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Photoredox Catalysts: Synthesis of the Bipyrazine Ligand

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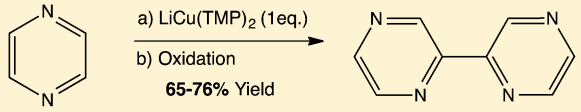
Supporting Information

ABSTRACT: The bipyrazine ligand is often employed in photoredox catalysts in order to increase the excited state oxidation potential of the catalyst. However, literature syntheses of the ligand are cumbersome and typically lead to low yields. This hampers use of the desired catalysts. We report here an efficient copper based synthesis of the bipyrazine ligand that affords the product in 65−76% yield on a multigram scale.

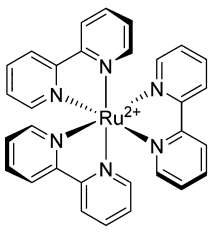


Photoredox catalysts offer a convenient and unique method for the generation and use of both radical cation and radical anion intermediates in synthesis.[1] Because of our long-standing interest in the radical cation intermediates that play a critical role in net oxidative cyclization reactions,[2,3] we were curious as to the chemical reactivity of the radical cations generated with the use of a photoredox catalyst and how that reactivity compared to that of radical cations generated at the surface of an anode.[4,5] We hoped to examine the reactivity of the radical cations using the same competition study methods employed for the analysis of the electrochemical reactions (Scheme 1).[6] Would the use of the photoredox conditions and the presence of the radical anion in the reaction alter the chemoselectivity of the radical cation reactions?

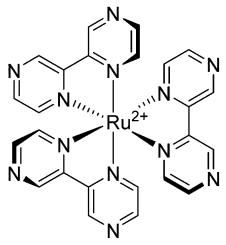
Scheme 1

1

X=Y= SMe, R=alkyl, R'=alkyl: $E_{p/2}$ = +0.9 V vs. Ag/AgCl
X=OMe, Y=H, R=alkyl, R'=H: $E_{p/2}$ = +1.4 vs. Ag/AgCl



2. Ru(bpy)32+
E(2+*/+) = 0.77V

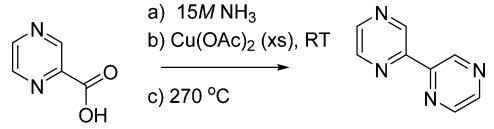


3. Ru(bpz)32+
E(2+*/+) = 1.45V

The substrates typically used for the electrochemical experiments (Scheme 1) have oxidation potentials that range from about +0.9 V vs Ag/AgCl to +1.4 V vs Ag/AgCl.[6] For this reason, the ruthenium derived photoredox catalyst using a bipyrazine ligand was selected for the photochemical oxidation.[7] This catalyst has an excited state with an oxidation potential of around +1.4 V.[8] For comparison, the bipyridine ruthenium catalyst has an excited state oxidation potential of +0.77 V.[8]

While the selection of an appropriate catalyst was straightforward, the overall plan ran into trouble when it came time to make the desired catalyst. The ligand proved difficult to synthesize on a scale that would allow for its use in multiple transformations. Many of the papers that describe the use of the bipyrazine ligand cite the work of Lafferty and Case for its synthesis.[9] This synthesis begins with the pyrazine carboxylic acid (Scheme 2), and utilizes a Cu-based aryl−aryl coupling reaction to generate the ligand. The reaction requires elevated temperatures and produces the ligand in a 7% yield.

Scheme 2

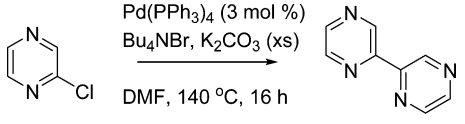


4 **5.** 7%

Yoon and co-workers published an improved synthesis of the bipyrazine ligand that took advantage of a Pd-catalyzed coupling reaction to afford a 42% yield of the product (Scheme 3).[10]

For our part, we sought an improved, scalable synthesis of the bipyrazine ligand that still took advantage of an Earth abundant metal catalyst. Of particular note was the Cu-based strategy developed by Lipshutz and co-workers for the

Scheme 3



6 **5.** 42%

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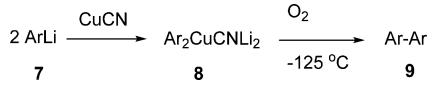
formation of mixed biaryl systems.[11] In this chemistry (Scheme 4), a mixed copper catalyst system is generated from an aryl

Scheme 4



lithium that was typically formed by metal halogen exchange with the corresponding aryl halide. Unfortunately, this method did not prove amenable to the synthesis of the bipyrazine ligand from the pyrazine halide.

Methods for generation of the aryllithium, the nature of the oxidant used, and the time and temperature of the reaction were all varied. The maximum yield obtained from these optimization efforts was only 35%. The amount of the initial pyrazine halide recovered from the reaction and the subsequent results discussed below indicated that the reaction was limited by formation of the necessary aryllithium species.

