), 4.90−4.83 (m, 1H), 4.19−4.14 (m, 1H), 3.63 (q, 1H, J = 6.2 Hz), 1.45 (d, 3H, J = 6.2 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.9, 131.2, 128.3, 128.1, 76.3, 61.6, 21.2. One Cq missing.

4-Ethyl-2-phenyl-4,5-dihydrooxazole (3n).[23] The general procedure yielded after flash chromatography (SiO_2, CH_2Cl_2, ethyl acetate, 8:2) the title compound as a colorless oil (155.8 mg, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.99−7.96 (m, 2H), 7.51−7.47 (m, 1H), 7.45−7.40 (m, 2H), 4.52−4.48 (m, 1H), 4.31−4.23 (m, 1H), 4.08 (t, 1H, J = 7.9 Hz), 1.85−1.75 (m, 1H), 1.69−1.58 (m, 1H), 1.02 (t, 3H, J = 7.5 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.4, 131.2, 127.9, 72.1, 68.0, 28.6, 10.0.

5-Methyl-2-(pyridin-4-yl)-4,5-dihydrooxazole (3o). The general procedure yielded after flash chromatography (SiO_2, ethyl acetate) the title compound as a colorless oil (150.7 mg, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (s, 2H), 7.79−7.78 (m, 2H), 4.94−4.85 (m, 1H), 4.21−4.15 (m, 1H), 3.65 (q, 1H, J = 6.2 Hz), 1.44 (d, 3H, J = 6.2 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.2, 150.2, 135.3, 122.0, 76.9, 61.7, 21.1. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_9H_{11}O_1N_2$ 163.0866; Found 163.0862.

4-Ethyl-2-(pyridin-4-yl)-4,5-dihydrooxazole (3p). The general procedure yielded after flash chromatography (SiO_2, ethyl acetate) the title compound as a colorless oil (165.5 mg, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.73 (s, 2H), 7.79 (s, 2H), 4.54−4.48 (m, 1H), 4.32−4.23 (m, 1H), 4.11−4.06 (m, 1H), 1.82−1.72 (m, 1H), 1.68−1.57 (m, 1H), 1.02−0.98 (m, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.8, 150.2, 135.2, 122.1, 72.5, 68.2, 28.5, 10.0. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{10}H_{13}O_1N_2$ 177.1022; Found 177.1020.

General Procedure for the Synthesis of 2-Substituted Oxazolines - 5 mmol Scale. In the glovebox, a flame-dried Schlenk was charged with [Cu(Cl)(IPr)] (0.1 mmol), NaOAc (0.5 mmol), the nitrile (5 mmol), and ethanolamine (10 mmol). The reaction was stirred at 100 °C for 16 h under solvent-free conditions. The conversion was determined by GC analysis or by ^{1}H NMR. The crude mixture was purified by column chromatography to give the desired compound.

2-(4-Trifluoromethylphenyl)-4,5-dihydrooxazole (3b). The general procedure yielded after flash chromatography (SiO_2, CH_2Cl_2, ethyl acetate, 8:2) the title compound as a colorless solid (990 mg, 92%). Mp 104−106 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, 2H, J = 8.2 Hz), 7.70 (d, 2H, J = 8.2 Hz), 4.50 (t, 2H, J = 9.4 Hz), 4.12 (t, 2H, J = 9.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.4, 132.8 (q, J_{C-F} = 33.2 Hz), 131.1, 128.5, 125.3 (q, J_{C-F} = 3.6 Hz), 123.8 (q, J_{C-F} = 272.4 Hz), 67.9, 55.1. ^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz): δ −62.19.

DOI: 10.1021/acs.joc.5b01382
J. Org. Chem. 2015, 80, 9910−9914

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_8F_3NO$ 216.0631; Found 216.0632.

2-(3-Bromophenyl)-4,5-dihydrooxazole (3g).[3] The general procedure yielded after flash chromatography (SiO_2, hexane, ethyl acetate, 1:1) the title compound as a colorless oil (927 mg, 82%). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.10 (t, 1H, J = 1.8 Hz), 7.87 (dt, 1H, J = 8.0 Hz, J = 1.3), 7.59 (dq, 1H, J = 8.0 Hz, J = 1.3), 7.27 (t, 1H, J = 8.0 Hz), 4.43 (t, 2H, J = 9.6 Hz), 4.06 (t, 2H, J = 9.6 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 163.4, 134.3, 131.2, 130.0, 129.8, 126.8, 122.4, 67.9, 55.0.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01382.

Optimization of reaction conditions, ^1H, $^{13}C\{^1H\}$, and $^{19}F\{1H\}$ NMR spectra of catalysis products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cc111@st-andrews.ac.uk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge the Royal Society (University Research Fellowship to C.S.J.C) for funding. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University.

■ REFERENCES

(1) (a) Tsuda, M.; Yamakawa, M.; Oka, S.; Tanaka, Y.; Hoshino, Y.; Mikami, Y.; Sato, A.; Fujiwara, H.; Ohizumi, Y.; Kobayashi, J. *J. Nat. Prod.* **2005**, *68*, 462. (b) Onishi, H. R.; Pelak, B. A.; Silver, L. L.; Kahan, F. M.; Chen, M.-H.; Patchett, A. A.; Galloway, S. M.; Hyland, S. A.; Anderson, M. S.; Raetz, C. R. H. *Science* **1996**, *274*, 980. (c) Li, Q.; Woods, K. W.; Claiborne, A.; Gwaltney, S. L., II; Barr, K. J.; Liu, G.; Gehrke, L.; Credo, R. B.; Hui, Y. H.; Lee, J.; Warner, R. B.; Kovar, P.; Nukkala, M. A.; Zielinski, N. A.; Tahir, S. K.; Fitzgerald, M.; Kim, K. H.; Marsh, K.; Frost, D.; Ng, S.-C.; Rosenberg, S.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 465. (d) Tsukamoto, M.; Murooka, K.; Nakajima, S.; Abe, S.; Suzuki, H.; Hirano, K.; Kondo, H.; Kojiri, K.; Suda, H. *J. Antibiot.* **1997**, *50*, 815. (e) Vizi, E. S. *Med. Res. Rev.* **1986**, *6*, 431. (f) Bergeron, R. J.; Xin, M. G.; Weimar, W. R.; Smith, R. E.; Wiegand, J. *J. Med. Chem.* **2001**, *44*, 2469.

