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ARTICLE

α-Arylation of (Hetero)aryl Ketones in Aqueous Surfactant Media

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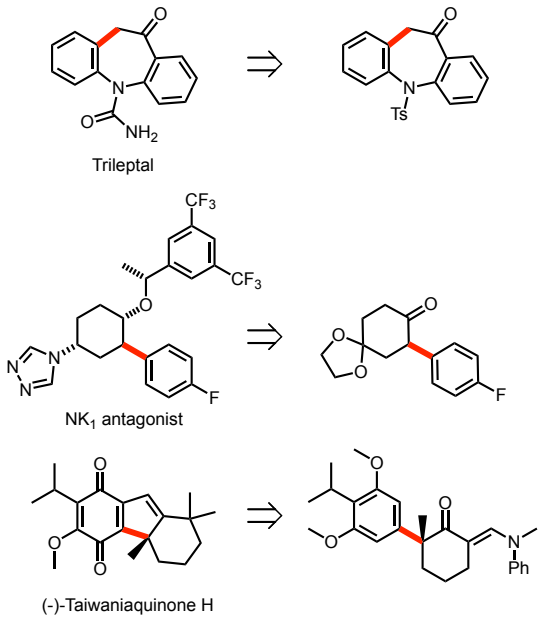
α-Arylation reactions can be performed in water, enabled by a designer surfactant,under mild conditions and in the absence of organic co-solvents. A multitude of aryl and heteroaryl ketones are amenable to coupling with functionalized aryl halides. Use of a lipophilic base that can gain entry to the micellar inner cores mediates enolization. In some cases, palladium loadings as low as 2500 ppm (0.25 mol %) are sufficient for coupling in a completely recyclable medium, exemplifying chemistry in water.

Introduction

Palladium-catalyzed α-arylations of ketones has emerged as an important approach to numerous synthetic targets, especially within the pharmaceutical and total synthesis arenas (Figure 1).[1] The standard approach to introduction of the desired C(sp^2)-C(sp^3) bonds between a ketone and aryl/heteroaryl halide or pseudohalide relies on enolization to arrive at an intermediate that participates in a transmetalation event with the newly generated Pd(II) species that ultimately leads, via reductive elimination, to the desired C-C bond.[2]

In the vast majority of cases to date, and independent of the base and temperature required, the reaction medium is a dry organic solvent, such as toluene, THF, DME, dioxane, etc.[3] The obvious explanation for these reaction conditions that rigorously exclude adventitious moisture is the lower pK_a for water relative to the intended ketone (i.e., ca. 15 vs. 20), thereby avoiding an obvious competitive situation. Therefore, performing α-arylations entirely in water seems counter-intuitive, and rather unlikely to lead to a successful outcome. However, as we and others have previously shown,[4] such reactions "in water" involving water-insoluble partners can, in fact, be carried out within hydrophobic micellar cores.[5] These nanoreactors easily accommodate not only the substrates, but also catalysts and bases that are judiciously chosen to maximize their binding constants with the inner lipophilic portions of the surfactants that constitute these micellar arrays.[6] And as to selection of the base, while *t*- butoxide leads to mainly hydroxide in water, its lipophilicity and equilibrium percentage allows for its presumed presence inside the micelle.[7] Proton abstraction, therefore, was anticipated, especially given the high concentrations of occupants within micellar cores. Hence, enolization followed by Pd-mediated arylation within a hydrophobic pocket seems quite reasonable, thereby not only avoiding strong bases (e.g., $LiN(TMS)_2$), dry media, and high temperatures (oftentimes >80 °C), but also the associated use of organic solvents and aqueous workups which continue to lead to massive amounts of waste creation while depleting our limited petroleum reserves. Thus, in this report are described efforts aimed at providing an environmentally responsible process in water for arriving at (mainly) mono-arylated ketones of both the aromatic and heteroaromatic varieties.[8] Also addressed is recognition of the continuing shortage of palladium, already today priced well beyond that of gold, thereby encouraging ppm level Pd catalysis as part of this newly developed technology.[9]

Figure 1: Intermediates towards API and natural product targets accessed via Pd-mediated α-arylations of ketones



