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TITLE:

[(DPEPhos)(bcp)Cu]PF_6: A General and Broadly Applicable Copper-Based Photoredox Catalyst

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SHORT ABSTRACT:

Detailed and general protocols are presented for the synthesis of [(DPEPhos)(bcp)Cu]PF_6, a general copper-based photoredox catalyst, and for its use in synthetic chemistry for the direct arylation of C-H bonds in (hetero)arenes and radical cyclization of organic halides.

LONG ABSTRACT:

Our group recently reported the use of [(DPEPhos)(bcp)Cu]PF_6 as a general copper-based photoredox catalyst which proved efficient to promote the activation of a broad variety of organic halides, including unactivated ones. These can then participate in various radical transformations such as reduction and cyclization reactions, as well as in the direct arylation of several (hetero)arenes. These transformations provide a straightforward access to a range of small molecules of interest in synthetic chemistry, as well as to biologically active natural products. Altogether, [(DPEPhos)(bcp)Cu]PF_6 acts as a convenient photoredox catalyst which appears to be an attractive, cheap and complementary alternative to the state-of-the-art iridium- and ruthenium-based photoredox catalysts. Here, we report a detailed protocol for the synthesis of [(DPEPhos)(bcp)Cu]PF_6, as well as NMR and spectroscopic characterization, and we illustrate its use in synthetic chemistry for the direct arylation of (hetero)arenes and radical cyclization of

organic halides. In particular, the direct arylation of *N*-methylpyrrole with 4-iodobenzonitrile to afford the corresponding 4-(1-methyl-1*H*-pyrrol-2-yl)benzonitrile and the radical cyclization of *N*-benzoyl-*N*-[(2-iodoquinolin-3-yl)methyl]cyanamide to afford natural product luotonin A are detailed. The scope and limitations of this copper-based photoredox catalyst are also briefly discussed.

INTRODUCTION:

Radical transformations have been known for decades to provide remarkably efficient pathways in synthetic chemistry which are often complementary to transformations based on cationic, anionic or pericyclic processes[1]. While particularly promising for various types of transformations, radical-based chemistry has however long been underexploited, mainly because of the need for highly toxic reagents which considerably limits its attractiveness. Moreover, radical processes have long been considered as transformations associated with poor levels of control in terms of regio- and/or stereoselectivity, or leading to extensive dimerization and/or polymerization issues.

Alternative strategies have recently been developed in order to facilitate the generation and better control the reactivity of radical species. Among them, photoredox catalysis has become one of the most powerful methods as it allows the convenient generation of radical species using a light-responsive compound, namely the photoredox catalyst, and visible light irradiation[2,3]. Visible light itself is indeed able to promote population of the excited state of the photoredox catalyst which becomes, consequently, both a stronger reductant and oxidant than in its corresponding ground state. These enhanced redox properties make single-electron transfer processes, not feasible in the ground state, possible under mild conditions from the excited state. Over the past decade, visible light photoredox catalysis has become an attractive and powerful technique in organic synthesis and has allowed the development of numerous remarkably efficient and selective transformations based on radical intermediates generated under sustainable, mild and user-friendly conditions.

While most photoredox processes reported to date are dominated by the use of iridium- and ruthenium-based photoredox catalysts, as well as by some organic dyes such as pyrylium and acridinium derivatives[4], cheaper alternatives are still highly demanded for the development of complementary processes of interest for industrial applications. In this regard, the use of copper-based photoredox catalysts appears particularly appealing as they are not only cheaper but also provide opportunities to activate a broader and/or different range of substrates, which therefore opens new perspectives in photoredox catalysis[5-8]. Despite some promising early works reported by the Kutal[9], Mitani[10] and Sauvage[11] groups, photoactivatable copper complexes have, however, only been scarcely used in photoredox catalysis, most probably because of their short-lived excited states compared to their ruthenium- and iridium-based congeners. More recently, recent remarkable contributions by Peters and Fu[12-15], Reiser[16-20] and other groups[21-25] have clearly brought attention back to copper-based photoredox catalysts and demonstrated their unique potential.

As part of our recent interest in copper-catalyzed radical processes[26,27], we recently reported a

general and broadly applicable copper-based photoredox catalyst, [(DPEPhos)(bcp)Cu]PF_6 (DPEPhos: bis[(2-diphenylphosphino)phenyl] ether; bcp: bathocuproine), which turned out to be particularly efficient for activation of organic halides under visible light irradiation (**Figure 1A**)[28-30]. Upon irradiation with visible light and in the presence of an amine as sacrificial reductant, a wide range of unactivated aryl and alkyl halides was shown to be easily activated by catalytic amounts of [(DPEPhos)(bcp)Cu]PF_6 and therefore to participate in various radical transformations including reductions, cyclizations and direct arylation of several electron-rich (hetero)arenes. Furthermore, [(DPEPhos)(bcp)Cu]PF_6 has also proven successful at promoting photoinduced radical domino cyclizations of ynamides and cyanamides, providing an efficient and straightforward access to complex tri-, tetra- and pentacyclic nitrogen heterocycles at the core structures of various natural products. This strategy permitted the efficient synthesis of rosettacin, luotonin A, and deoxyvasicinone, natural products that exhibit anticancer, antimicrobial, anti-inflammatory and antidepressant activities. These transformations are illustrated in **Figure 1C**. From a mechanistic standpoint, the photoinduced activation of organic halides with [(DPEPhos)(bcp)Cu]PF_6 proceeds through a rare Cu(I)/Cu(I)*/Cu(0) catalytic cycle, which has been confirmed by extensive mechanistic and photophysical studies. In particular, excitation of the ground state [(DPEPhos)(bcp)Cu]PF_6 [Cu(I)] upon irradiation by visible light leads to the formation of the corresponding excited complex [(DPEPhos)(bcp)Cu]PF_6* [Cu(I)*] which is then reduced by the sacrificial amine to generate the corresponding [(DPEPhos)(bcp)Cu]PF_6 [Cu(0)] species. This Cu(0) intermediate is reducible enough to reduce the carbon–halogen bond of various organic halides to generate the corresponding radicals, which can then participate in the aforementioned transformations, together with regeneration of the starting catalyst (**Figure 1B**).

In the following section, we first describe the protocol to synthesize the photoactivatable [(DPEPhos)(bcp)Cu]PF_6 (whose NMR and spectroscopic characterizations are presented in the representative results section). The synthesis is straightforward and particularly convenient, and simply requires addition of 1 equivalent of DPEPhos and 1 equivalent of bcp to a solution of tetrakisacetonitrile copper(I) hexafluorophosphate in dichloromethane. The desired [(DPEPhos)(bcp)Cu]PF_6 is then isolated by precipitation from diethyl ether and can be easily obtained on a multigram scale (**Figure 2A**). Importantly, the isolated copper complex is not particularly sensitive to oxygen and moisture and can therefore be conveniently handled with no specific precautions other than being stored away from light.

