Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700707

Link to VoR: http://dx.doi.org/10.1002/adsc.201700707

10.1002/adsc.201700707

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Selective C(sp^3)–H Monoarylation Catalyzed by a Covalently Cross-linked Reverse Micelle-Supported Palladium Catalyst

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. In this work, we illustrate the performance of a solvated micelle-supported ligand as a platform for coordination with palladium for C–H arylation. The micelle-supported ligand is one of the first applications of a micelle-supported ligand for C–H arylation, and provides a tunable support for future elaboration. The use of a spatially constrained system promoted selectivity trends influenced by both the sterics and electronics of the system, differing from the homogeneous catalyst, with high yields and selectivities.

Keywords: C – H activation; Micelle; Palladium catalysis; Supported catalyst; Monoarylation

Introduction

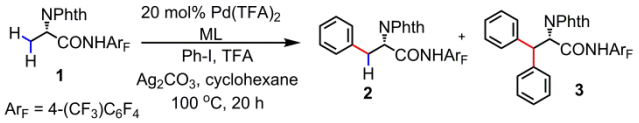
Development of methods for direct insertion into C–H bonds has attracted substantial attention over the past two decades due to the abundance of these bonds. Unfortunately, the typical C(sp^3)–H bond is highly inert and thermodynamically stable, requiring eloquent catalytic strategies to activate the bond compared to conventional C–H functionalization methods.[1,2] Transition-metal-catalyzed directed C–H activation has been extensively explored by installing powerful directing groups,[3-12] and the scope of the transformations can be further expanded through the incorporation of ligands into the catalysis.[13-22] Recent studies of specific ligand design for coordination with palladium have proved to be critical for C–H activation, and advantageously require less synthetic steps.[13] Tuning the coordination environments of palladium catalysts with various ligands has been used to selectively activate different types of C(sp^3)–H bonds.

One of the first examples of Pd(II)-catalyzed C(sp^3)–H arylation was reported in 2005, where pyridine acted as a directing group. Considering C(sp^3)–H arylation could be directed by a pyridine moiety, it was reasoned that bidentate coordination between the active palladium center and an aminoquinoline species would benefit the reaction specificity.[23] Later, the reaction was honed for specific monoarylation employing substituted aryl iodides not requiring steric bulk, such as a *tert*-butyl group, which allowed for further functionalization strategies. The Yu group employed a non-natural amino acid starting material with excess amounts of aryl iodides, and identified 2-picoline as a ligand for selective monoarylation using homogeneous palladium(II) trifluoroacetate.[13]

While homogeneous Pd catalysts have been widely used in C(sp^3)–H arylation, relatively high catalyst loadings are often required to obtain good yields in these C(sp^3)–H activation/C–C bond-forming reactions, since the catalysts are prone to decomposition under harsh reaction conditions. One way to enhance the turnover numbers (TONs) and better utilize the ligand and metal species is to

