

Photocatalytic Hydrogen-Evolution Cross-Couplings: Benzene C–H Amination and Hydroxylation

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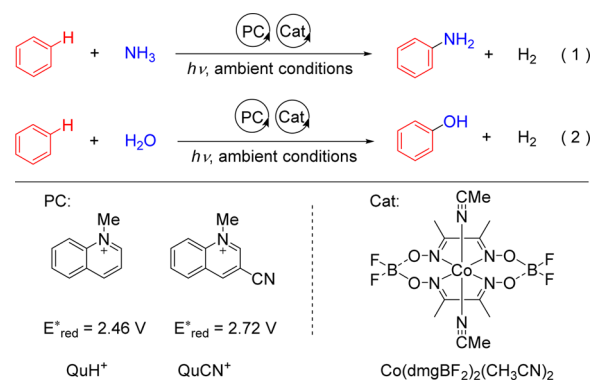
S Supporting Information

ABSTRACT: We present a blueprint for aromatic C–H functionalization via a combination of photocatalysis and cobalt catalysis and describe the utility of this strategy for benzene amination and hydroxylation. Without any sacrificial oxidant, we could use the dual catalyst system to produce aniline directly from benzene and ammonia, and phenol from benzene and water, both with evolution of hydrogen gas under unusually mild conditions in excellent yields and selectivities.

Aniline, phenol, and their derivatives are widely used intermediates in the manufacture of agrochemicals, pharmaceuticals, polymers, dyes and pigments, and optoelectronic materials. Aniline is produced in industry by hydrogenation of nitrobenzene, which is prepared by nitration of benzene with concentrated mixed acid.¹ Reducing the nitro group uses either Béchamp (with Fe/HCl as a reducing system)² or sulfide reduction (with H₂S or NaHS as a reducing agent)³ technology. These processes use stoichiometric reducing agents and create large amounts of environmentally toxic waste. Currently, phenol is produced in industry by the cumene process that involves three steps: propylation of benzene, autooxidation to cumene hydroperoxide, and Hock rearrangement.⁴ These reactions are carried out under high temperature, high pressure, and very acidic conditions. The overall yield of phenol from benzene is <5%. In recent years, one-step amination of benzene with ammonia, producing aniline,⁵ and one-step oxygenation of benzene to phenol^{6,7} by using various kinds of catalysts have been extensively studied. However, such processes are often carried out under severe conditions and afford very low yields and poor selectivities of aniline and phenol. Clearly, it is highly desirable to develop methods for amination and hydroxylation of benzene into aniline and phenol, respectively, that are economically feasible without toxic waste production and are performed with high chemoselectivity under mild conditions.

Herein we report two dream chemical reactions: one-step amination of benzene to aniline and one-step hydroxylation of benzene to phenol. As shown in Scheme 1, aniline was produced from the reaction of benzene with ammonia (reaction 1) and phenol from the reaction of benzene with water (reaction 2). An equivalent amount of hydrogen gas was the

Scheme 1. Photocatalytic Benzene C–H Amination and Hydroxylation with Hydrogen Evolution



sole byproduct in both reactions. These reactions were carried out under unusually mild conditions, and aniline and phenol were produced in excellent yields.

The above synthetic reactions show significant atom economy and step economy. These reactions can be regarded as improved dehydrogenative cross-coupling reactions with benzene as one partner and ammonia or water as another partner. During the past decade, the catalytic dehydrogenative cross-couplings between two C–H bonds and between one C–H bond and one heteroatom–hydrogen (X–H) bond, that build a C–C and a carbon–heteroatom (C–X) linkage, respectively, have become a potential synthetic strategy to synthesize various kinds of functional arenes.⁸ Compared with the conventional cross-couplings where aryl halides are usually used as one partner, such coupling reactions allow use of less functionalized reagents, thus reduce the number of steps to the target molecule and minimize waste production.⁹ However, although these reactions are termed as “dehydrogenative cross-coupling”, hydrogen gas is not usually the byproduct. Such reactions often involve the use of stoichiometric amounts of sacrificial oxidants such as peroxides, high-valent metals (Cu salts, Ag salts), and iodine(III) oxidants.⁹ This leads to low atom economy and possible generation of toxic wastes. Our approach, namely *hydrogen-evolution cross-couplings*, combines a