Secondly, we describe the protocols to activate organic halides using [(DPEPhos)(bcp)Cu]PF_6 under visible light irradiation by focusing on two different transformations. The first reaction is the direct arylation of *N*-methylpyrrole with 4-iodobenzonitrile using catalytic amounts of [(DPEPhos)(bcp)Cu]PF_6 as photoredox catalyst, dicyclohexylisobutylamine as the sacrificial reductant and potassium carbonate as the base under irradiation at 420 nm (**Figure 2B**). The second reaction is the radical cyclization of *N*-benzoyl-*N*-[(2-iodoquinolin-3-yl)methyl]cyanamide, using the same catalyst and sacrificial reductant, whose cyclization directly leads to luotonin A, a natural product displaying interesting anticancer activities (**Figure 2C**). Detailed protocols are provided for both transformations.

PROTOCOL:

1. Synthesis of [(DPEPhos)(bcp)Cu]PF_6

1.1. Add 3.73 g (10.00 mmol) of tetrakisacetonitrile copper(I) hexafluorophosphate and 5.39 g (10.00 mmol) of DPEPhos to a 2 L round bottom flask equipped with a magnetic stir bar.

1.2. Fit the round bottom flask with a three neck vacuum adapter connected to a vacuum line and an argon line.

1.3. Evacuate the flask under vacuum and backfill with argon three times. Replace the three neck vacuum adapter by a rubber septum.

NOTE: The reaction can be performed under air with slightly reduced efficiency (see discussion section for details).

1.4. Add 800 mL of dry dichloromethane.

NOTE: Dichloromethane is freshly distilled from CaH_2. The reaction can also be performed in regular dichloromethane (99.8%) with similar efficiency (see discussion section for details).

1.5. Stir the reaction mixture for 2 h in the dark (reaction flask covered with aluminum foil) at 23 °C under an argon atmosphere.

1.6. Add 3.60 g (10.00 mmol) of bcp to a 500 mL round bottom flask.

1.7. Fit the round bottom flask with a three neck vacuum adapter connected to a vacuum line and an argon line.

1.8. Evacuate the flask under vacuum and backfill with argon three times. Replace the three neck vacuum adapter by a rubber septum.

1.9. Add 200 mL of dry dichloromethane and gently shake the flask until complete dissolution of the bcp.

1.10. Add the solution of bcp in dichloromethane to the reaction mixture using a cannula.

1.11. Stir for an additional hour in the dark (reaction flask covered with aluminum foil) at 23 °C under an argon atmosphere.

1.12. Filter the mixture through a pad of Celite, wash with ca. 100 mL of dichloromethane and concentrate the filtrate to ca. 50-100 mL under reduced pressure.

1.13. Add the concentrate dropwise to 1 L of diethyl ether with vigorous stirring to induce

precipitation of the desired complex.

1.14. Collect the precipitate by filtration through a fritted glass (pore size 3) and wash the precipitate with ca. 100 mL of diethyl ether.

1.15. Dry the bright yellow precipitate under vacuum at 23 °C for 5 h to recover 10.1 g (91% yield).

NOTE: A 75% yield was obtained when the reaction was performed under air using distilled dichloromethane; a 89% yield was obtained when the reaction was performed under argon using regular dichloromethane; when performing the reaction under air with regular dichloromethane, the reaction was found to be less efficient and led to much lower purity (ca 70%, as estimated by ^{1}H NMR with an internal standard).

1.16. Characterize [(DPEPhos)(bcp)Cu]PF_6 as previously reported[31].

2. Direct arylation of *N*-methylpyrrole with 4-iodobenzonitrile

2.1. Add 55 mg (0.05 mmol) of [(DPEPhos)(bcp)Cu]PF_6, 59 mg (0.25 mmol) of dicyclohexylisobutylamine (Cy_2N*i*Bu), 138 mg (1.0 mmol) of K_2CO_3 and 114 mg (0.50 mmol) of 4-iodobenzonitrile to an oven-dried 10 mL vial equipped with a magnetic stir bar.

2.2. Seal the vial with a rubber septum, evacuate the vial under vacuum and backfill with argon three times.

2.3. Add 5 mL of acetonitrile and 890 µL (10.00 mmol) of *N*-methylpyrrole. Replace the rubber septum by a screw cap.

NOTE: Acetonitrile is freshly distilled from CaH_2 and degassed using freeze-pump-thaw cycles prior to use to ensure high yields and reproducibility.

2.4. Stir the reaction mixture for 3 days at 23 °C in a photoreactor under 420 nm wavelength irradiation.

NOTE: As an alternative to the use of a photoreactor, the reaction can also be conveniently performed using blue LEDs strips or a photochemistry device with a blue LED lamp (440 nm, 34 W). These experimental setups are shown in **Figure 3** (see Representative results) and a discussion on their respective results is provided in the “Discussion” section.

2.5. Filter the reaction mixture through a pad of Celite, wash with ca. 5 mL of diethyl ether and concentrate the filtrate under reduced pressure.

2.6. Purify the crude residue by flash column chromatography over silica gel (eluent system petroleum ether/EtOAc: 90/10).

2.7. Dry the pure compound under vacuum at 23 °C for 3 h to recover 65 mg (72% yield).

NOTE: The use of blue LEDs strips afforded a 76% yield (69 mg) while the use of a photochemistry device with a blue LED lamp (440 nm, 34 W) afforded an 86% yield (78 mg).

2.8. Characterize the pure compound as previously reported[32].

3. Cyclization of *N*-benzoyl-*N*-[(2-iodoquinolin-3-yl)methyl]cyanamide to luotonin A

3.1. Add 37 mg (0.09 mmol) of *N*-benzoyl-*N*-[(2-iodoquinolin-3-yl)methyl]cyanamide, 9 mg (9.0 µmol) of [(DPEPhos)(bcp)Cu]PF_6, 11 mg (0.04 mmol) of Cy_2N*i*Bu and 25 mg (0.18 mmol) of K_2CO_3 to an oven-dried 7 mL vial equipped with a magnetic stir bar.

3.2. Seal the vial with a rubber septum, evacuate the vial under vacuum and backfill with argon three times.

3.3. Add 2 mL of acetonitrile. Replace the rubber septum by a screw cap.

NOTE: Acetonitrile is distilled from CaH_2 and degassed using freeze-pump-thaw cycles prior to use to ensure high yields and reproducibility.