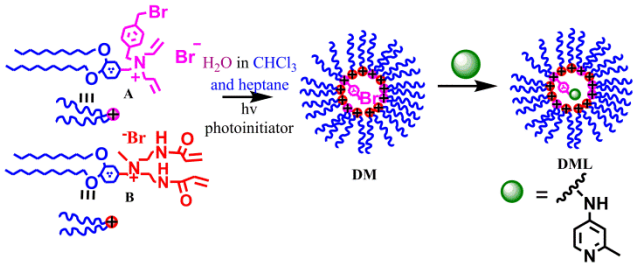
recover and recycle these components. However, in many cases, reuse of homogeneous transition metal catalysts remains a significant challenge. We have recently demonstrated the feasibility of reuse of Pd(II) combined with Yu's mono-dentate pyridine ligands and have shown that the catalyst, both ligand and metal, can be recovered and recycled, modestly improving the TON. Using soluble polymeric supports with tailorable structures, we also demonstrated that the supported Pd species could impart altered (relative to the homogeneous catalyst) selectivity trends using several model substrates.[24] Other types of supported catalysts have also been utilized in C–H activation, with use of metal organic framework (MOF) supported Pd,[25,26] and Pd-nanoparticles embedded in various supports[27,28] as examples. A particularly attractive support that has not yet been explored for Pd catalysts in C–H activation reactions is a micelle, which has classically been employed with both homogeneous and heterogeneous catalysts that can exploit this unique microenvironment,[29-31] but also can provide a very tunable and recoverable catalytic platform. Solvated micelles have been used as transition metal catalyst supports, for example coordinating palladium inside the micelle core for C–N bond formation and C–C bond formation; however, the use of a micelle for C–H activation has not been reported to this point.[32,33] In this work, we demonstrate the use of micelles as a reusable support for Pd-catalyzed C–H monoarylation reactions as an initial example, and subsequently a cross-linked, reverse micellar design with tunable spatial constraints around the supported ligands used to bind palladium that imparts selectivity by restricting the space around the metal-ligand complex. Previous reports have used ligand control for achieving monoarylation versus diarylation selectivity,[13] and the micelle support creates a well-defined catalytic nanoenvironment that can be reused with high selectivity.

Results and Discussion



Scheme 1. Pd-catalyzed C(sp^3)–H monoarylation.

The design of the catalytic micelle began with identification of key properties to tune, such as the alkyl density of surfactant tails,[34,35] size of the hydrophilic core,[34] and ligand functionalization within that core. After exploiting the hydrophilic head group and hydrophobic alkyl tail, the resulting micelles were interfacially cross-linked to provide thermal stability,[30] necessary for the Pd-catalyzed C(sp^3)–H monoarylation shown above (Scheme 1). In classic micelles, there is dynamic mixing of surfactant and internal contents of the core, whereas the cross-linked core of our micelles restricts the internal catalytic core and support from mixing contents, and helps retain the ligand and palladium for future reuse.



Scheme 2. General preparation of cross-linked micelle-supported ligand

As seen above in Scheme 2, polymerizable surfactant **B** with functionalizable double-tail surfactant **A** , or (not pictured) a functionalizable triple tail analogue were dissolved in a 1:5 ratio of **A:B**. This ratio allows the surfactants to cross-link on their own, rather than add any additional crosslinker, and ensures surfactant **A** and **B** polymerize together, limiting the self-polymerization of surfactant **B**, which would occur if the ratio were larger. Surfactant **A** was designed and synthesized to contain a benzyl bromide functional handle within the core for further substitution with 4-amino 2-methylpyridine used as the ligand in the C(sp^3)–H monoarylation. The micelles then self-assembled in H_2O and heptane, and were cross-linked using a photoinitiator at 365 nm to create DM, the double-tail micelle. The functionalizable benzyl bromide was substituted with amine containing ligand moieties to form the double-tail micelle with ligand (DML) and further coordinated in situ with a palladium precursor to yield the precatalyst. Next, optimization of the reaction conditions with various amounts of DML (Table S1), palladium, and aryl iodide was completed (Table S2).

The first generation of the cross-linked micelle provided a tunable platform for catalyst design, and the first example of micelle-supported Pd(II)-catalyzed C(sp^3)–H monoarylation. The initial tunable property of the micelle explored was the surfactant-alkyl density of surfactant **B**. The alkyl density played a significant role in the catalytic activity of the micelle,[35] altering the number of hydrophobic tails covalently bound to a hydrophilic head group between two and three. The second property of the micelle to be evaluated was the size of the catalytic core. In the synthesis of the catalytic micelle, various amounts of water were introduced in the first step of Scheme 2 to vary the size of the micelle core, known as W_0. The combination of assorted W_0 values paired with different numbers of alkyl hydrophobic tails potentially allows for size selectivity as well as creation of a diffusive barrier for substrates and products.