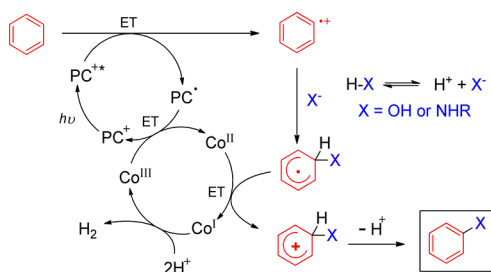
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photocatalyst with a metal cocatalyst to create a dual catalyst system.¹⁰ The former catalyst uses light energy as the driving force for the cross-coupling, while the later catalyst may capture electrons from the substrates and/or reaction intermediates to reduce the protons eliminated from the C–H and X–H bonds into molecular hydrogen.¹¹ Thus, without use of any sacrificial oxidant, the dual catalyst system may afford cross-coupling products and an equivalent amount of H₂ as sole byproduct. This kind of cross-coupling is particularly useful for the reactions that involve species sensitive to oxidation.

Our design is outlined in Scheme 2. Here, an onium is used as the photocatalyst (PC⁺). Upon excitation, the generated

Scheme 2. Proposed Pathway for Functionalization of Benzene

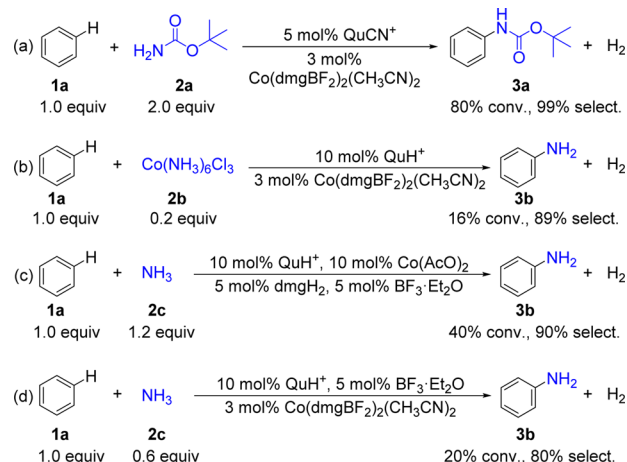


excited state(s) of photocatalyst (PC⁺*) may undergo single electron transfer from benzene to produce benzene radical cation and photocatalyst radical (PC^{*}). The later species may give an electron to the metal cocatalyst (for example, Co^{III}) to produce Co^{II} and ground state photocatalyst (PC⁺), thus completing the photocatalysis cycle. The former species reacts with an anionic nucleophile (X⁻) to give a dienyl radical. This adduct may transfer an electron to Co^{II} producing Co^I and dienyl cation, which upon deprotonating affords the desired substituted benzene. The Co^I may use the received two electrons in each catalyst turnover to reduce the two protons eliminated from X–H and benzene C–H into a molecule of H₂ and returns to Co^{III}, thus completing the cobalt catalysis cycle. The synergistic combination of photocatalysis and metal catalysis enables the direct installment of a functional group (X) in the place of a C–H bond of benzene and production of equivalent amount of H₂.

The crucial step for the initiation of the hydrogen-evolution cross-couplings is the electron transfer oxidation of benzene. The one-electron oxidation potential of benzene is high ($E_{\text{ox}} = 2.48$ V vs SCE in acetonitrile);¹² thus, the photocatalyst must have extremely strong oxidizing ability upon excitation. Several photocatalysts able to oxidize benzene have been reported, and we found that among them commercial available 1-methylquinolinium ion (QuH⁺) and 3-cyano-1-methylquinolinium ion (QuCN⁺) ($E_{\text{red}} = 2.46$ and 2.72 V vs SCE at excited state, respectively;^{7a} Scheme 1) performed well. On the other hand, Co(dmgBF₂)₂(CH₃CN)₂ (dmg = dimethylglyoximate, Scheme 1) was established to be an efficient catalyst for reduction of protons to H₂.¹³ Thus, in this work we select QuH⁺ClO₄⁻ or QuCN⁺ClO₄⁻ as the photocatalyst and Co(dmgBF₂)₂(CH₃CN)₂ as the metal cocatalyst for the amination and hydroxylation of benzene.