3.4. Stir the reaction mixture for 5 days at 23 °C in a photoreactor under 420 nm wavelength irradiation.

3.5. Filter the reaction mixture through a pad of Celite, wash with ca. 2 mL of dichloromethane and concentrate the filtrate under reduced pressure.

3.6. Purify the crude residue by flash column chromatography over silica gel (eluent system: petroleum ether/EtOAc 60:40).

3.7. Dry the pure compound under vacuum at 23 °C for 3 h to recover 20 mg (79% yield).

3.8. Characterize the desired luotonin A as previously reported[29].

REPRESENTATIVE RESULTS:

Synthesis of [(DPEPhos)(bcp)Cu]PF_6

As shown by the protocol described in the above section, the synthesis of [(DPEPhos)(bcp)Cu]PF_6 is particularly convenient and can be easily performed on a multigram scale. The ^1H and ^{13}C NMR spectra indicate formation of the pure complex (**Figure 4A,B**). The spectroscopic data correspond to those previously reported[31].

^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.83 (s, 2H), 7.60-7.47 (m, 12H), 7.40-7.32 (m, 2H), 7.29-7.17 (m, 8H), 7.11-6.94 (m, 18H), 2.52 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 158.5, 150.3, 144.0,

136.5, 133.9, 133.1, 133.0, 132.9, 132.5, 132.2, 132.0, 131.7, 130.1, 129.6, 129.5, 129.2, 128.7, 128.7, 128.6, 125.8, 125.8, 125.5, 125.4, 120.4, 27.5.

The UV/Vis absorption and emission spectra have also been recorded and are shown in **Figure 4C,D**. The UV/Vis absorption spectrum (acetonitrile, 10^{-4} M) displays two main absorption bands with two maxima at 385 nm and 485 nm. The emission spectrum (acetonitrile, 10^{-4} M), obtained by excitation at 445 nm, displays a maximum at 535 nm.

Copper-catalyzed photoredox direct arylation of (hetero)arenes with aryl halides

The direct arylation of *N*-methylpyrrole with 4-iodobenzonitrile is representative of the general transformation in which [(DPEPhos)(bcp)Cu]PF_6 acts as an efficient photoredox catalyst to promote the direct arylation of various electron-rich (hetero)arenes under visible light irradiation. The scope of the transformation is depicted in **Figure 5**. These results are briefly discussed in the next section.

As for the characterization of 4-(1-methyl-1*H*-pyrrol-2-yl)benzonitrile, the ^{1}H and ^{13}C NMR spectra indicate formation of the pure compound (**Figure 6A,B**). The spectroscopic data correspond to those previously reported[32].

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 6.78 (app. t, *J* = 2.1 Hz, 1H), 6.35 (dd, *J* = 3.7 and 1.8 Hz, 1H), 6.23 (dd, *J* = 3.7 and 2.7 Hz, 1H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 137.8, 132.7, 132.3, 128.4, 125.9, 119.1, 110.8, 109.8, 108.7, 35.6.

Figure 3 illustrates the three experimental setups that have been successfully used to perform the direct arylation of (hetero)arenes with aryl halides under photoredox conditions. The reaction can be performed in a photoreactor with irradiation at 420 nm wavelength (**Figure 3A**), using commercially available blue LEDs strips (**Figure 3B**), or using a photochemistry device with a blue LED lamp (440 nm, 34 W) (**Figure 3C**). A brief discussion on the difference in efficiency between the three experimental setups is given in the next section.

Photoinduced radical domino cyclization of ynamides and cyanamides

The cyclization of *N*-benzoyl-*N*-[(2-iodoquinolin-3-yl)methyl]cyanamide to luotonin A is representative of the general transformation in which [(DPEPhos)(bcp)Cu]PF_6 acts as an efficient photoredox catalyst to promote the radical domino cyclization of ynamides and cyanamides containing a suitably-placed iodoaryl subunit. These cyclizations, which provide an efficient and straightforward access to tri-, tetra- and pentacyclic nitrogen heterocycles at the core structures of various natural products, are shown in **Figure 7**. These results are briefly discussed in the next section.

The ^{1}H and ^{13}C NMR spectra indicate formation of the pure natural product luotonin A (**Figure 8A,B**). The spectroscopic data correspond to those previously reported[33].

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.49-8.41 (m, 3 H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 7.5 Hz,

1 H), 7.89-7.82 (m, 2 H), 7.71-7.66 (m, 1 H), 7.58 (t, *J* = 8.1 Hz, 1 H), 5.34 (s, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.8, 152.7, 151.3, 149.5 (2 C), 134.7, 131.6, 130.8 (2 C), 129.5, 128.9 (2 C), 128.6, 128.0, 127.5, 126.5, 121.4, 47.4.

FIGURE LEGENDS:

Figure 1. [(DPEPhos)(bcp)Cu]PF_6 as a general copper-based photoredox catalyst. (**A**). General properties of [(DPEPhos)(bcp)Cu]PF_6. (**B**). General mechanism for the activation of organic halides. (**C**). Representative transformations including reduction, direct arylation and cyclization reactions.

Figure 2. Synthesis of [(DPEPhos)(bcp)Cu]PF_6 and application in organic/natural product synthesis. (**A**). Synthesis of [(DPEPhos)(bcp)Cu]PF_6. (**B**). Direct arylation of *N*-methylpyrrole. (**C**). Radical cyclization to luotonin A.

Figure 3. Experimental setups used for the direct arylation of (hetero)arenes under photoredox conditions. (**A**). Photoreactor. (**B**). Blue LEDs strips. (**C**). Photochemistry device and blue LED lamp.

Figure 4. Characterization of [(DPEPhos)(bcp)Cu]PF_6. (**A**). ^{1}H NMR spectrum. (**B**). ^{13}C NMR spectrum. (**C**). UV/Vis absorption spectrum. (**D**). Emission spectrum.

Figure 5. Copper-catalyzed photoredox direct arylation of (hetero)arenes with aryl halides. Substrate scope.

Figure 6. Characterization of 4-(1-methyl-1H-pyrrol-2-yl)benzonitrile. (**A**). ^{1}H NMR spectrum. (**B**). ^{13}C NMR spectrum.

Figure 7. Photoinduced radical domino cyclization of ynamides and cyanamides. Substrate scope.

Figure 8. Characterization of luotonin A. (**A**). ^{1}H NMR spectrum. (**B**). ^{13}C NMR spectrum.