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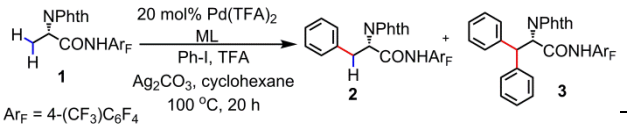
Table 1. Micelle-supported ligands with various W_0 and micelle shell in Pd-catalyzed C(sp^3)–H arylation[a,b]



Ar$_F$ = 4-(CF$_3$)C$_6$F$_4$

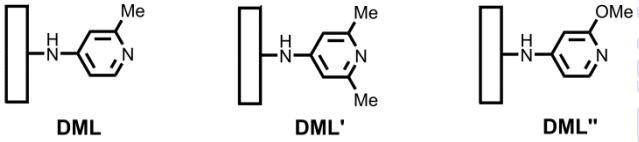
Entry	Micelle-Ligand	W_0	Yield (%)[b]	**2**:**3**[b]	Selectivity (%)[b]
1	DML	0	20	20:0	100
2	DML	2	24	24:0	100
3	DML	5	99	83:17	83
4	DML	10	76	66:10	87
5	TML	2	24	24:0	100
6	TML	5	55	51:4	93
7	TML	10	52	49:3	94
8	TML (48h)	10	65	61:4	94

[a] Reaction conditions: substrate (0.05 mmol), Pd(TFA)$_2$ [palladium(II) trifluoroacetate] (0.01 mmol), DML/TML (10 mg), Ag_2CO_3 (0.075 mmol), TFA (0.01 mmol), iodobenzene (0.15 mmol), and cyclohexane (0.3 mL) were added. The reaction vessel was sealed and the mixture was stirred at room temperature for 10 min and then heated to 100 °C for 20 h with vigorous stirring. [b] The yield percentage and ratios of **2** and **3** were determined by ^{1}H NMR using CH_2Br_2 as the internal standard.

Table 1 displays the catalytic results highlighting the optimized micelle shell and core structure, which is comprised of a 1:5 ratio of surfactant **A** and **B** with differing core diameters, denoted W_0. The double tail micelle supported ligand (DML) maintained the proper amphiphilic characteristics to form the initial dynamic micelle in solution, and further provided a stable reverse cross-linked micelle. Entries 1, 2, and 5 all had small W_0, and corresponding low yields of monoarylated product **2**. A larger core, with W_0 = 5 or 10, appeared to allow for an increase in conversion of starting material, displaying the necessity for a core large enough to accommodate starting materials and product. There was not a large difference in selectivity with core sizes 5 or larger, which was unexpected. We anticipated with the larger core, product **2** would have the opportunity to interact with the palladium catalyst and convert to the diarylated product **3** more readily; however, this was not observed.

The triple tail micelle supported ligand (TML) displayed lower yields across various W_0, with a higher selectivity. Unfortunately, TML W_0 = 10 with extended reaction time did not display significantly increased yield. This may be associated with the thick hydrophobic shell the TML possessed, while increased yield was demonstrated with the DML. The thick shell imparted a restriction on transport properties of substrates into the core, highlighted with the extended reaction time needed to allow for diffusion into the core (Table 1 below, entries 7 and 8), but no appreciable increased yield was observed after 48 hours. The DML hydrophobic shell is less crowded, with double tails compared to triple, and therefore we hypothesize it presented a more penetrable barrier to the active micelle core. After the examination of both the micelle core size and hydrophobicity of the micelle shell, the DML micelle with W_0 = 5 was carried through for further exploration in the C(sp^3)–H monoarylation.

