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Insights on Bimetallic Micellar Nanocatalysis for Buchwald-Hartwig Aminations

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ABSTRACT: A nanocatalyst for micellar Buchwald-Hartwig aminations is developed, thoroughly characterized, and applied on a variety of substrates. The catalyst is stable under ambient conditions for at least six months. The catalyst retained its activity after several cycles, and its structure remained intact as confirmed by NMR spectroscopy. Association of Pd nanoparticles with Cu by a phosphine ligand is revealed by ³¹P NMR spectroscopy and their linkage with the activated carbon surface is revealed by XAS analysis. Control NMR experiments revealed the binding of the ligand with both the Cu and Pd, and all phosphine molecules are under the same environment. In addition to NMR and XAS analysis, the catalyst is characterized by SEM, HRTEM, XPS, and TGA. Reactions are highly reproducible at variable scales. Environmentally benign, proline-based amphiphile PS-750-M is critical for catalytic activity, which is achieved under mild conditions in water as the reaction medium. The inherent sustainability of these conditions coupled with a low E factor achievable through robust recycling of catalyst and reaction medium demonstrates the significant utility of this technology.

KEYWORDS. micellar catalysis, chemistry in water, cross-couplings, heterogeneous catalysis, E factor

Introduction. Aiming to replace highly toxic organic solvents, Kobayashi,¹ Lipshutz,² Uozomi,³ Krause,⁴ and our group^{5,6} have recently developed technologies that use water as a recyclable reaction medium. This aqueous chemistry works by harnessing the hydrophobic effect either "on water"7,8 or inside nanomicelles. Excellent work on the use of nanomicelles for C-H activation has very recently been reported by Ackermann and coworkers.9 Despite these advances, nano-organometallic catalysis in water is still at its infancy.¹⁰⁻¹² NP-mediated micellar Suzuki-Miyaura^{11,12} and Sonogashira¹³ couplings have been very well documented. The NP catalysts in these cases are more efficient and robust than their corresponding organometallic molecular complexes.¹⁴ Despite the high catalytic efficiency. better recyclability, broader scope, and potential benefit of the hydrophobic effect in these reactions, the NP-mediated micellar Buchwald-Hartwig amination reaction^{15,16} remains challenging. This challenge may be due to the association of the amine coupling partner with the NP surface, which interferes in the desired catalytic cycle and shuts down catalysis. Micelleenabled aminations using a molecular complex as the catalyst have been reported.17,18 These protocols suffer from poor catalyst recyclability and share a common requirement for (allyl)palladium (Pd). Recently, our group documented the role of allyl species in the catalytic cycle when a molecular organometallic complex was used as a catalyst for convenient sp²–sp³ couplings of nitroalkanes with aryl bromides.⁵ The role of the allyl group was as an ancillary ligand to tune the electronics for achieving the active catalytic species.¹⁹ However, translating the (allyl)Pd molecular complex to a NP catalyst may cause problematic side reactions with the allyl group. On the catalytically active NP, allyl fragments may participate in Heck coupling and polymerization side reactions due to the higher surface area and change in surface free energy. Therefore, (allyl)Pd may not be the right choice for the development of NP catalysts for C–N couplings. The requirement of (allyl)Pd for micellar aminations poses a difficulty to design a recyclable nanocatalyst that can work well in the aqueous micellar medium.



Figure 1. Synergy between Cu-Pd-C-micelle in water for sustainable C–N couplings.

A nanocatalyst that harnesses the synergy between Pd and another earth-abundant metal could potentially solve the issues mentioned above. Such synergy could exist when both the metals are in close proximity by sharing the same ligand while immobilized on a heterogeneous surface (Fig. 1). The heterogeneous surface or solid support must bind with the surfaces of both metals NPs to hold two metals nearby for optimal catalytic activity. The resulting catalyst must also have