We began our investigation with the amination of benzene by using a Boc-protected ammonia (Boc-NH₂, 2a, Boc = *t*-butoxycarbonyl), an activated ammonia, as the amination reagent (Scheme 3a). The reaction conditions were optimized

Scheme 3. Photocatalytic Amination of Benzene^a



^aλ > 300 nm, in CH₃CN, ambient conditions. Selectivity = yield/conversion.

by irradiating the solution of benzene (1a, 40 mM), 2a (2 equiv), QuCN⁺ClO₄⁻ (5 mol%), and Co(dmgBF₂)₂(CH₃CN)₂ (3 mol%) in dry and degassed acetonitrile with a light of wavelength >300 nm at room temperature. The progress of the reaction was followed by ¹H NMR spectroscopy (Figure S1), and the reaction time profiles are shown in Figure S2. The amount of produced hydrogen was measured by GC analysis. Generally, after 5 h irradiation the conversion of benzene was ~80%. The yield of both Boc-protected aniline (3a) and hydrogen gas based on the consumption of benzene was close to 100%. Control experiments confirmed that the photocatalyst, cobalt catalyst, and light irradiation are necessary for the amination to occur. It was noted that solvent is critical for the amination reaction (Table S1). Use of methanol or *N,N*-dimethylformamide (DMF) as solvent resulted in no product formation. In contrast, use of the mixture of acetonitrile and dichloromethane as solvent gave comparable product yields as in acetonitrile in the same irradiation time. We suggest that in the solvents able to coordinate to the cobalt catalyst, the acetonitrile molecule(s) in Co(dmgBF₂)₂(CH₃CN)₂ complex might be replaced by the solvents (Figure S3), and the generated complexes are inactive for the catalysis of the proton reduction. Another possibility for the inhibition of the amination in methanol or DMF is that the excited state of the photocatalyst is quenched by the large amount of such solvents. The substrate scope of the amination with 2a was also examined. Carbonyl-substituted benzenes and phenyl halides could be smoothly aminated with high selectivities under the above conditions (Figure S4).

In the above photocatalytic reaction 3a is the sole amination product. Even at high conversion no further amination products (multiaminobenzene) were detected. When 3a instead of benzene was used as the starting material the photocatalytic reaction under the identical conditions could not occur after prolonged irradiation. One can expect that the photoinduced electron transfer from 3a to QuCN⁺ excited state should occur, because the oxidation peak potential of 3a is smaller than that of benzene (Figure S5). Indeed, 3a can quench the luminescence of QuCN⁺. Possibly, the pair of 3a cation radical and QuCN^{*} generated by the photoinduced electron transfer undergoes rapid back electron transfer to