Table 2. Micelles with various pyridine-based ligands in Pd-catalyzed C(sp^3)–H arylation[a,b]



Entry	Micelle-Ligand	W_0	Yield (%)[b]	**2**:**3**[b]	Selectivity (%)[b]
1	DML	5	99	83:17	83
2	DML'	5	55	50:5	91
3	DML'(48h)	5	73	64:9	88
4	DML''	5	26	26:0	100

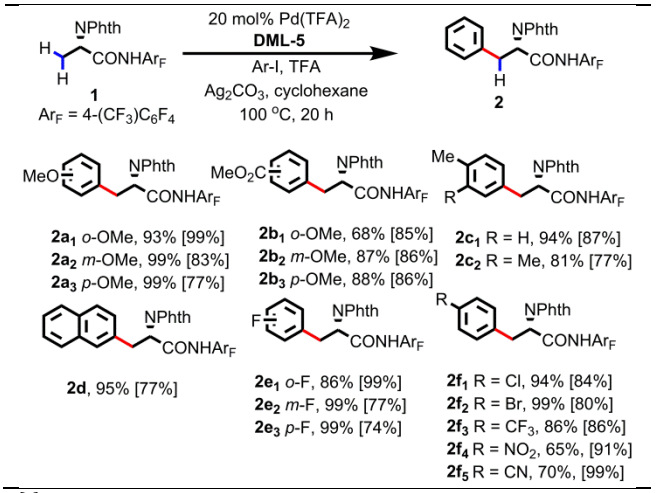
[a] Reaction conditions: substrate (0.05 mmol), Pd(TFA)$_2$ [palladium(II) trifluororacetate] (0.01 mmol), DML/DML'/DML'' (10 mg), Ag_2CO_3 (0.075 mmol), TFA (0.01 mmol), iodobenzene (0.15 mmol), and cyclohexane (0.3 mL) were added. The reaction vessel was sealed and the mixture was stirred at room temperature for 10 min and then heated to 100 °C for 20 h with vigorous stirring. [b] The yield percentage and ratios of **2** and **3** were determined by ^{1}H NMR using CH_2Br_2 as the internal standard.

In previous studies, the ligand in DML (Table 2) was used to carry out the C(sp^3)–H arylation homogeneously,[13] and selectivity trends for product **2** relative to **3** were also studied with a linear polymer supported ligand, which provided a platform for improvement.[24] The DML micelle with W_0 = 5 produced a selectivity of 83% for the monoarylated product after 20 h; however, incorporation of a different ligand in the micelle core could further improve the selectivity. Ligand DML' was chosen because of its similar electronic structure to the original ligand DML, but also providing added steric constraints inside the core. With a slightly bulkier ligand in the core, we hypothesized this would help force the newly formed product **2** out of the core, leading to increased selectivity for monoarylation. As has been seen with previous reports,[13] the activity for C(sp^3)–H monoarylation is highly sensitive to the ligand, and decreased yield of product **2** was observed with the sterically more hindered ligand DML'.

DML'' was also selected to probe the effect of different electronics around the pyridine ligand, incorporating a strong electron donating group *ortho*- to the pyridine nitrogen, while maintaining a similar steric influence to DML. The additional electron density in DML'' dramatically reduced yield, and correspondingly high selectivity was observed. In contrast to the homogeneous case, the incorporation of all ligand cases did not increase the amount of diarylated product **3**,[13] supporting the benefit of a spatially constrained catalytic pocket for improved selectivity by elimination of bulkier products. To this end, it appears the micelle core provided a valuable steric limitation for the prevention of the formation of the diarylated product. Previously, an optimal balance of sterics and electronics for the ligand-controlled C(sp^3)–H arylation was demonstrated through the evaluation of multiple ligands, varying both sterics or electronics.[13,15,36,37] This particular C(sp^3)–H arylation was exceptionally sensitive to the ligand present, as seen in the homogeneous case, so the decreased yield for non-optimal ligands was not entirely unexpected.[13,24]

Having identified a suitable micelle catalyst structure with (i) two alkyl tails and a core size large enough to accommodate both starting material and product, and (ii) the proper ligand to promote monoarylation, which produced encouraging activity with the model substrate, further investigation of substrate substituent effects was conducted. The catalytic micelle showed excellent activity and selectivity with both electron donating and withdrawing substituents present on the iodobenzene partner at the *ortho*-, *meta*-, and *para*-positions, as presented below in Table 3.