 Table 1. Optimization study aiming to develop the desired supported NP catalyst^a



entry	deviations from standard conditions	3 (%) ^b
1	none ^c	85
2	no Pd	traces
3	no Cu	62
4	5 mol % FeCl ₃ instead of Cu	8
5	Ni(OAc) ₂ instead Cu	traces
6	CoCl ₂ instead Cu	traces
7	0.5 mol % Pd(OAc) ₂ instead 1 mol %	61
8	t-BuXPhos instead cBRIDP	20
9	XPhos instead cBRIDP	7
10	SPhos instead cBRIDP	12
11	chitin instead carbon	59
12	chitosan instead carbon	46
13	Fe ₂ O ₃ instead carbon	17
14	Cu(OTf) ₂ instead Cu(CH ₃ CN) ₄ PF ₆	19
15	CuI instead Cu(CH ₃ CN) ₄ PF ₆	77
16	K ₃ PO ₄ instead KOH	80
17	Et ₃ N instead KOH	40
18	<i>i</i> -PrNEt ₂ instead KOH	24
19	3.0 equiv KOH ^d	95
20	water instead PS-750-M, 3.0 equiv KOH ^d	20
21	THF instead PS-750-M, 3.0 equiv KOH ^d	78

^aAll reactions were performed on 0.25 mmol scale; ^bGCMS yields; ^cstandard conditions: [0.25 mmol **1**, 0.3 mmol **2**, 1 mol % Pd(OAc)₂, 2 mol % Cu(CH₃CN)₄PF₆, 3 mol % cBRIDP, 1 equiv. carbon, 4 equiv. KOH, 0.5 mL 3 wt % PS-750-M in H₂O, 60 °C, 12 h; ^a3.0 equiv KOH instead 4.0 equiv. For details, see Supporting Information, Section 2.

Results and Discussion. Aiming at the development of highly recyclable supported nanocatalysts that address many questions related to micellar catalysis and are general, convenient to synthesize, suitable for mild conditions, recyclable, and use water as the reaction medium, we report a supported Cu-Pd

nanocatalyst that displays a strong synergy between each component of the catalyst and with micelles of our engineered amphiphile PS-750-M. Optimization study revealed the dependence of nanocatalyst activity on the presence of Pd, Cu, cBRIDP as a ligand, PS-750-M as an amphiphile, and activated carbon as support (Table 1, also see Supporting Information, Tables S1-S3, S7). Admixing of 1 mol % Pd(OAc)₂, 2 mol % Cu(CH₃CN)₄PF₆, and 3 mol % cBRIDP in THF, followed by addition of 1.0 equiv. activated carbon particles and subsequent addition of an aqueous solution of PS-750-M spontaneously affords the NP catalyst, which can be used as such or isolated as solid material after removal of volatiles in vacuo. The isolated catalyst is highly stable for at least six months and retains the catalytic activity (see SI, page S10). Although the Cu-free NP catalyst was moderately active, no catalytic activity was observed in the absence of Pd in the NP catalyst (entries 2, 3). Poor catalytic activity was observed in the absence of amphiphile PS-750-M (entry 20). Conversion in neat water was only 20%, which is indicative of the importance of the amphiphile in catalytic activity. Replacing Cu from the standard nanocatalyst with other earth-abundant metals, such as Fe, Ni, and Co afford catalytically inactive NP (entries 4–6). Chitin, chitosan, and Fe₂O₃ were ineffective as supports, presumably due to the incompatible electronic environment (entries 11–13). Notably, Cu(CH₃CN)₄PF₆ was the most efficient Cu source (entries 14, 15). KOH was found to be the optimal base (entries 16-19). Optimal stoichiometry of aryl halide and amine coupling partners was 1:1.2 (see SI, Table S9). Reaction in neat water and THF was not as efficient as in aqueous PS-750-M (entries 20, 21).

Table 2. Substrate scope^a



^aConditions: ArBr (0.3 mmol), aryl amine (0.36 mmol), nanocatalyst (9 mg, 1 mol % based on Pd), KOH (0.9 mmol, 3.0 equiv), 3 wt % PS-750-M in H_2O (0.6 mL), 60 °C. All yields are isolated.