DISCUSSION:

Synthesis of [(DPEPhos)(bcp)Cu]PF_6

The synthesis of [(DPEPhos)(bcp)Cu]PF_6 is typically performed using dry dichloromethane (distilled prior to use) and under argon to ensure the highest yield, purity and good reproducibility. As mentioned in the protocol, the synthesis of [(DPEPhos)(bcp)Cu]PF_6 can be performed with regular dichloromethane (99.8%) and/or under air with variable efficiencies. Indeed, while the use of regular dichloromethane under argon afforded the same efficiency (89% yield), performing the reaction with distilled dichloromethane under air only provides the desired complex in a 75% yield. Lastly, performing the reaction with non-distilled dichloromethane under air affords the desired complex with a noticeably lower purity (ca 70% as estimated by ^{1}H NMR using an internal standard). As a consequence, one may conclude that the quality of the dichloromethane used does not have a strong impact on the efficiency of the reaction (high yield

and purity), providing that the reaction is conducted under argon. On the other hand, performing the reaction under air is not recommended, as it affords the desired complex with reduced efficiency and, even more importantly, with lower purity when combined with non-distilled dichloromethane.

Copper-catalyzed photoredox direct arylation of (hetero)arenes with aryl halides

As illustrated in **Figure 5**, the reaction was found to be rather general with a series of 2-arylated pyrroles being obtained in fair to good yields. Noteworthy, aryl iodides substituted with a bromide or a boronate are convenient starting materials and therefore afford a starting point for further functionalization and valorization of the corresponding biaryls. Boc-protected pyrroles were also shown to be readily arylated with a variety of aryl iodides while the reaction could also be extended to the arylation of some electron-rich benzene rings such as 2,4,6-mesitylene, 2,4,6-trimethoxybenzene and 1,3-dimethoxybenzene. Finally, more challenging electron-poor aryl bromides could also be used for the direct arylation of *N*-methylpyrrole while unactivated aryl bromides and aryl chlorides are not reactive under the reaction conditions, which probably represent the main limitation of this procedure. Altogether, these results show that [(DPEPhos)(bcp)Cu]PF_6 efficiently activates the carbon – halogen bond of several aryl halides to promote the direct arylation of some (hetero)arenes which have to be used in large excess to achieve good efficiency. This main limitation is, however, common to most procedures reported to date promoting the same transformation.

As mentioned in the protocol section, the copper-catalyzed photoredox direct arylation of (hetero)arenes with aryl halides is mainly performed using a photoreactor with irradiation at 420 nm. Alternatively, the use of simpler and more readily available experimental setups has also been demonstrated, with the use of commercially available blue LEDS strips, as well as of a photochemistry device with a blue LEDs lamp (440 nm, 34W). Interestingly, small but noticeable differences in efficiency are observed using these three devices. While the photoreactor and blue LEDs strips afford the desired arylated product in comparable yields (72% and 76%, respectively), the photochemistry device with a blue LED lamp affords the highest yield in desired product (86%). This is most probably due to the amount of light that actually penetrates into the reaction mixture, as it is well known that visible light penetration in solution containing photoactive species is quite low. As a consequence, the amount of photoredox catalyst that is actually activated in solution, and that is responsible for catalysis, is also quite low and can be the limiting factor. Among the three experimental setups used for the direct arylation of *N*-methylpyrrole with 4-iodobenzonitrile, the photochemistry device with a blue LED lamp certainly is the most intense, which leads to amount of excited complex and thus, to higher efficiency. Such considerations are also critical for scaling up such photoinduced processes which are probably more conveniently performed under continuous flow conditions on larger scales[34,35].

Photoinduced radical domino cyclization of ynamides and cyanamides

As illustrated in **Figure 7**, [(DPEPhos)(bcp)Cu]PF_6 was shown to be an effective promoter under visible light irradiation for the radical domino cyclization of various ynamides and cyanamides, affording tri-, tetra- or pentacyclic nitrogen heterocycles, in fair to good yields from readily available precursors, at the core structures of various natural products. This strategy permitted

the synthesis of rosettacin, luotonin A, and deoxyvasicinone, natural products of great interest as they possess anticancer, antimicrobial, anti-inflammatory and antidepressant activities. Noteworthy, the cyclization of ynamides and cyanamides had already been described by Malacria using more classical tin-based conditions[33,36], or under photoredox conditions by Yu using the highly reducing *fac*-Ir(ppy)$_3$ as photoredox catalyst[37]. When compared to those previously reported methods, the new copper-based photoredox system we reported appears to be an attractive alternative as it provides similar substrate scope and yields while avoiding the use of highly toxic Bu_3SnH (Malacria) or expensive *fac*-Ir(ppy)$_3$ (Yu). Overall, this system has proven its efficiency for the activation of various unactivated aryl- or alkyl- carbon – halogen bonds leading to key structures in organic synthesis, as well as in drug discovery and natural product synthesis.

Altogether, the results discussed above highlight the efficiency of [(DPEPhos)(bcp)Cu]PF_6 as an alternative to iridium- and ruthenium- based photocatalysts. Similar levels of efficiency can be obtained with a copper-based catalyst that is both much easier to prepare and much less expensive. The synthesis of the copper-based photocatalyst is in addition highly modular, which paves the way for the design and development of second generation catalysts addressing the main limitations met with [(DPEPhos)(bcp)Cu]PF_6 (i.e., the rather high catalyst loading still required in most case and its unability to activate some aryl bromides and aryl chlorides).

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DISCLOSURES:

The authors have nothing to disclose.