Table 3. Substrate scope of the Pd-catalyzed C(sp^3)–H arylation using DML-5[a,b]

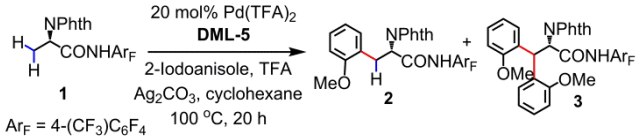


[a] Reaction conditions: substrate (0.05 mmol) $Pd(TFA)_2$ [palladium(II) trifluoroacetate] (0.01 mmol), DML-5 (10 mg), Ag_2CO_3 (0.075 mmol), TFA (0.01 mmol), iodobenzene (0.15 mmol), and cyclohexane (0.3 mL) were added. The reaction vessel was sealed and the mixture was stirred at room temperature for 10 min and then heated to 100 °C for 20 h with vigorous stirring. [b] The yield percentage and seelctivities of **2** and **3** in brackets were determined by ^1H NMR using CH_2Br_2 as the internal standard.

The monoarylation proceeded in high yields and selectivities for both electron-withdrawing and electron-donating substituents on the aryl iodide with the micelle-supported ligand and palladium.[38] The selectivity can be highlighted in products **2a$_1$** and **2e$_1$** (as seen in Table 3). These two coupling partners have second substitutions *ortho*- to the active iodo group, imparting an increase in selectivity. Notably, the same selectivity is not seen with the *para*-substituted compounds **2a$_3$** and **2e$_3$** that are electronically similar. Interestingly, this selectivity pattern has not been observed with other Pd-catalyzed monoarylation reactions; in fact, conversely, the yield is typically decreased with *ortho*- substitutions due to steric hindrance.[39] Both **2a$_3$** and **2e$_3$** had excellent yields of 99% and similarly decreased selectivities of 77 and 74%. The high reactivity of both the *para*- and *meta*-substituted aryl iodides contributed to the decreased selectivity toward monoarylation. This selectivity at the *ortho*-position is hypothesized to be an electronically-influenced steric effect within the micelle core. A previously reported heterogeneous polymer support[24] incorporated a polar, hydrogen-bonding amide backbone to increase the concentration of polar substrates in the nonpolar solvent, and we can extrapolate similar activity trends within the polar, cross-linked micelle core. The reduced freedom of movement for the ligands within the micelle core is hypothesized to create an active catalytic pocket, filled with potential hydrogen-bonding partners. Hypothesized within the active pocket, the coordinated palladium complex is sterically encouraged to interact with the starting materials and coupling partners. The substrates that participate in hydrogen-bonding within the core, such as **2a** and **2e**, have increased selectivity for *ortho*-substituted aryl halides, presumably due to hydrogen-bonding capability near the active substitution, drawing the starting material toward the Pd active site. These substitutions are electronically favored at the *ortho*-/*para*-positions because of the electron donating behavior of the methoxy, as well as slight electron withdrawing but *ortho*-/*para*- activation for the fluoro-substituted starting material, such that we speculate facilitation of reactivity near the active site of substitution. Alternatively hypothesized, the micelle core concentration is high and the *ortho*- substitution encumber the

stacking of molecules more so compared to the *para*- substituted aryl iodides, thus accommodating the smaller space and increased diarylated product. Similar activity is not observed for **2b** compounds, because the carbonyl group can weakly coordinate to Pd(II), which promotes the second C–H insertion to give more diarylated product. Therefore, similar selectivity trends are not seen with methyl ester aryl iodides. Generally, stronger electron-withdrawing functionality added to the substrate decreased the yield slightly; however the selectivity remains high, as seen in compound **2f**. This tolerance for many functional handles on the starting materials, paired with excellent yields, has the potential to be exploited in the future with C–H activation. Overall, this micelle-supported palladium catalyst showed high tolerance for both electron withdrawing and donating groups, as well as selectivity toward monoarylated products in all cases.[40]