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After obtaining the desired nanocatalyst and establishing the optimal reaction conditions, substrate scope was then explored to find out whether the nanocatalyst is generally applicable on a variety of substrates or not. Many representative cases afforded good-to-excellent yields (Table 2). Both aryl amines and alkyl amines were well tolerated. Electron-deficient (5, 6, 14, 15, 19, 22, 24) as well as rich (7, 8, 10, 11-12, 19, 23) aryl bromides displayed excellent reactivity. Amine coupling partners where reactive nitrogen is either inside the aromatic ring (7, 14, 15, 18, 19, 22, 23, 25) or a substituent on the ring (3, 5, 8-10, 12, 13, 16, 17, 20) displayed good-to-excellent reactivity. A range of aromatic and heteroaromatic arrays in either coupling partner, containing both electron-rich as well as electron-deficient rings were well tolerated. Functionalities such as benzyl (17, 25), Boc (16), chloro (9, 14), fluoro (24), nitrile (15), and trifluoromethyl (5, 6, 17, 22, 24) can be found among these examples. Transformations were clean in the cases where the resulting product's structure is ligand-like (18, 19); there was no issue with these products, not strongly binding with the surface of the nanocatalyst to adversely affect the potential catalysis. Notably, with this technology, photocatalyst-like molecules (22, 23) can be conveniently obtained.20

Next, isolated nanoparticle catalyst was analyzed by SEM, TEM, XPS, and TGA analysis (Fig. 2 A–F). As illustrated in

Figure 2A, the catalyst has a clear association with the long chains of amphiphile PS-750-M, which caused a nest-like morphology of the material. HRTEM of the finely-ground material enabled detection of metal NPs that were 2.5 nm in diameter on average (Fig. 2B-D). XPS analysis revealed that the material is composed of significant amounts of carbon (82%), oxygen (16.6%), phosphorus (0.6%), Cu (0.5%), and Pd (0.15%) (see SI, Table S17). The high levels of oxygen are associated with residual THF and amphiphile integrated within these clusters; the C-O appears as a shoulder in the C1s spectrum (284.5 eV; see SI, Fig. S13.a). Remarkably, only 0.5% Cu (Cu(I) and Cu(II), 2p3/2 peak at 932.8 eV and 935.8, respectively; see SI, Fig. S13b) and 0.15% Pd (Pd 3d5/2, 3d3/2, 337.2 and 334.7 eV; Fig. 2E, also see SI, Fig. S13e) were found on the surface of the nanocatalyst, which was obtained from 2 mol % Cu(II) and ca. 1 mol % Pd(OAc)₂; this translates into only 110 ppm Pd and 340 ppm Cu present on the surface based on total weight. The oxidation states of Cu as +1 and +2 while Pd as in zero and +2 states were detected. Most likely, under catalytic reaction conditions, the +2 states of Cu and Pd are reduced to +1 and zero, respectively. TGA analysis of the nanocatalyst revealed that the catalyst is thermally stable up to 200 °C.



Figure 2. Catalyst characterization. (A) SEM analysis; (B, C) HRTEM analysis; (D) particle size distribution; (E) XPS analysis; (F) TGA analysis of nanocatalyst.



Figure 3. ³¹P NMR suggesting the association of phosphine with nanoparticle.

NMR experiments were performed to confirm the association of the phosphine ligand with both metals (Figure 3). Pd-bound cBRIDP displayed a strong deshielding, and its ³¹P signal was detected at 102.8 ppm. Cu-bound cBRIDP was found at 49.5 ppm in ³¹P NMR. A sample containing Pd, Cu, and cBRIDP in 1:2:3 ratio displayed two signals at 102.8 and 49.5 were indicative of ligation of both the Pd and Cu by cBRIDP. Mixing the activated carbon powder with the analyte containing Pd, Cu, and cBRIDP under the conditions where the nanocatalyst was formed, provided a new ³¹P signal at 69.6 ppm. The presence of a new signal was indicative of ligation of a *P*-atom to both the Pd and Cu.



Figure 4. ³¹P NMR predicting the association of amine with nanoparticle.

From the NMR study illustrated in Figure 3, it was clear that cBRIDP ligand binds with both the Cu and Pd via a lone pair of

phosphorus. Whether this type of association stays in the presence of aryl amine or not was still questionable. Therefore, control ³¹P NMR experiments of the nanocatalyst were conducted in the presence of stoichiometric as well as excess *p*-toluidine. A clear association of *p*-toluidine with the catalyst was observed when stochiometric *p*-toluidine (1:1 with respect to catalyst) was added to the catalyst. This association is likely to facilitate the transmetallation step of the catalytic cycle. As illustrated in Figure 4, the ³¹P NMR signal of a catalyst shifted from 69.6 to 59.1. This upfield shift was due to the binding of *p*-toluidine with the catalyst, no significant change in the NMR suggested the stability of a catalyst even in the presence of excess amine.