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Figure 1

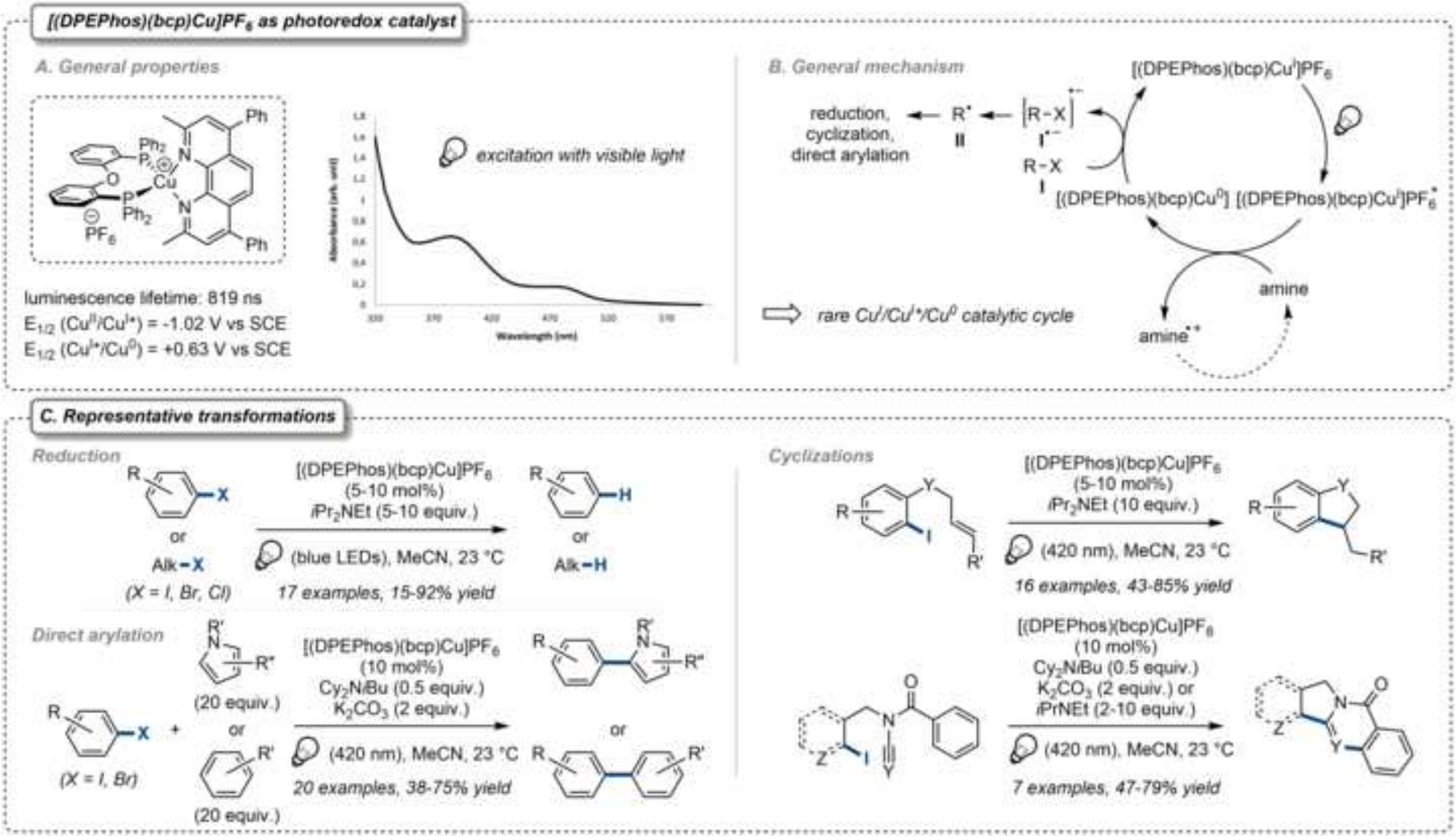

Figure 2

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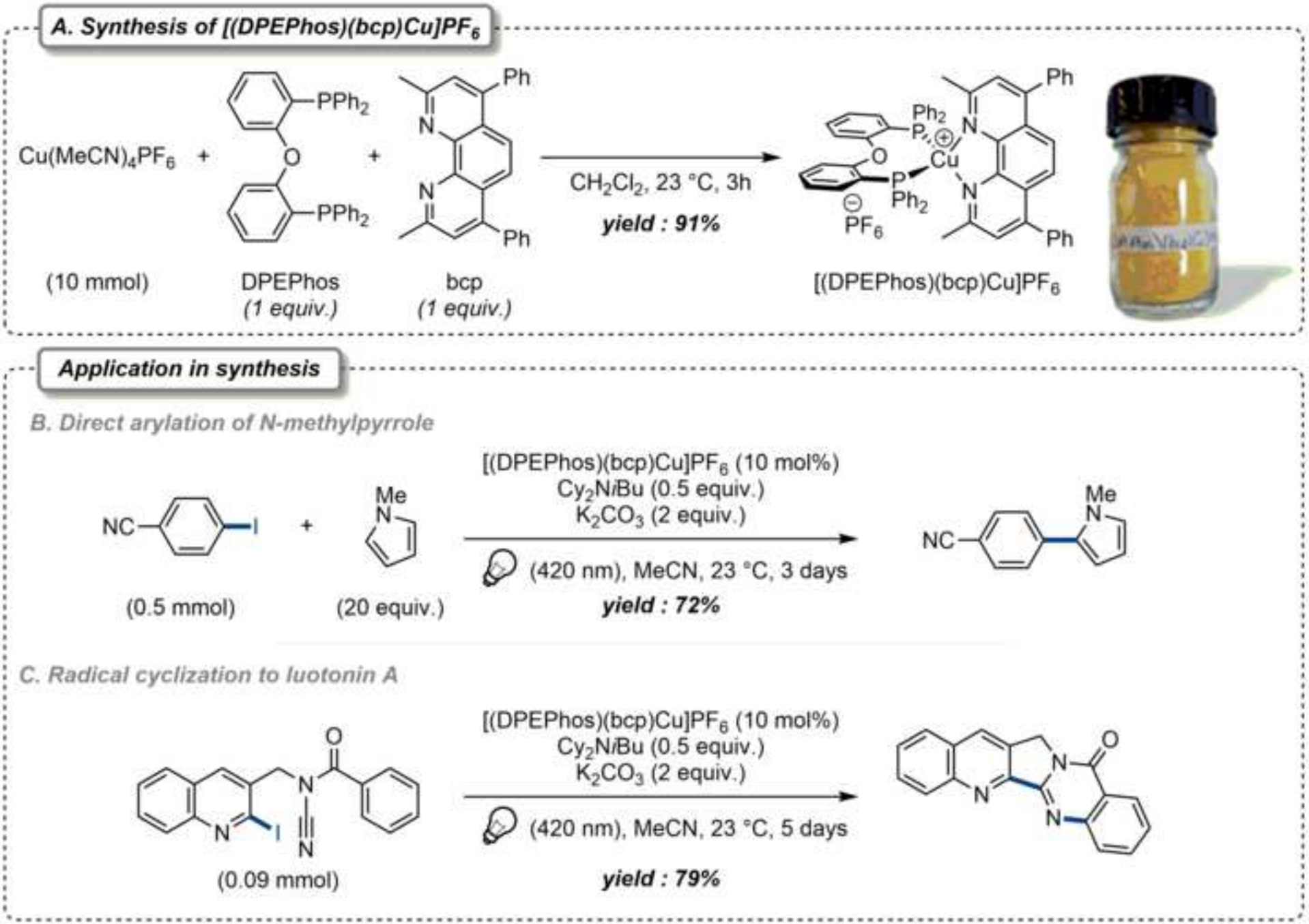