(2) (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505.

(3) (a) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483. (b) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837. (c) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297.

(4) (a) Saravanan, P.; Corey, E. J. *J. Org. Chem.* **2003**, *68*, 2760. (b) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-S.; Park, H.-G. *Org. Lett.* **2005**, *7*, 3207.

(5) For selected examples, see: (a) Wu, X. − F.; Neumann, H.; Neumann, S.; Beller, M. *Chem. - Eur. J.* **2012**, *18*, 13619. (b) Boissarie, P. J.; Hamilton, Z. E.; Lang, S.; Murphy, J. A.; Suckling, C. J. *Org. Lett.* **2011**, *13*, 6256. (c) Doherty, S.; Knight, J. G.; Hashmi, A. S. K.; Smyth, C. H.; Ward, N. A. B.; Robson, K. J.; Tweedley, S.; Harrington, R. W.; Clegg, W. *Organometallics* **2010**, *29*, 4139. (d) Maekawa, K.; Sasaki, T.; Kubo, K.; Igarashi, T.; Sakurai, T. *Tetrahedron Lett.* **2004**, *45*, 3663. (e) Garg, P.; Chaudhary, S.; Milton, M. D. *J. Org. Chem.* **2014**, *79*, 8668.

(6) For selected examples about the cyclodehydration of β-hydroxy amides, see: (a) Xu, Q.; Li, Z. *Tetrahedron Lett.* **2009**, *50*, 6838. (b) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (c) Petersson, M. J.; Jenkins, I. D.; Loughlin, W. A. *Org. Biomol. Chem.* **2009**, *7*, 739.

(7) (a) Ishihara, M.; Togo, H. *Tetrahedron* **2007**, *63*, 1474. (b) Sayama, S. *Synlett* **2006**, *2006*, 1479. (c) Takahashi, S.; Togo, H. *Synthesis* **2009**, *2009*, 2329. (d) Kangani, C. O.; Day, B. W. *Tetrahedron Lett.* **2009**, *50*, 5332. (e) Cwik, A.; Hell, Z.; Hegedus, A.; Finta, Z.; Horvath, Z. *Tetrahedron Lett.* **2002**, *43*, 3985. (f) Wipf, P.; Wang, X. *J. Comb. Chem.* **2002**, *4*, 656. (g) Ilkgul, B.; Gunes, D.; Sirkecioglu, O.; Bicak, N. *Tetrahedron Lett.* **2010**, *51*, 5313.

(8) Mohammadpoor-Baltork, I.; Mirkhani, V.; Moghadam, M.; Tangestaninejad, S.; Zolfigol, M. A.; Abdollahi-Alibeik, M.; Khosropour, A. R.; Kargar, H.; Hojati, S. F. *Catal. Commun.* **2008**, *9*, 894.

(9) Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Hojati, S. F. *Catal. Commun.* **2008**, *9*, 1153.

(10) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Synlett* **2005**, *18*, 2747.

(11) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Catal. Commun.* **2007**, *8*, 200.

(12) Ge, H. X.; Liu, P.; Li, X. N.; Sun, W.; Li, J. L.; Yang, B. Q.; Shi, Z. *Tetrahedron* **2013**, *69*, 6591.

(13) Fu, G. C.; Lou, S. *Org. Synth.* **2010**, *87*, 310.

(14) Li, X. N.; Zhou, B. Y.; Zhang, J.; She, M. Y.; An, S. J.; Ge, H. X.; Li, C.; Yin, B.; Li, J. L.; Shi, Z. *Eur. J. Org. Chem.* **2012**, *2012*, 1626.

(15) Wang, L.; Guo, B.; Li, H.-X.; Li, Q.; Li, H.-Y.; Lang, J.-P. *Dalton Trans.* **2013**, *42*, 15570.

(16) Lazreg, F.; Slawin, A. M. Z.; Cazin, C. S. J. *Organometallics* **2012**, *31*, 7969.

(17) Bidal, Y. D.; Lazreg, F.; Cazin, C. S. J. *ACS Catal.* **2014**, *4*, 1564.

(18) Songis, O.; Boulens, P.; Benson, C. G. M.; Cazin, C. S. J. *RSC Adv.* **2012**, *2*, 11675.

(19) (a) Egbert, J. D.; Cazin, C. S. J.; Nolan, S. P. *Catal. Sci. Technol.* **2013**, *3*, 912. (b) Lesieur, M.; Lazreg, F.; Cazin, C. S. J. *Chem. Commun.* **2014**, *50*, 8927.

(20) Trose, M.; Lazreg, F.; Lesieur, M.; Cazin, C. S. J. *Green Chem.* **2015**, *17*, 3090.

(21) Santoro, O.; Collado, A.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. *Chem. Commun.* **2013**, *49*, 10483.

(22) A mixture of mono- and disubstitution results when the reaction is performed using less than 4 equiv of the aminoalcohol.

(23) Uma Maheswari, C.; Sathish Kumar, G.; Venkateshwar, M. *RSC Adv.* **2014**, *4*, 39897.

DOI: 10.1021/acs.joc.5b01382
J. Org. Chem. 2015, 80, 9910−9914