Cu K-edge and Pd K-edge XAS analyses were performed to further confirm the Cu-Pd interactions, the phosphine ligand, and carbon support. The results of the fitting of the Cu and Pd K-edge XAS spectra are summarized in Table 3.

 Table 3. Best fitting parameters for the Cu K edge and Pd

 K edge EXAFS spectra

Edge	Scattering path	Ν	R(Å)	$\sigma^2(\text{\AA}^2)$
Cu K	Cu-C/O/N	3.8	2.00	0.004
	Cu-P	0.4	2.31	0.005
Pd K	Pd-C/O/N	0.7	1.99	0.007
	Pd-P	0.3	2.31	0.006
	Pd-Pd	4.4	2.75	0.006

* Refinement uncertainties are estimated as: $N = \pm 10\%$,⁴⁹ R = ± 0.01 Å;²¹ σ^2 was held constant due to the high correlation with N. The value of σ^2 for Cu-C/N/O was iteratively refined and is in close agreement with previously reported Cu-O.²² σ^2 for Cu-P was set from the average refined value reported for various complexes.²² The value of Pd-C/N/O was iteratively refined and is in close agreement with that of reported Pd-O.^{23,24} σ^2 for Pd-P was set from the average reported for various complexes.^{25,26}

In the Cu K edge X-ray absorption near edge structure (XANES) spectra (Fig. 5A), the presence of a pre-edge peak at approximately 8982 eV suggested the presence of copper as Cu(I) with potentially a degree of Cu(II). The shifted nature of Cu(I) compared to a bulk Cu₂O has previously been noted in Cu-zeolite materials with a peak position at approximately 8982 eV.²⁷ These oxidation states were similar to that detected by XPS analysis (see SI, Fig. S13). Notably, due to the absence of suitable references for this system, linear combination fitting was not possible to determine the exact Cu(I):Cu(II) ratio.

EXAFS analysis revealed Cu-C and Cu-P interactions, the corresponding fitting to the $|\chi(R)|$ and the $R(\chi(R))$ are illustrated in Figure 5B. The coordination sphere around Cu was found to mainly consist of C/O/N with a refined coordination number of 3.8. A minor component of P was also found a low, i.e., 0.4. The coordination number suggested that not all Cu atoms bind to the phosphine ligand in a solid phase. The Cu-P contribution

to the fitting was considered significant from inspection of the Q space (Fig. 5C). The absence of any Cu-Cu contributions was indicative of the nature of Cu as isolated ions. Furthermore, no significant direct interaction of Pd and Cu was detected from the Cu K edge EXAFS analysis.

Pd K edge XANES suggested a mixture of oxidation states (Fig. 5D). A comparison between PdO and metallic Pd. The sample suggested a partial metallic structure and a small oxidized second component visible from the small shift in the Pd K edge position and increase in the white line intensity compared to metallic Pd. The FT of the EXAFS region was consistent with this interpretation with a small contribution between 1-2 Å

associated to a light scattering near neighbour around the Pd absorber (Fig. 5E). The large contribution between 2-3.5 Å was fitted with a Pd-Pd coordination number of 4.4 suggests the Pd as small nanoparticles. EXAFS analysis also revealed the Pd-C/O/N and Pd-P interactions. Although the refined coordination numbers were low, 0.7 and 0.3 respectively, their contribution was significant by inspection of the Q-space (Fig. 5F). The presence of a Pd-P interaction was also confirmed by NMR spectroscopy. No significant direct interaction of Pd and Cu was detected from the Pd K edge EXAFS analysis. Based and these results and NMR analysis, Cu and Pd may share the same ligand.



Figure 5. XAS analysis of nanocatalyst: (A) Cu XANES; (B) Cu EXAFS fitting to the FT EXAFS spectra; (C) Cu EXAFS fitting; (D) Pd XANES; (E) Pd EXAFS fitting to the FT EXAFS spectra; (F) Pd EXAFS fitting.

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Scheme 1. Comparative recycle study: molecular catalyst versus nanocatalyst.