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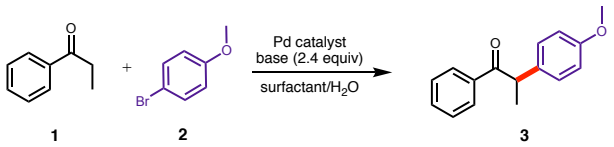
Results and Discussion

As a model α-arylation, propiophenone (**1**) and 4-bromoanisole (**2**) were selected to screen palladium catalysts for activity (Scheme 1). All reactions were run in micellar media consisting of 2 wt % TPGS-750-M/H_2O (DL-α-tocopherol methoxypolyethylene glycol succinate) at 45 °C. Initially, the catalyst was evaluated at either 2 mol % utilizing either a Pd(II) salt/ligand mixture (1:1.2 ratio), or as the pre-complexed palladium(II) salt precursor which generates the desired Pd^0 catalyst *in situ*. Among the catalysts tested (see Supporting Information), only pre-catalyst Pd[dtbpf]Cl_2 was found to produce **3** when used in the presence of LiO-*t*-Bu or KO-*t*-Bu as base. This finding is in line with an early report from Hartwig and co-workers[10] indicating that the bulkiness of the ligand affects the rate of reaction, specifically the reductive elimination step. Excellent yield (90%, isolated) of the α-arylated adduct **3** was isolated using this catalyst (2 mol %) together with 2.4 equivalents of KO-*t*-Bu at a global concentration of 1.0 M in this aqueous micellar medium.



Scheme 1: Optimization studies of propiophenone (**1**) and 4-bromoanisole (**2**) to form arylated ketone (**3**).

Attempts to reduce catalyst loading to ≤5000 ppm (0.5 mol %) Pd led to a marked decrease in conversion, and hence, isolated yield (38%). Further reductions of catalyst, likewise, led to only trace levels of conversion by TLC. We turned to the Pd(I) dimer class of pre-catalysts, inspired by the recent success of Sperger and Schoenebeck employing such catalysts (2 mol % in toluene) for related purposes.[11] Indeed, use of 1 mol % of the palladium(I) bromide dimer [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$ afforded conversion to adduct **3** in 97% yield, under otherwise identical conditions used earlier with Pd[dtbpf]Cl_2. As a control reaction, *in situ* formation of ostensibly the same catalyst from the combination of $Pd(OAc)_2$/(*t*-Bu)$_3$P at a 1:1.2 metal to ligand ratio led to similar conversion in water. Nonetheless, to avoid handling pyrophoric tri-*t*-butylphosphine, the air stable Pd(I) bromide dimer catalyst was selected for further study. Fortunately, and more importantly, this commercially available catalyst significantly outperformed Pd[dtbpf]Cl_2 at far lower loadings, catalyzing formation of product **3** in 97% yield using only 2500 ppm Pd (0.125 mol % of catalyst dimer) with respect to starting bromide. Additional screening of other ligands, some known[12] to be effective for α-arylations in organic solvents and utilized at 1 mol % Pd level in water, afforded little-to-no conversion (see Supporting Information).

The choice in base was also found to be crucial to arrive at high levels of conversion to the coupled product. Initial studies using catalytic Pd[dtbpf]Cl_2 and *t*-butoxide as base indicated a trend in cation dependency, with potassium giving higher yields relative to that from either sodium or lithium (K > Na > Li; see Supporting Information).[13] Results from further evaluation of various potassium bases, as well as organic bases, together with the more active catalyst dimer complex (at 0.125 mol %) are shown in Table 1 for the model reaction leading to α-arylated product **3**.

Table 1. Screening of the base used for α-arylation in model reaction (Scheme 1) in water

entry	base	pK_a conjugate acid	yield (%)
1	**KO-*t*-Bu**	**17**	**97**
2	KOH	15.7	63
3	KOH (on water)	15.7	40
4	KOH / TIPSOH	14.9	35
5	$K_3PO_4 \cdot H_2O$	12.3	57
6	Et_3N	10.8	trace

Reactions performed using 0.125 mol % (1250 ppm) [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$ in 2 wt % TPGS-750-M/H_2O at 1.0 M at 45 °C and 2.4 equiv base.