Table 4. Recycling DML-5 in Pd-catalyzed C(sp^3)–H arylation [a,b,c]



Entry	Micelle	$Pd(TFA)_2$ (mol%)	Yield (%)[b]	Selectivity (%)[b]
1	DM-5	20	68	>99
2	DML-5	0	N.R.[c]	N.D.[d]
3	DML-5	20	93	>99
	Recycled			
4	DML-5 from entry 3	0	11	>99
	Recycled			
5	DML-5 from entry 3	20	77	>99
	Recycled			
6	DML-5 from entry 4	0	N.R.	N.D.
	Recycled			
7	DML-5 from entry 5	20	52	>99

[a] Reaction conditions: substrate (0.4 mmol) $Pd(TFA)_2$ [palladium(II) trifluoroacetate] (0.08 mmol), DML-5 (80 mg), Ag_2CO_3 (0.6 mmol), TFA (0.08 mmol), 2-iodoanisole (1.2 mmol), and cyclohexane (2.4 mL) were added. The reaction vessel was sealed and the mixture was stirred at room temperature for 10 min and then heated to 100 °C for 20 h with vigorous stirring. [b] The yield percentage and selectivity in brackets were determined by ^{1}H NMR using CH_2Br_2 as the internal standard. [c] NR = no reaction. [d] ND = not determined.

Realizing the micelle-supported Pd has a high compatibility and selectivity with multiple functional handles similar to the homogeneous reaction, recycled micelle was explored for catalytic activity as one way to enhance the total TON. The micelle-support alone (without added ligand L), showed activity, reaching 68% yield of monoarylated product, which is expected due to the potential for Pd coordination with the amide groups of the cross-linked core. Next, the micelle with immobilized ligand (DML-5) was run under standard reaction conditions (Table 4, entry 3), and subsequently recycled as seen in Table 4, entries 5 and 7. The micelle catalyst was successfully reused from ^{1}H NMR (Figure S5) in its as-recovered form, as well as with fresh palladium added, which yielded dramatically different results. Recycled micelle with no added palladium showed drastically reduced activity, producing 11 % of product **2**, while with fresh Pd added it yielded 77% (Table 4, entries 4 and 5). This demonstrated that the supported ligand was successfully recycled, albeit not robustly after multiple runs (Table 4, entries 6 and 7). Elemental analysis of the recycled micelle (Table S5) showed residual palladium, and the UV/vis spectrum of used DML-5 has characteristics of both the micelle and palladium present[30] (Figure S1), but only at a 1.5 mol% loading, which explains its very low productivity in its as-recovered form. Also from elemental analysis (Table S5), there was a decrease in nitrogen content over multiple cycles, which was likely due to the displacement of the initial bromide counter ions in the amide cross-linked core with free iodide ions from excess aryl iodide in solution, causing the micelle core to become more crowded with larger counter ions present. The recycle of the micelle demonstrates the ability to reuse the ligand, without the metal, which is not unexpected with a weakly coordinated monodentate ligand and fixed micelle core. For entry 5 in Table 4, there is a notable decrease of yield, giving similar performance to entry 1 in Table 4. A possible explanation for this observation is the spatial constraints and limited mobility of the ligand within the micelle core could reduce the capability for bidentate coordination of Pd with two ligands, thus forcing the Pd to coordinate weakly with the amide cross-linkages, thereby reducing the probability for metal recycle. Another possible explanation is that the monodentate ligand allows for coordination of other species in reaction solution with the ligand, and as the reaction progresses and starting materials are consumed, other reactants take the place of the previously coordinated starting material or metal.[41]