Figure 3

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Figure 4

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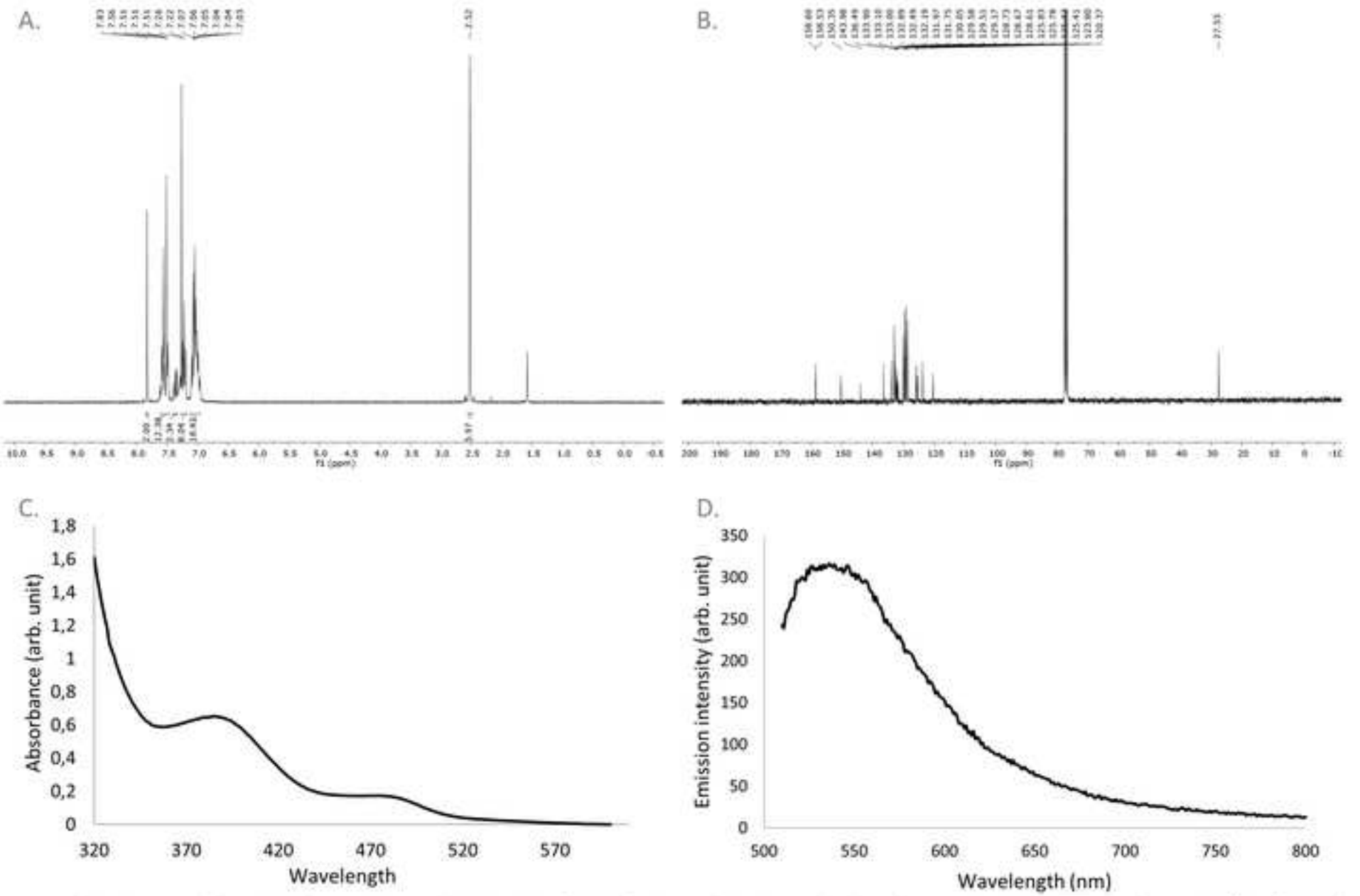

A and B. Recorded in $CDCl_3$ at 400 and 100 MHz (23 °C). C and D. Recorded under argon in acetonitrile at 10^{-4} M (23 °C).