The large disparities in conversions between that seen with the more lipophilic *t*-butoxide (entry 1) and those using all other bases, e.g., KOH (entry 2), is not unexpected. Beyond the difference in pK_a of the conjugate acid for each base,[14] previous studies in micellar media have shown that increasing the branching and lipophilicity of the alkyl moiety in and around an alkoxide can greatly improve levels of conversion.[7] Moreover, since hydroxide is polar and hence, is unlikely to gain entry to the lipophilic nonpolar micellar interior, proton abstraction must be happening external to the reaction chamber, perhaps at the interface or within the nearby PEG layer slowing the overall process. Switching to the 1:1 combination of KOH/TIPSOH (triisopropylsilanol; entry 4) provides an even more lipophilic silanoxide as base, having previously been used very effectively in a somewhat related capacity under aqueous conditions.[15] However, in this case, inferior results were obtained presumably due to the relatively low pK_a of TIPS-OH (ca. 14.9)[16] compared to the targeted α-proton, slowing arylation. A weak inorganic base such as $K_3PO_4 \cdot H_2O$ (entry 5) gave a similar result compared to that obtained with KOH, while the weak organic base Et_3N (entry 6) gave only traces of product.

Screening of the reaction medium was also explored. While the Pd(I) dimer catalyst is relatively stable in air, it is very oxygen sensitive when in solution;[17] therefore, the water was rigorously degassed with argon prior to use. A series of surfactants, including several nonionic and ionic surfactants, were tested in order to determine the optimal nanoreactors for these α-arylations (Table 2).

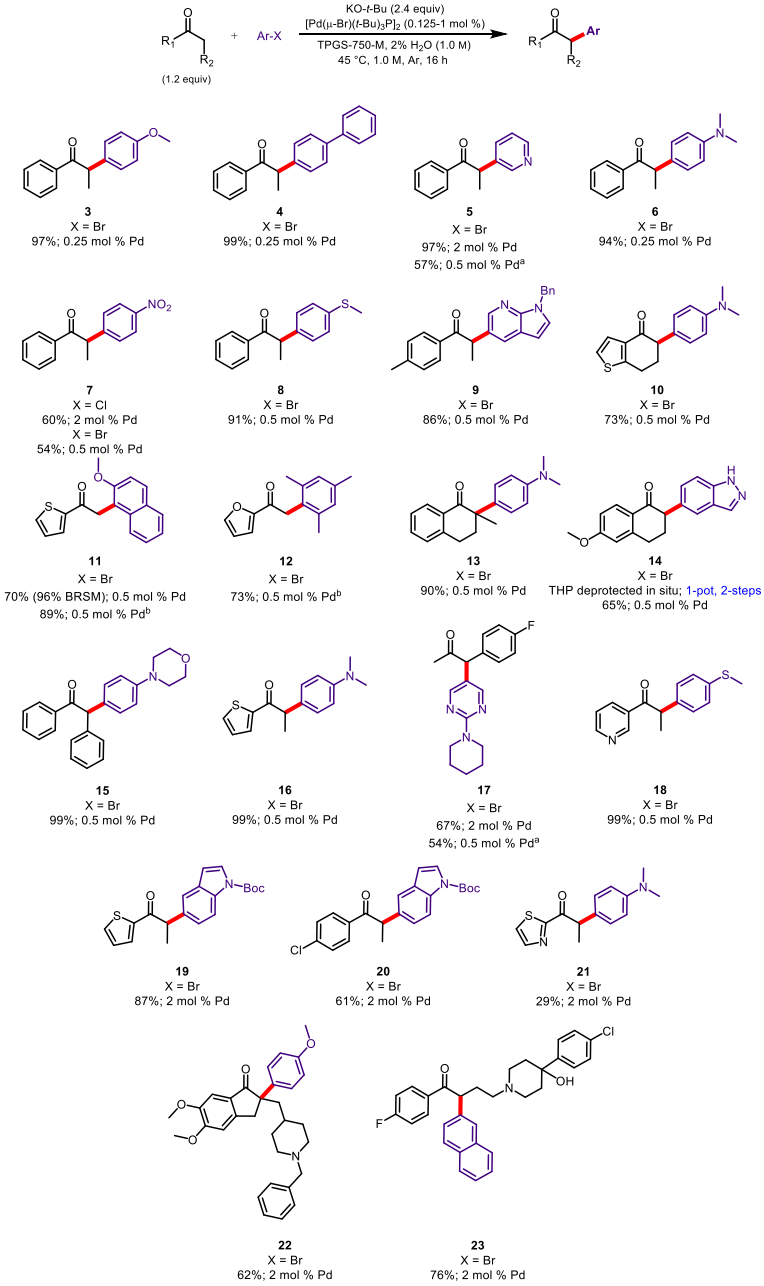
Table 2. Screening the reaction medium for the model reaction (Scheme 1)