return the starting material. Such a mechanism is well precedented.⁷

Boc-NH₂ serves as the amination reagent in the above reaction. Accordingly, an additional synthetic step was required to liberate the desired aniline, although such deprotection of the amine group can be easily pursued. Subsequently we carried out the amination of benzene directly using either ammonia or an ammonium salt as the amination reagents. We found that under the above optimized conditions direct use of ammonia as the amination reagent does not lead to the production of aniline. It has been well established that coordination of ammonia to a transition metal ion¹⁴ or to BF₃¹⁵ would decrease the strength of the N–H bonds of ammonia and cause a higher acidity of the protons. Therefore, such ammine–metal or ammine–BF₃ complexes might be able to aminate benzene. Thus, we first use hexaamminecobalt(III) chloride (**2b**) as an amination reagent (Scheme 3b, Table S2). Irradiation of the solution of benzene (10 mM), **2b** (0.2 equiv), QuH⁺ClO₄[−] (10 mol%), and Co(dmgBF₂)₂(CH₃CN)₂ (3 mol%) in 10 mL of acetonitrile for 10 h resulted in ~16% conversion of benzene, and the yield of aniline was ~89% based on the consumption of benzene. The unreacted benzene could be quantitatively recovered. We then explored whether a catalytic amount of cobaltous acetate can activate ammonia (**2c**) for the amination reaction (Scheme 3c). We prepared the solution of benzene (10 mM), ammonia (0.6 equiv), QuH⁺ (10 mol%), Co(AcO)₂ (10 mol%), dmgH₂ (5 mol%), and BF₃·Et₂O (5 mol%) in 10 mL of dry acetonitrile. We believe that the latter three components can produce Co(dmgBF₂)₂(CH₃CN)₂ with the solvent (see Supporting Information), and the excess of Co(AcO)₂ can form a complex with ammonia. The as-generated Co(dmgBF₂)₂(CH₃CN)₂ and the cobalt–ammonia complex¹⁴ can serve as the cocatalyst and amination reagent, respectively (Table S3). Irradiation of the above-prepared solution for 10 h led to 30% conversion of benzene. The yield of aniline was ~90%, and that of hydrogen was quantitative. We found that use of excess of ammonia led to low conversion, possibly due to the quenching of the excited QuH⁺ by ammonia. Indeed, addition of ammonia to the solution with six portions each of 0.2 equiv could improve the conversion of benzene to over 40% under identical conditions, and the selectivity of aniline and hydrogen remained unchanged. Subsequently, we use catalytic amount of BF₃ to activate ammonia (Scheme 3d). Irradiation of the solution of benzene (10 mM), ammonia (0.6 equiv), QuH⁺ (10 mol%), Co(dmgBF₂)₂(CH₃CN)₂ (3 mol%), and BF₃·Et₂O (5 mol%) in 10 mL of acetonitrile for 5 h led to ~20% conversion of benzene, and the yield of aniline based on the consumption of benzene was ~80%. The unreacted benzene was quantitatively recovered. Evidently, BF₃·Et₂O with ammonia formed complex BF₃·NH₃, thus ammonia was activated.

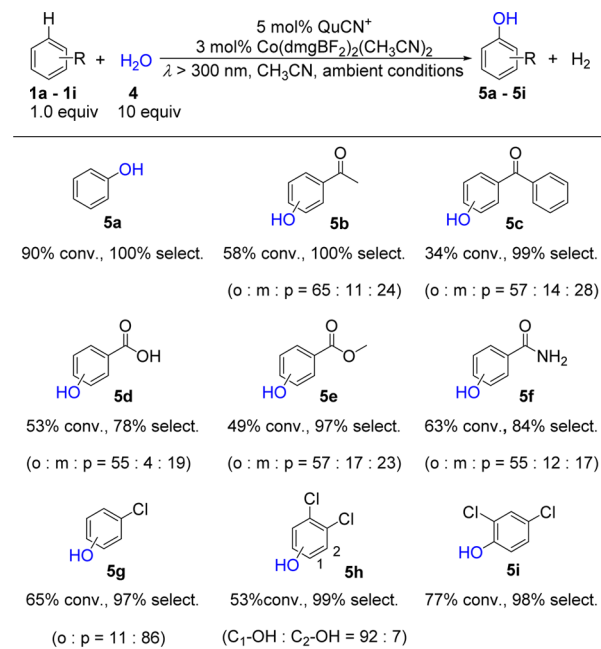
The dual catalyst system was successfully extended to the hydroxylation of benzene. Irradiation of the degassed solution of benzene (40 mM) and water (10 equiv) in acetonitrile with 5 mol% QuCN⁺ClO₄[−] as photocatalyst and 3 mol% Co(dmgBF₂)₂(CH₃CN)₂ as proton reduction catalyst for 5 h gave ~90% conversion of benzene, and the yields of phenol (**5a**) and hydrogen were >95% based on the consumption of benzene (Figure S6). To evaluate whether this catalyst system could be applied to large scale production of phenol, a preparative gram-scale photocatalytic reaction was also performed (see Supporting Information). After irradiation for 26 h, the isolated yield of phenol was 41%, and an equivalent amount of H₂ was

obtained. The remainder of the mass balance was attributed to unreacted benzene.