Figure 5

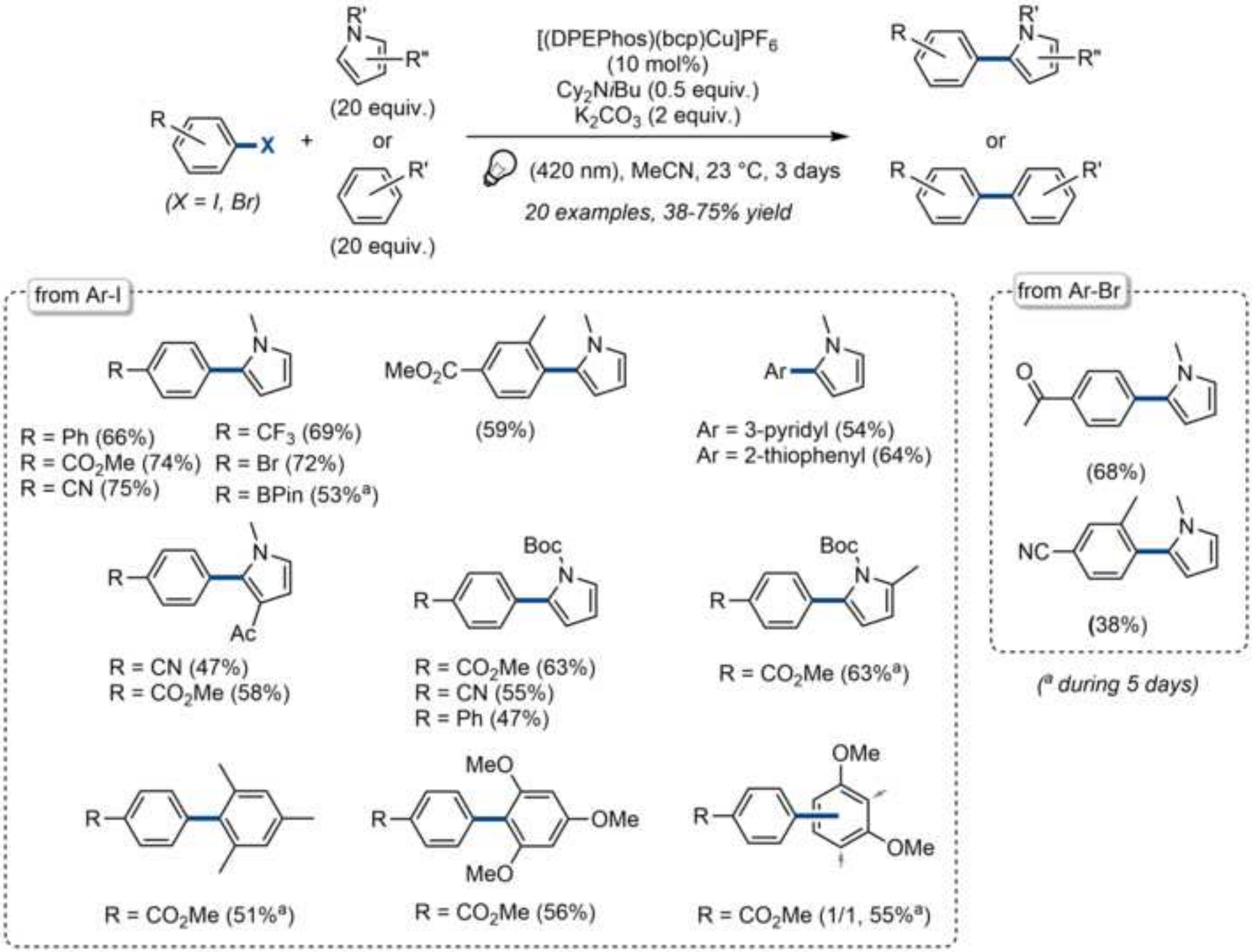

Figure 6

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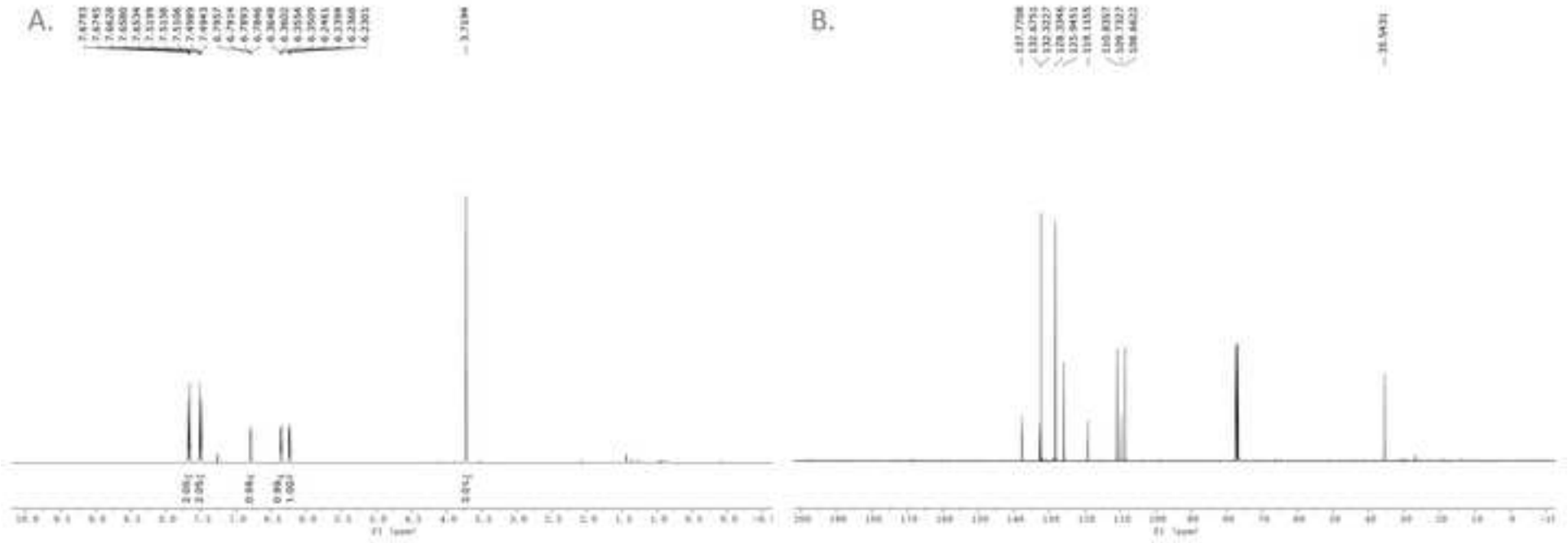
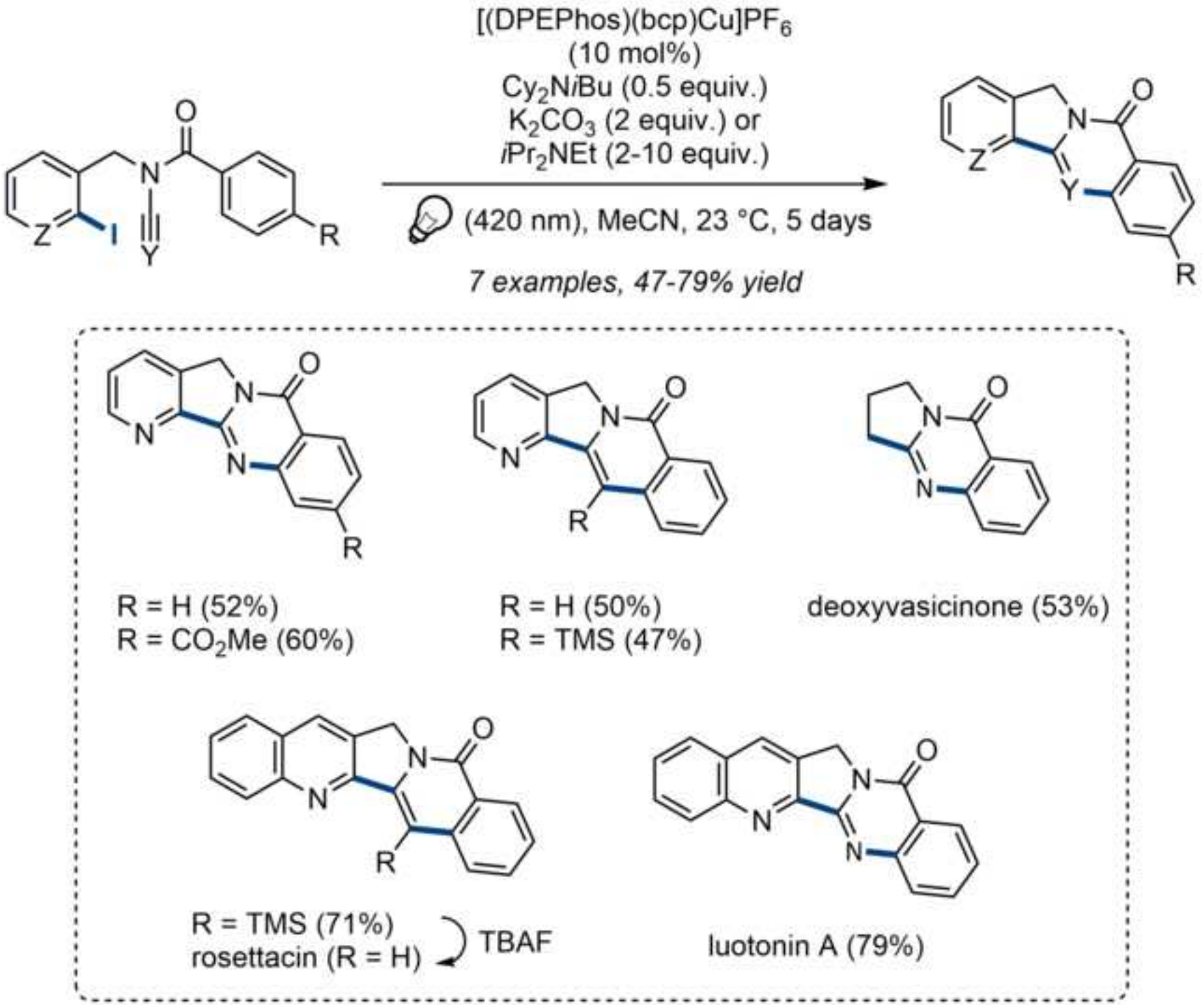