entry	medium	yield[a] (%)
1	H_2O	76
2	**TPGS-750-M, 2 wt % in H_2O**	**97**
3	Nok, 2 wt % in H_2O	80
4	Coolade, 2 wt % in H_2O	89
5	Triton X-100, 2 wt % in H_2O	82
6	Brij-35, 2 wt % in H_2O	39
7	PTS, 5 wt % in H_2O	74
8	SDS, 2 wt % in H_2O	45
9	toluene (1.0 M)	48
10	toluene (0.2 M)	60

[a] Yields based on isolated mass of product **3**. Unless otherwise noted, reactions were run at 1.0 M at 45 °C, 0.125 mol % $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$, with 2.4 equiv of KO-*t*-Bu.

Under otherwise identical reaction conditions, a broad range of isolated yields of **3** were obtained with variations in surfactant, albeit using the same 2 wt % in water (i.e., 20 mg surfactant in 1 mL water). An aqueous medium containing TPGS-750-M (entry 2) gave a significantly higher yield (97%) as compared to other nonionic surfactants (entries 3-7). The background, alternative "on-water"[18] reaction (entry 1), although giving rise to the desired product in modest yield (76%), is not competitive with respect to use of "in water" conditions involving TPGS-750-M or other nonionic surfactants (e.g., Coolade, entry 4; 89%).[19] Use of 2 wt % Brij-35 (entry 6; PEGylated lauryl alcohol)[20] which forms aggregates of smaller micelles in water, afforded the lowest yield. Neither anionic surfactant sodium dodecyl sulfate (SDS; entry 8) nor a traditional organic solvent (toluene) at varying concentrations (entries 9-10) lead to synthetically competitive results.

Optimized conditions for α-arylations of ketones, therefore, were found to be: $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$ as pre-catalyst in 2 wt % TPGS-750-M/H_2O containing of KO-*t*-Bu (2.4 equiv) as base. Exploration of reaction scope led to the results shown in Scheme 2. Couplings between various aromatic bromides and propiophenone afforded products **3**-**9**. Altering the aryl halide indicated that electron-rich (**3**, **6**, **8**) and neutral (**4**) substrates afforded excellent yields, some of which were observed to reach completion in only 1-2 hours. Electron-poor halides, however, were not very effective at a Pd loading of 0.5 mol %. For example, while product **5** could be obtained in 97% yield, 2 mol % catalyst was required. The lower loading (0.50 mol %) afforded only a 57% yield, although the remaining mass was starting materials. Coupling of the aryl chloride precursor leading to **7** also needed the same higher catalyst loading (2 mol %), whereas the corresponding bromide achieved the same outcome but at the 0.50 mol % loading of Pd. *N*-Benzyl-protected azaindole **9** was realized in very good yield (86%) in the presence of ppm levels of Pd, whereas the unprotected nitrogen resulted in no net conversion even at higher catalyst loadings. *N,N*-Dimethyl-4-bromoaniline proved to be an excellent reaction partner, resulting in good-to-excellent yields of thiophene-containing α-arylated products **10** and **16**. The quaternary center in **13** was also prepared in high yield from α-methyltetralone using this same coupling partner without recourse to increased temperature or catalyst loading.