Another aim behind the development of this nanotechnology was to attain high in-flask recyclability of catalyst as well as reaction medium, which has not been viable with molecular catalysts. Therefore, a comparative recycle study was performed under micellar conditions (Scheme 1). Notably, only a fraction of catalyst was recycled when the molecular catalyst was employed in the reactions as illustrated in Scheme 1. On the other hand, the nanocatalyst was highly recyclable along with reaction medium, and 3, 9, and 13 were obtained in excellent yields in each cycle.

Recycling of the nanocatalyst was also performed on gramscale reactions (Scheme 2A). A coupling between 26 and 27 affords clean adduct 6. Separation of 6 from the reaction mixture leaves the nanocatalyst in the aqueous phase. The recycled catalyst was as active as the fresh catalyst, as evidenced by a coupling between 1 and 2 mediated by the recycled catalyst. Notably, after the first reaction, the recycled catalyst was analyzed by ³¹P NMR spectroscopy before applying to the next reaction. The chemical shift of the recovered catalyst was exactly the same as for the fresh catalyst (Scheme 2B). No additional phosphorus signal was detected, which suggests no disintegration of catalyst. In each recycle, only coupling partners and KOH were added. In-flask recycling of catalyst and reaction medium was also performed to access the recyclability at small scale reactions; the catalyst displayed high recyclability as illustrated in Scheme 2C. However, reaction yield dropped in the 3rd and 4th recycles, which may be due to the loss of catalyst during work-up. Addition of extra copper in the recycled catalyst did not improve the efficiency of recycled catalysts (see SI, Section 10). A low E factor of 5.6, use of environmentally benign proline-based amphiphile PS-750-M in water as reaction medium, and high catalyst recyclability demonstrate the greenness of this technology.



To rule out the role of leached Pd or Cu in catalysis, an aqueous solution of PS-750-M containing base and the catalyst was stirred under reaction conditions. The aqueous solution was

filtered and subjected to the catalytic reaction between 26 and

. However, no desired product **6** was detected, which was indicative of no leaching of metal (Scheme 2D). Neither dehalogenation nor homocoupling side products were detected.

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It was still questionable whether the reaction rates with the recycle catalyst were the same as with fresh.²⁸ With micellar catalysis and the use of heterogenous catalyst, it is nearly impossible to accurately study the reaction kinetics, especially due to the quasi-homogeneous nature of the reaction mixture and the presence of a wide range of different sized micelles. However, we attempted to obtain the reaction kinetics by following a plan as described in the Scheme S10. As illustrated in Figure 6, reaction rate slightly decreased in each cycle, which may be either due to slight deactivation of catalyst or loss of catalyst during work-up in each cycle.



Figure 6. Valid assessment of catalyst stability: rate constant with recycled catalyst.

Control experiments were also conducted to verify the role of micelles. PS-750-M likely serves to keep the NPs intact and to accommodate the nanocatalyst and substrate in the optimal hydrophobic micellar interior. Notably, micelles of our PS-750-M amphiphile are designed to mimic DMF, DMSO, and 1,4dioxane. To further confirm the accommodation of substrate in the micellar core, dynamic light scattering (DLS) experiments were conducted at room temperature (Figure 7). The average diameter was increased to 535 nm when nanocatalyst was dispersed in the aqueous solution of PS-750-M, indicating the binding of the nanocatalyst with either interface or inner core of the micelles. On the other hand, the increase in diameter was more significant when bromonaphthalene was dissolved, i.e., 683 nm, which clearly indicates its accommodation inside the micellar core. The increase in size was larger in the case where bromonaphthalene and nanocatalyst were dissolved in surfactant solution, i.e., 1220 nm, clearly indicating the higher solubility of the coupling partner inside the micellar core and nanocatalyst at the interface. Thus, during the exchange process, the delivery of nanoparticle catalysts to the nanomicelles results in effective catalysis via the 'nano-tonano' effect.

Similar trends in the DLS study was observed when experiments were carried at 60 °C (see SI, Fig. S4). The particle size was generally larger at the elevated temperature, which may be due to the fast exchange process and merging of smaller particles. The average diameter of micelle increased to 1839 nm upon dissolution of 1-bromonaphthalene. The particle size further increased to 2466 nm upon dissolution of catalyst and 3628 nm upon dissolution of both the catalyst and 1bromonaphtalene. This increase in the micelle size was indicative of accommodation of both the coupling partners and the catalyst within the micelle at elevated temperature.



Figure 7. Dynamic light scattering (DLS) experiments.