A and B. Recorded in $CDCl_3$ at 400 and 100 MHz (23 °C).

Figure 7



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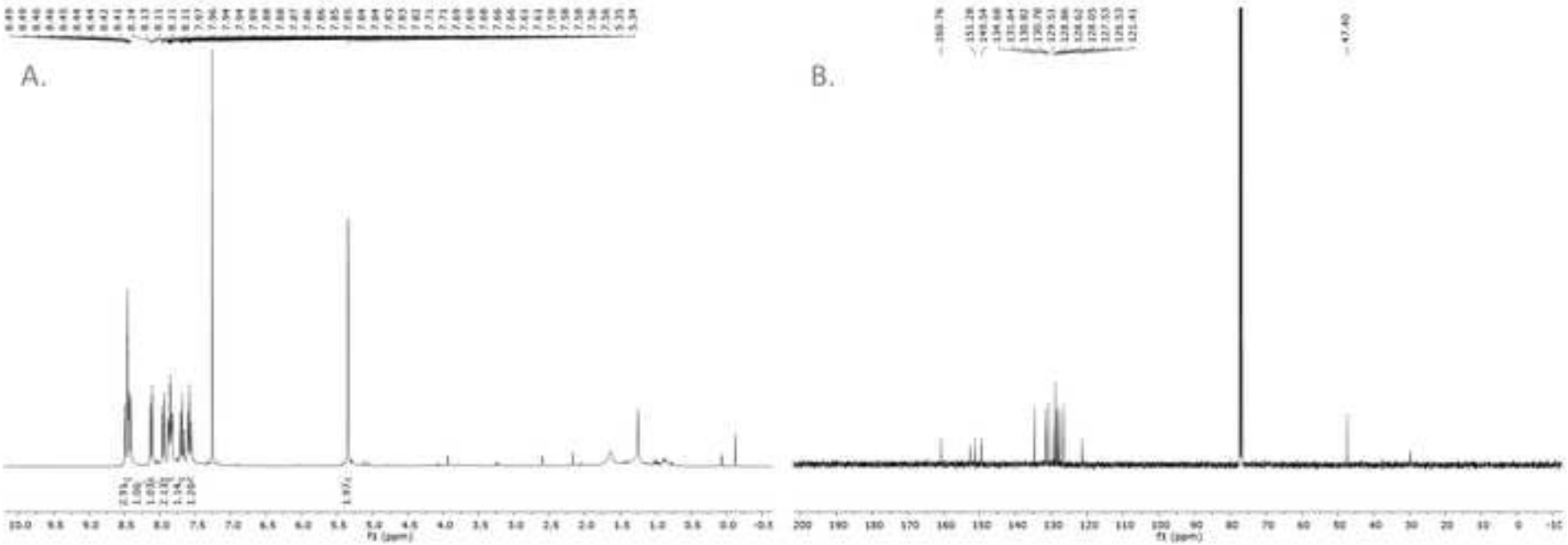

A and B. Recorded in $CDCl_3$ at 300 and 75 MHz (23 °C).

Name of Material/ Equipment	Company	Catalog Number	Comments/Description
Material			
Bathocuproine (bcp)	Acros	161340010	
Acetonitrile, 99.9+	Acros	326811000	
Celite 545	Acros	349670025	
Bis[(2-diphenylphosphino)phenyl] ether (DPEphos)	Acros	383370050	
Calcium hydride	Acros	C/1620/48	
Dichloromethane, 99.8%	Fisher Chemical	D/1852/25	
Dietyl ether, >= 99%	Fisher Chemical	D/2400/MS21	
Ethyl acetate	Fisher Chemical	E/0900/25	
N -Methylpyrrole, 99%	Sigma Aldrich	M78801	
4-Iodobenzonitrile, 98%	Combi-Blocks	OR-3151	
Petroleum ether (40-60 °)	Fisher Chemical	P/1760/25	
Potassium carbonate, anhydrous	Fisher Chemical	P/4120/60	
Tetrakisacetonitrile copper(I) hexafluorophosphate, 97%	Sigma Aldrich	346276	
Equipment			
^{1}H and ^{13}C NMR spectrometer	Bruker	Avance 300 Spectrometer	
^{1}H and ^{13}C NMR spectrometer	Varian	VNMRS 400 Spectrometer	
420 nm light tubes	Luzchem	LZC-420	

Blue LEDs lamp	Kessil	H150-Blue
Blue LEDs strips	Eglo	92065
Photochemistry Device	Hepatochem	HCK1006-01-016
PhotoRedOx Box		
Photoreactor	Luzchem	CCP-4V
Spectrofluorimeter	Shimadzu	RF-5301PC
UV/Vis spectrometer	Perkin Elmer	Lambda 40

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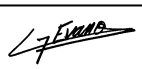
Signature:	
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Dr. Bing Wu
Review Editor
JoVE

Brussels, February 21 2019,

Dear Dr. Bing Wu,

Enclosed please find our revised manuscript entitled *"[(DPEPhos)(bcp)Cu]PF_6: A General and Broadly Applicable Copper-Based Photoredox Catalyst - Applications to the synthesis of small molecules and natural products"* that we are submitting for publication in *JoVE*.

According to the editorial comments, the following changes have been made:

EDITORIAL COMMENTS:

1. "Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues."
   - This has been done.
2. "Multiple references should be separated by commas, or a dash for inclusive number (example[2], [5] refers to references [2] and [5] while example[2-5] refers to references [2] through [5])."
   - This has been corrected.
3. "For each figure, please provide a title and a short description in Figure Legend after Representative Results. Please bold the title."
   - This has been corrected. Figures 4 and 7 do not require a short description.

Hoping that this revised manuscript will be suitable for publication in *JoVE*.

Yours sincerely,

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