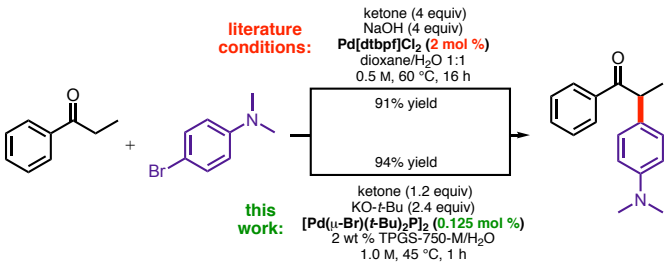
Unless otherwise noted, standard conditions include $[Pd(\mu\text{-}Br)(t\text{-}Bu)_3P]_2$, aryl halide (1.0 equiv), ketone (1.2 equiv), and K-O-*t*-Bu (2.4 equiv) in 2 wt % TPGS-750-M/H_2O at 1.0 M at 45 °C under argon for 16 h. All yields reflect isolated material. [a] Reaction run at 70 °C. [b] 1.7 equiv of aryl ketone used.

Scheme 2: Representative α-arylations under aqueous micellar conditions.

Aryl methyl ketones, such as the thiophene and furan ketone starting materials ultimately affording products **11** and **12** (Scheme 2), respectively, led to double α-arylation (see examples; *vide infra*) for most aryl halides. However, *o,o'*-disubstituted aryl bromides could be used to selectively mono-arylate, whereas maximum yield was obtained by increasing the ketone ratio to 1.7:1 compared to the bromide. A 2-step, 1-pot sequence could also be readily achieved. Thus, after monoarylation using 0.5 mol % of catalyst and without isolation, lowering the pH to <1 led to deprotected tetralone derivative **14** in 65% overall yield.

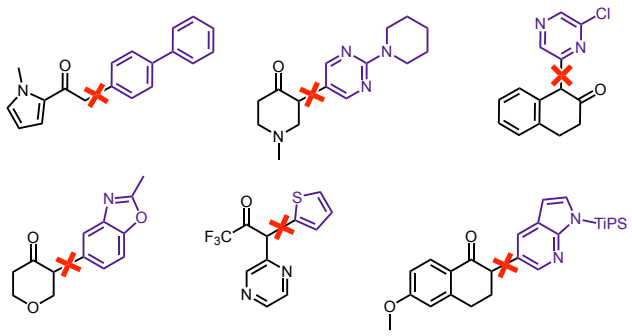
Dialkyl ketone **17** was also prepared selectively in moderate yield via arylation at the more acidic site. Coupling of a 3-pyridyl ketone and 4-bromothioanisole formed product **18** in quantitative yield. Doubling the scale of this reaction to 1.0 mmol afforded no loss in yield (98%). *N*-Boc-Protected 6-bromoindole led to arylated products **19** and **20**, although both arylations required increased catalyst loading (2 mol %). Surprisingly, α-arylation involving a 2-acylated thiazole yielded compound **21** in poor yield. Late-stage functionalization of APIs donepezil and haloperidol leading to new derivatives **22** and **23**, respectively, could also be achieved in water in reasonable yields, although here again, 2 mol % of the Pd catalyst was required.

A direct comparison with a typical literature example was performed, in this case one that used an aqueous dioxane reaction medium.[21] Coupling of propiophenone with 4-bromo-*N,N*-dimethylaniline is illustrative of the significant improvements that can be anticipated using a micellar medium. The reaction run in recyclable water required less ketone, less base, lower temperature, and nearly an order of magnitude less palladium, resulting in a slightly higher yield of the α-arylated product in significantly less time.



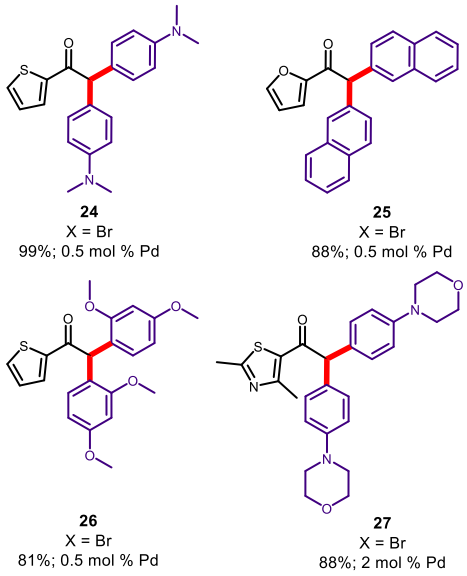
Scheme 3: Direct comparison of an α-arylation with a literature example.[21]

A number of ketones and aryl halide combinations were found to be incompatible with α-arylation chemistry in water (Scheme 4). For example, *N*-methyl-2-acetylpyrrole was unreactive under optimized conditions. Furthermore, non-aryl ketones or those unactivated by an (hetero)aryl group were found to give rise to hydrodehalogenation of the aryl bromide.[22]



Scheme 4: Aryl halide/ketone combinations that were unreactive under "standard" conditions.