With that conclusion, we sought an alternative method to make the necessary cuprate. One method of interest modified the Lipshutz approach with a direct ortho cupration.[12] In this work, Wheatley, Uchiyama, and co-workers made use of an amino-base cuprate to deprotonate the aryl group and generate the arylcuprate without any need to generate the aryllithium species. They demonstrated that the resulting arylcuprates can either be trapped with electrophiles or treated with oxidants to provide the biaryl homocoupling product. When the same conditions were attempted with pyrazine, the reaction led to a 20% yield of the homocoupling product along with 20% of the recovered starting material. It appeared that the oxidative step of the process was hindering the reaction.

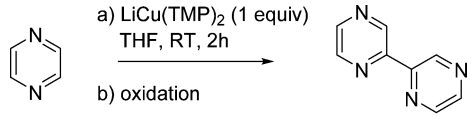
Mongin and co-workers demonstrated that a similar approach could be used for the formation of biaryls from heterocycles.[13] For this chemistry, the nature of the cuprate was modified and a stronger oxidant used. These conditions turned out to be the best starting point for our optimization of a route to the bipyrazine ligand (Table 1). Initially (entry 1), conditions identical to those employed by Mongin and co-workers were used. The reaction led to a 41% yield of the bipyrazine product. Mongin and co-workers also utilized *p*-dinitrobenzene as an oxidant for the reaction. The use of this oxidant led to a 39% of the bipyrazine (entry 2). As a control, only 10% of the product was generated in the absence of an oxidant (entry 3).

Iyoda and co-workers showed that duroquinone could serve as a successful oxidant for the generation of biaryl systems from arylcopper species.[14] When this observation was combined with the Nguyen approach and applied to the formation and oxidation of pyrazinyl cuprate, the reaction led to a 45% yield of product (entry 4).

In each of the cases tried, the addition of pyrazine to the reaction led to the formation of a solid suspended in the THF. The result was a poor yield of the desired product combined with low recovery (20−25%) of the starting material. This observation was most consistent with the poor solubility of the cuprate hindering the oxidation step in the sequence.

One method to circumvent such issues by improving the solubility of the cuprate is to heat the reaction. In the case of bipyrazine generation this led to decomposition of the starting material and no evidence of product formation (entry 5). A second method was suggested by Lipschutz and co-workers.

Table 1. Optimization of Bipyrazine Formation



entry	oxidant	conditions	variation	yield
1	Chorinal	60 °C, 16 h	--	41%
2	Dinitro-benzene	RT, 16 h	--	39%
3	--	RT, 16 h	--	10%
4	Duroquinone	60 °C, 16 h	--	45%
5	Duroquinone	Reflux, 16 h	--	--
6	Duroquinone	60 °C, 16 h	5.0 equiv TMEDA	39%
7	Duroquinone	Sonicated, 10 min	--	56%
8	**Duroquinone**	**Sonicated, 60 min**	--	**76%**
9	--	Sonicated, 60 min	--	18%
10	Duroquinone	Sonciated, 60 min	0.5 equiv oxidant	54%
11	Methyl-anthraquinone	Sonicated, 60 min	--	58%
12	Cloranil	Sonicated, 60 min	--	25%
13	Benzoquinone	Sonicated, 60 min	--	45%
14	Duroquinone	Sonicated, 60 min	1.25 equiv $LiCu(TMP)_2$	43%
15	Duroquinone	Sonicated, 60 min	0.5 equiv. $LiCu(TMP)_2$	50%
16	Duroquinone	Sonicated, 60 min	$Li_2Cu(TMP)_2CN$	25%

For their reactions, they report that the addition of TMEDA to the reactions before the oxidation step afforded higher yields of the biaryl product.[15] The authors hypothesized that the addition of the TMEDA led to chelation of lithium ions in solution, a change that activated the cuprate complex for oxidation. We hoped that the addition might help solublize the copper complex. However, the addition led to no improvement in the reaction (entry 6).

In a third attempt to solubilize the cuprate, the reaction was sonicated for 10 min following addition of the duroquinone oxidant to the mixture. The yield of the reaction improved to 56% (entry 7). When the duration of the sonication/oxidation step was increased to 60 min, the yield of bipyrazine product climbed further to 76% (entry 8). From the reaction mixture, a 23% yield of recovered pyrazine was obtained. In addition, 90% of the original mass of the duroquinone oxidant was recovered. When the oxidant was removed from the reaction (entry 9), the yield dropped to only 18%. When 0.5 equiv of the oxidant was used (entry 10), the reaction proceeded to just over 50% completion. Hence, the oxidant was required for reductive elimination of the aryl rings from the cuprate intermediate. Sonication alone was not enough.

With the optimized conditions for the reaction established, several different oxidants with varying oxidation potentials were screened for their ability to trigger the reductive elimination reaction (entries 11−13). However, none of these were as effective as duroquinone for the reaction.