The origin of the hydroxyl group in phenol and molecular hydrogen was confirmed by the experiments using benzene-*d*₆ and D₂O or H₂¹⁸O as the starting materials (Figure S7). The solution of benzene-*d*₆, water, QuCN⁺ClO₄[−], and the cobalt catalyst in acetonitrile was irradiated. After the irradiation was completed, the sample was analyzed by GC-MS. A mass peak was observed at *m/z* = 99 (phenol-*d*₅) in the crude solution, and H₂/DH/D₂ in the gas phase was detected by GC. Similarly, H₂/DH/D₂ was also detected in the reaction of benzene and D₂O. On the other hand, after irradiation of the solution containing benzene, H₂¹⁸O, and the catalysts, the produced phenol showed a mass peak at *m/z* = 96 (Ph¹⁸OH). These observations unambiguously indicate that water serves as the source of O-atom in the produced phenol, and one proton in the hydrogen molecule comes from benzene the other proton from water. Fukuzumi and co-workers reported their excellent results on photocatalytic oxygenation of benzene to phenol in the presence of an oxidant.⁷ The O-atom in the product originates from the oxidant. Use water as the source of O-atom to oxidize alcohols to carboxylate salts and amines to amides by employing Ru pincer complexes as catalyst has also been recently reported.¹⁶ However, these reactions do not concern arene hydroxylation and amination and are not photocatalytic reactions. To our knowledge, our above work is the first report for the reaction of benzene with water producing phenol and hydrogen gas under mild conditions.

As in the photocatalytic amination, the produced phenol cannot undergo further photocatalytic reaction to yield dihydroxybenzene even at high conversion. This is in contrast to the cases of one-step oxygenation of benzene to phenol, where over-oxygenation occurs and the selectivity of phenol production is low. To confirm this observation we carried out the photocatalytic hydroxylation of phenol under the same conditions. Indeed, after prolonged irradiation the starting material was quantitatively recovered. Again, this selectivity might originate from the fact that the photoinduced pair of **5a** cation radical and QuCN[•] undergoes fast recombination to return to the starting material.⁷

Since 2-hydroxy aromatic ketones and halides are useful synthetic intermediates for the preparation of various oxygen-containing and halogen-containing heterocycles and key building blocks for certain drugs,¹⁷ we subsequently studied the photocatalytic hydroxylation of several carbonyl-substituted benzenes and phenyl halides by use of the above optimized reaction conditions. A variety of substituted benzenes such as phenyl ketones, benzoic acid, benzoate, benzamide, and halides (**1b–1i**) were transformed into the corresponding phenol products (Table 1). Generally after 5 h irradiation the conversion of substituted benzenes could reach to ~60%, and the yields of the substituted phenols and molecular hydrogen were excellent based on the consumption of the starting material. The hydroxylation products involve *ortho*, *meta*, and *para* isomers, and among them the *o*-hydroxylation products are dominated (55–65%) for phenyl ketones, benzoic acid, benzoate and benzamide, while for phenyl halides the *p*-hydroxylation products are preferably formed. For benzamide (**1f**), in addition to hydroxylation product **5f**, the amidation product (**5f'**, 14% selectivity; see Supporting Information) was also isolated. We have prepared the above samples but without photocatalyst QuCN⁺. Irradiation of such samples led to no conversion of the starting materials. This expelled the

Table 1. Scope of Photocatalytic Hydroxylation of Arenes^a

^aThe data in parentheses denote the ratio of the yields of *ortho*, *meta*, and *para* isomers of hydroxylation products.

possibility that the above reactions are initiated by direct excitation of the substrates. As aromatic ketones, acids, esters, amides, and halides are common scaffolds in drugs and natural products, this photocatalytic reaction can potentially open a facile route to rapid access of hydroxylated analogues of a broad range of substrates.