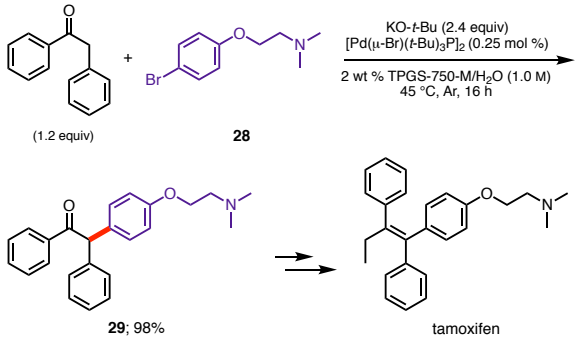
As previously noted (*vide supra*), aryl *methyl* ketones may result in doubly arylated product formation due to the high acidity of the initially formed singly-arylated intermediate, as well as the unhindered nature of the initially generated mono-arylated product. Hence, products of double α-arylation **24** and **25** (Scheme 5) were readily formed in high yields using 5000 ppm Pd. Using an aryl bromide coupling partner containing *ortho*-substitution, such as in product **26**, still led to double arylation. Likewise, substitution on the heteroaryl ring of the starting ketone nonetheless afforded the doubly arylated product **27**, although 2 mol % Pd catalyst was required to reach completion.



Unless otherwise noted, standard conditions involve catalyst [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$, ketone (1.2 equiv), aryl halide (1.0 equiv), and KO*t*-Bu (2.4 equiv) in 2 wt % TPGS-750-M/H_2O at 1.0 M at 45 °C under argon for 16 h

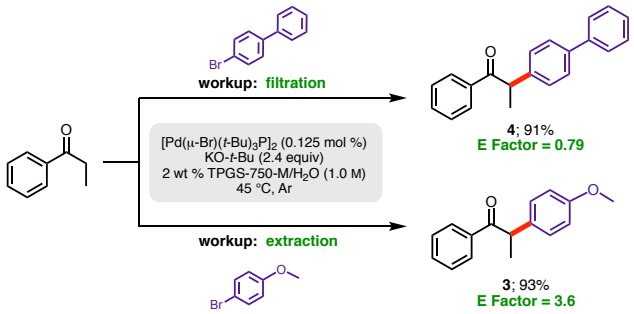
Scheme 5: Double α-arylation of heteroaryl methyl ketones under micellar conditions.

One representative example of the application of α-arylation of aryl ketones in water is the synthesis of an intermediate (**29**) towards tamoxifen, an estrogen receptor modulator used to prevent and treat breast cancer (Scheme 6).[23] The key transformation in this sequence calls for α-arylation of deoxybenzoin utilizing commercially available bromide **28**. This coupling occurs in 2 wt % TPGS-750-M in water using 1.2 equivalents of aryl ketone. Only 5000 ppm Pd (0.25 mol % of the palladium dimer complex) was needed which, in the presence of excess KO-*t*-Bu, resulted in product **29** in very high isolated yield (98%).



Scheme 6: Synthesis of a key intermediate *en route* to tamoxifen.

An evaluation of the associated E Factors[24] is shown in Scheme 7. Two potential protocols for reaction workup were tested that should be independent of scale: (1) filtration of the water-insoluble product, and (2) extraction of the product using minimal amounts of a single, recyclable organic solvent.



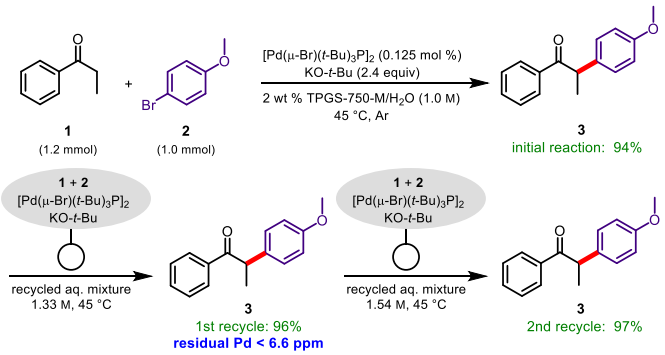
Scheme 7: E Factors of ppm Pd arylations of ketones in water using either filtration or an extractive workup.