The nature of the cuprate intermediate was also examined using the optimized reaction conditions (entries 14−16). Once

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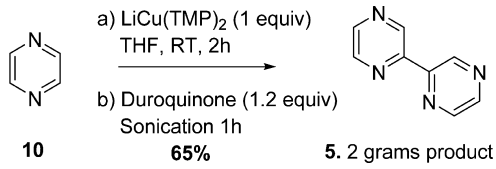
again, the original cuprate derived from direct deprotonation of pyrazine proved to be the best.

Finally, the scalability of the reaction was examined (Scheme 5). To this end, the reaction was run on a multigram scale leading to 2.05 g (ca. 65%) of the bipyrazine ligand.

Scheme 5



In conclusion, a rapid, convenient synthesis of the bipyrazine ligand needed for higher oxidation potential Ru-based photoredox catalysts has been developed. The availability of this method should greatly improve the availability of the catalyst.

EXPERIMENTAL SECTION

General Information. Tetrahydrofuran (THF) was dried by distilling over sodium and benzophenone. 2,2,6,6-Tetramethylpiperidine (TMP) was dried over molecular sieves prior to use. All remaining reagents were purchased commercially and used without further purification.

Preperation of $CuCl_2$·TMEDA Complex. Synthesis was taken and modified from previous literature procedure.[16] In a flame-dried 1000 mL round-bottom flask, 23.86 g (140 mmol) copper(II) chloride dihydrate was suspended in 700 mL butanol and refluxed. 21 mL (140 mmol) *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) was dissolved in 50 mL butanol and added slowly to the refluxing copper solution. Refluxing continued for 15 min before cooling to room temperature. The resulting copper complex was precipitated with hexane, filtered, and dried under vacuum. 74% yield (25.9 g) of $CuCl_2$·TMEDA was obtained.

Cuprate Mediated Synthesis of Bipyrazine. In a flame-dried 25 mL round-bottom flask, 500 mg $CuCl_2$·TMEDA (2.0 mmol) was suspended in 5 mL THF and cooled to 0 °C. The copper(II) suspension was reduced with the dropwise addition of 1.25 mL (2.0 mmol) *n*-butyllithium solution (1.6 M in hexanes) resulting in a light green Cu(I) solution. (Note: Butyllithium solution must be free of lithium salts. Also, it should be added slowly under sufficient stirring to avoid over-reduction of copper).

In a separate, flame-dried 10 mL round-bottom, 0.63 mL (4.0 mmol) TMP was dissolved in 2 mL THF and cooled to 0 °C. 1 equiv *n*-butyllithium was added before warming to room temperature.

The LiTMP was then added slowly to the Cu(I) mixture at 0 °C yielding a dark yellow solution containing the necessary $LiCu(TMP)_2$ complex. 160 mg (2.0 mmol) pyrazine was dissolved in 1 mL THF before dropwise addition to the copper solution. Upon completion, the mixture was allowed to warm to room temperature and stir for 2 h resulting in the formation of a dark brown precipitate. The cuprate suspension was oxidized with 394 mg (1.2 equiv) duroquinone while sonicating for 1 h. The resulting mixture was quenched with water and extracted with dichloromethane. All organic layers were combined, dried over magnesium sulfate, filtered, and solvent removed under reduced pressure. Crude product was purified by column chromatography using 1:1 ethyl acetate in hexanes. 120 mg bipyrazine (76% yield, MW = 158.16 g/mol) was obtained with no further purification needed.

*Bipyrazine (**5**).*[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.61 ppm (s, 2H); 8.67 (s, 4H).

Large Scale Synthesis of Bipyrazine. In a flame-dried 1000 mL Morton flask (to maintain sufficient agitation of reaction mixture), 10.0 g $CuCl_2$·TMEDA (40.0 mmol) was suspended in 100 mL THF and cooled to 0 °C. 25 mL (40.0 mmol) *n*-butyllithium solution (1.6 M in hexanes) was added dropwise yielding Cu(I) solution.

In a separate, flame-dried 100 mL round-bottom flask, 13.6 mL (80.0 mmol) TMP was dissolved in 40 mL THF and cooled to 0 °C. 1 equiv *n*-butyllithium was added before warming to room temperature.

The LiTMP was then added slowly to the Cu(I) mixture at 0 °C yielding a dark yellow solution containing the necessary $LiCu(TMP)_2$ complex. 3.2 g (40.0 mmol) pyrazine was dissolved in 1 mL THF before dropwise addition to the copper solution. Upon completion, the mixture was allowed to warm to room temperature and stir for 2 h. Oxidation occurred with the addition of 7.88 g (1.2 equiv) duroquinone and sonicated for 1.5 h. The resulting mixture was quenched with water and extracted with dichloromethane. All organic layers were combined, dried, filtered, and solvent removed in vacuo. Crude product was purified by column chromatography using 1:1 ethyl acetate in hexanes yielding 2.05 g bipyrazine (65%).

ASSOCIATED CONTENT

Supporting Information

^{1}H spectrum of bipyrazine product (Table 1, Entry 8). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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