To summarize, we have developed a new type of reactions, namely hydrogen-evolution cross-coupling reactions, that combine a photocatalyst with a metal cocatalyst. By this strategy, in the absence of any oxidant, we successfully accomplished the amination and hydroxylation of benzene with ammonia (or Boc-protected amine) and water as a partner of the cross-couplings, respectively. These reactions were accompanied by liberation of hydrogen gas. The yields and selectivities of anilines and phenols were excellent, and the reactions were carried out under unusually mild conditions. We hope that this general method for combining activation of arene C–H bonds with proton reduction will result in the development of additional transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05498.

Synthetic details and spectral data, including Tables S1–S3 and Figures S1–S7 (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Downing, R. S.; Kunkeler, P. J.; van Bekkum, H. *Catal. Today* **1997**, *37*, 121.
- (2) Liu, Y.; Lu, Y.; Prashad, M.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 217.
- (3) Ratcliffe, C. T.; Soled, S. L.; Signorelli, A. J.; Mador, I. L. U.S. Patent 4,326,081, Apr 20, 1982.
- (4) Schmidt, R. J. *Appl. Catal., A* **2005**, *280*, 89.
- (5) (a) Del Pesco, T. W. U.S. Patent 4,001,260, Jan 4, 1977. (b) Del Pesco, T. W. U.S. Patent 4,031,106, Jun 21, 1977. (c) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science* **2015**, *349*, 1326. (d) Yuzawa, H.; Yoshida, H. *Chem. Commun.* **2009**, *46*, 8854.
- (6) (a) Niwa, S.-i.; Eswaramoorthy, M.; Nair, J.; Raj, A.; Itoh, N.; Shoji, H.; Namba, T.; Mizukami, F. *Science* **2002**, *295*, 105. (b) Morimoto, Y.; Bunno, S.; Fujieda, N.; Sugimoto, H.; Itoh, S. *J. Am. Chem. Soc.* **2015**, *137*, 5867.
- (7) (a) Ohkubo, K.; Kobayashi, T.; Fukuzumi, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 8652. (b) Ohkubo, K.; Fujimoto, A.; Fukuzumi, S. *J. Am. Chem. Soc.* **2013**, *135*, 5368.
- (8) (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (d) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048.
- (9) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780.
- (10) The successful merger of photocatalysis with metal catalysis or organocatalysis in organic synthesis has been developed by MacMillan, Doyle, and co-workers and Yoon and co-workers: (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (b) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. (c) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392.
- (11) Meng, Q.-Y.; Zhong, J.-J.; Liu, Q.; Gao, X.-W.; Zhang, H.-H.; Lei, T.; Li, Z.-J.; Feng, K.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 19052.
- (12) Merkel, P. B.; Luo, P.; Dinnocenzo, J. P.; Farid, S. *J. Org. Chem.* **2009**, *74*, 5163.
- (13) Xiang, M.; Meng, Q.-Y.; Li, J.-X.; Zheng, Y.-W.; Ye, C.; Li, Z.-J.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Chem. - Eur. J.* **2015**, *21*, 18080.
- (14) Eßmann, R. *J. Mol. Struct.* **1995**, *351*, 91.
- (15) (a) van der Vlugt, J. I. *Chem. Soc. Rev.* **2010**, *39*, 2302. (b) Bauschlicher, C. W., Jr.; Ricca, A. *Chem. Phys. Lett.* **1995**, *237*, 14.
- (16) (a) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (b) Khusnutdinova, J. R.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2014**, *136*, 2998.
- (17) (a) Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070. (b) Singh, P. P.; Thatikonda, T.; Kumar, K. A. A.; Sawant, S. D.; Singh, B.; Sharma, A. K.; Sharma, P. R.; Singh, D.; Vishwakarma, R. A. *J. Org. Chem.* **2012**, *77*, 5823.