Filtration of product **4** was carried out by initially diluting the reaction mixture with water. Since no organic solvent was used for the reaction itself, the E Factor was calculated (see Supporting Information) on the basis of *t*-BuOH, as well as the 20% excess propiophenone used, resulting in an E Factor = 0.79. Extraction to isolate product **3** generates some organic waste, assuming no recycling of this organic solvent. Arylated ketone **3** could be isolated following extraction with MTBE (see Supporting Information). The E Factor following this workup (including the base and reagents as above) still gave a value of only 3.6.

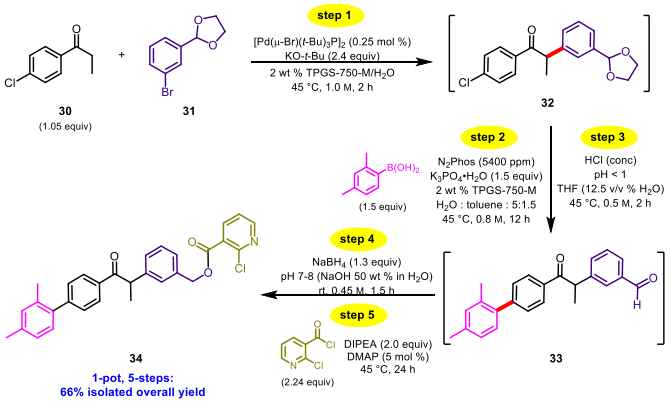
To further showcase the "greenness" of this methodology, the 2 wt % surfactant aqueous phase used to produce **3** could be recycled multiple times (Scheme 8). After an initial α-arylation, degassed MTBE was added to the reaction mixture under argon and the product extracted under air-free conditions (see Supporting Information). While some volume of the aqueous phase was lost during extraction, there was no need to supplement with fresh reaction medium while maintaining the same 1.0 mmol scale reaction. This led to a slightly increased reaction concentration over each of the two recycles, entirely due to handling. Nonetheless, only fresh catalyst, base, and starting materials need be added under an inert atmosphere after each coupling. No loss of yield was observed at any point. Recycling was halted, however, after the second reaction (i.e., after three total sequences), as salt buildup was noted which impeded retrieval of the aqueous surfactant mixture for use in subsequent reactions.

Importantly, ICP-MS analysis of the first recycled reaction product, after standard workup and purification, resulted in a residual metal level of 6.6 ppm Pd, less than the FDA minimum allowance of 10 ppm Pd/dose/day.[25] A second example using 2500 ppm Pd as catalyst leading to product **4**, purified directly from the first reaction, also exhibited a low level of residual Pd (4.8 ppm Pd).

Another major benefit of aqueous micellar catalysis comes in the form of providing a common reaction medium, water, in which a growing number of reactions can now be run. This, in turn, enables sequential, tandem processes to be carried out in a 1-pot operation, thereby avoiding workup and purification at each step. Such "telescoping" has tremendous potential in synthesis, with one such sequence illustrated in Scheme 9. Note that this series of reactions involves a key α-arylation of a ketone as part of this 5-step sequence, with an overall isolated yield of 66%.



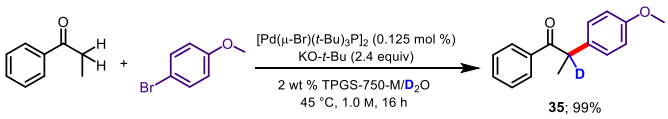
Scheme 8: Recycling of 2 wt % TPGS-750-M/H_2O, as well as residual Pd in isolated product from recycled aqueous mixture.



Scheme 9: 1-pot, 5-step sequence starting with α-arylation of ketone **30**.