The activity of the nanocatalyst was also accessed over Suzuki and Sonogashira couplings (Scheme 3). The nanocatalyst displayed excellent activity for both coupling types. Sonogashira coupling products from electron-rich (28, 29) and deficient (30) aryl halides were obtained in excellent yields. Activity for Suzuki couplings was accessed over challenging substrates, and excellent reactivity was observed with good isolated yields of 31 and 32. In these reactions, the nanocatalyst was also recyclable (see SI, Tables S13, S14).



Scheme 3. Broader application of nanocatalyst.

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Since high recyclability of the catalyst had been demonstrated, the probability of carrying over the metal content to product was expected to be minimal. This assumption was verified by ICP-MS analysis of products for trace amounts of Pd and Cu (Scheme 3C, also see SI, page S32) in crude product **18**. Virtually no Pd and Cu were detected in the product, which demonstrates the sustainability this nanotechnology.

Conclusions. In conclusion, an aqueous technology has been developed by harnessing the synergy between Pd and Cu on a suitable donor surface along with the hydrophobic effect exerted by the micelles of PS-750-M. The catalyst is recyclable, enables Buchwald-Hartwig aminations catalyzed by nanoparticles associated with the micelles of proline-based amphiphile. A broad substrate scope and diverse recycle study proved the effectiveness of the technology. Phosphine is bound with both the Cu and Pd, presumably bridged with both metals as suggested by ³¹P NMR and XAS analysis. Coordination of the carbon support with both Cu and Pd is responsible for high recyclability and optimal catalytic activity. Catalyst stability over an extended period is another excellent feature of this technology for its utility by broad users.

Experimental Method.

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XAS Analysis. Time-resolved XAS measurements at the Cu K edge (8979 eV) and Pd K edge (24350 eV) were performed at the Super XAS beamline of the SLS using the QEXAFS setup using a channel-cut Si(111) crystal monochromator.²⁹ The polychromatic X-ray beam from the 2.9 Tesla bending magnet was collimated by a Si-coated collimating mirror (for Cu) or a Pt-coated mirror (for Pd) at 2.5 mrad. Focusing was achieved by a toroidal mirror located after the monochromator yielding a beam size of 1mm by 0.2 mm at the sample position. A Pt coating of the toroidal mirror Pt was used for Pd K-edge measurements and a Rh coating for the Cu K-edge. Transmission geometry XAS spectra were collected using 15 cm ion chambers filled with 2 bar N for the Cu K edge and 2 bar N, 1 bar Ar at the Pd K edge. The data collection was performed with 1Hz repetition rate and averaged over a 10minute data acquisition period. Energy calibration was performed by consideration of the maximum derivative of Cu and Pd metal foils. The spectra were processed using Butterworth filtering for high frequency noise reduction and interpolation onto a constant energy grid by application of radial basis functions using an in-house developed software. Analysis of the EXAFS was undertaken using the Demeter software package.30

Catalytic Reactions with Isolated Catalyst. (Hetero)aryl bromide (0.3 mmol), (aryl)alkyl amine (0.36 mmol), nanocatalyst (9.0 mg), and KOH (50.4 mg, 0.9 mmol) were added into a 4-mL oven-dried reaction vial containing a PTFE-coated stirrer-bar. The reaction vial was closed with a rubber septum. The reaction vial was evacuated and back-filled with argon three times. A 0.6-mL volume of 3.0 wt % aqueous PS-750-M was added to the reaction mixture. The reaction mixture was purged with argon for 2 min. The reaction vial was heated at 60 °C.

After the complete consumption of starting material as monitored by TLC and GCMS, the mixture was cooled to room temperature. The septum was removed and 0.5 mL MTBE or EtOAc was added to the reaction mixture, which was then stirred for a minute at rt. Stirring was stopped and the organic layer was allowed to separate from the aqueous layer. The organic layer was removed by pipette. This extraction process was repeated an additional time. Combined organic layers were dried over anhydrous sodium sulfate and volatiles were removed under reduced pressure to obtain crude product. Crude product was further purified by flash chromatography over silica gel using EtOAc and hexanes as eluent.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Supporting Materials include materials and methods, optimization details, figures, tables, analytical data, and references (file type, i.e., PDF).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ^{*}These authors contributed equally.

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