Conclusions

The present work demonstrated a micelle-supported ligand used for Pd-catalyzed C(sp^3)–H monoarylation. The micelle was designed and synthesized with tunable properties that can be further enhanced for future use with C–H activation, as well as other reactions that benefit

from spatial constraints of a catalytic pocket. Specifically, one can imagine creation of active pockets with multiple functional sites operating congruently. The micelle-supported ligand imparted a selectivity unseen by previous polymer-supported Pd-catalyzed C(sp^3)–H arylation reactions, and was reused a second time. Enhanced recyclability is expected using systems that exploit multidentate ligands, reducing loss of metal from the designed microenvironments.

Experimental Section

General preparation of cross-linked micelle (DM)

Water (5.7 μL, 0.30 mmol) was added to solution of surfactant **A** (10.3 mg, 0.012 mmol) and surfactant **B** (50.0 mg, 0.06 mmol) in heptane (3.0 mL) and $CHCl_3$ (0.1 mL). The mixture was hand shaken and sonicated at room temperature to give an optically clear solution. After addition of 2,2-Dimethoxy-2-phenylacetophenone (5 mol%), the mixture was irradiated in a Rayonet photoreactor for ca. 12 h until most alkenic protons in surfactants were consumed. The organic solvents were removed by rotary evaporation and the residue was washed by chilled methanol to give a yellowish power (52 mg) (Scheme S4).

General immobilization of ligand in cross-linked micelle (DML)

4-Amino-2-methylpyridine (14 mg) was added into micelle (100 mg) solution in $CHCl_3$ and stirred at 50 ^{0}C for 48 h. The organic solvent was removed in *vacuo*, and the residue was washed by cold methanol to remove unreacted 4-amino-2-methylpyridine. The final light brown powder will be obtained by drying under vacuum (Scheme S5).

General arylation procedure

Substrate (0.05 mmol), $Pd(TFA)_2$ (0.01 mmol), ligand (0.02 mmol), and Ag_2CO_3 (0.075 mmol) were weighed out open to air and placed in a pressure tube (5 mL) with a magnetic stir bar. The aryl iodide (0.15 mmol), TFA (0.01 mmol), and solvent (0.3 mL) were added. The reaction vessel was sealed and the mixture was first stirred at room temperature for 10 min and then heated to 100 °C for 20 h with vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. All yields were determined by analysis of the crude ^{1}H NMR ($CDCl_3$) spectrum using CH_2Br_2 as the internal standard after filtration of the reaction mixture through a pad of silica gel.

General micelle recycling procedure

Substrate (0.4 mmol), $Pd(TFA)_2$ (0.08 mmol), ligand (0.16 mmol), and Ag_2CO_3 (0.6 mmol) were weighed out open to air and placed in a pressure tube (5 mL) with a magnetic stir bar. The aryl iodide (1.2 mmol), TFA (0.08 mmol), and solvent (2.4 mL) were added. The reaction vessel was sealed and the mixture was first stirred at room temperature for 10 min and then heated to 100 °C for 20 h with vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. Reaction mixture is then filtered through a pad of silica gel with ethyl acetate, and chloroform to filter AgI and Ag_2CO_3 solid species from solution, while the micelle and products passed through. All yields were measure via crude ^{1}H NMR using CH_2Br_2 as the internal standard. Next, the solvent was evaporated and the remaining solid was washed with cold MeOH, to remove reaction products and reactants and precipitate the recycled micelle. The solid micelle was analyzed by ^{1}H NMR, and dried overnight for further experiments.

Acknowledgements

We would like to thank the NSF under the Center for selective C – H functionalization (CCHF) (No. CHE-1205646) for funding of this research. Special thanks given to Andrew Gorman, Paul Balding, and Dr. Paul Russo for assistance with dynamic light scattering of micellar supports.

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10.1002/adsc.201700707

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