Thus, an initial α-arylation of ketone **30** with the 1,3-dioxolane-containing aryl bromide **31** resulted in aryl chloride **32** using 5000 ppm (0.5 mol %) of Pd catalyst. The resulting aryl chloride was then utilized directly in a Suzuki-Miyaura coupling upon treatment with 2,4-dimethylphenylboronic acid. This transformation *utilizes the same palladium used for the α-arylation*; however, switching the ligand *in situ* simply by adding N_2Phos dissolved in toluene as co-solvent results in the coupling of the aryl chloride with the boronic acid in water.[26] Aldehyde **33** was then generated by lowering the pH of the medium to <1. Without isolation, reduction of the resulting aldehyde with $NaBH_4$ followed, after pH adjustment to neutrality (using NaOH). The newly formed benzylic alcohol was then treated with 2-chloronicotinoyl chloride to afford ester **34**, isolated in 66% overall yield *via* a 5-step, 1-pot sequence.

Given the enolization involved in formation of α-arylated products, and the protic nature of the bulk aqueous reaction medium, a 1-pot α-deuteration/arylation was explored using D_2O. As shown in Scheme 10, both processes smoothly took place to form product **35** in close to quantitative yield. Interestingly, the desired α-arylation required significantly more time, as the reaction in D_2O yielded only 61% of the arylated product in the usual three hours, whereas in H_2O the reaction proceeds to completion in nearly quantitative yield within two hours. Since the product was a mixture of H/D isotopes at the α-position after three hours, the decrease in reaction rate in D_2O may reflect a fast proton/deuterium exchange prior to arylation, where deuterium abstraction is significantly slower given the less acidic C-D bond under otherwise similar conditions. Increasing the reaction time to 16 hours led to complete conversion in quantitative yield with >90% deuterium incorporation at the α-carbon by HRMS and ^{1}H analysis.



Scheme 10: Single pot α-arylation / deuteration using D_2O as bulk reaction medium.

Conclusions

In summary, new methodology has been developed for α-arylations of aryl and heteroaryl ketones in water, using a highly active and commercially available pre-catalyst [Pd(μ-Br)(*t*-Bu)$_3$P]$_2$. Couplings afford arylated ketone products and rely, in may cases, on only 0.50 mol % Pd metal loading, enabled by an aqueous micellar medium, being run at a global concentration of 1.0 M at 45 °C. A broad substrate scope has been documented, including late-stage functionalization of pharmaceutically relevant compounds. A known intermediate towards the antitumor agent tamoxifen was also prepared from commercially available compounds in near quantitative yield using similar ppm levels of palladium. The aqueous micellar medium involved can be easily recycled without additional handling or processing, while the residual level of Pd found in the product after standard purification was found to be less than 10 ppm. Using E Factors based on solvent usage as a measure of greenness, the calculated values suggest that such α-arylations, overall, are environmentally responsible. Finally, a 1-pot, 5-step sequence in water, including an initial ppm Pd-catalyzed α-arylation, has been documented, indicative of the potential for chemistry in water to be applied to complex targets in the fine chemicals industry. These are the subject of ongoing investigations and will be described in future reports from these laboratories.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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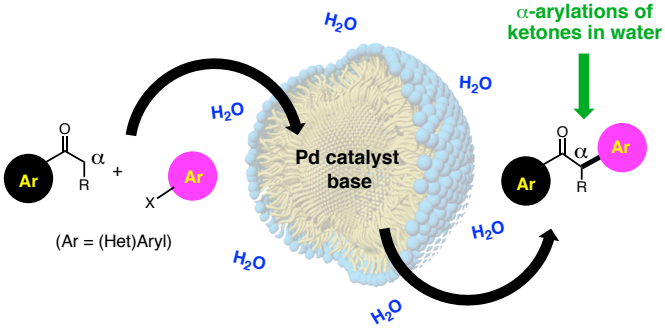
Notes and references

1 (a) S. T. Sivanandan, A. Shaji, I. Ibnusaund, C. C. C. J. Seechurn, T. J. Colacot, *Eur. J. Org. Chem.*, 2015, **1**, 38-49; (b) P, Devendar, R. -Y. Qu, W. -M. Kang, B. He, G. -F. Yang, *J. Agric. Food Chem.*, 2018, **66**, 8914-8934; (c) C. J. Borths, S. D. Walker, *Isr. J. Chem.,* 2020, **60**, 340–350; (d) O. Dirat, J. M. Elliott, R. A.

Jelley, A. B. Jones, M. Reader, *Tetrahedron Lett.,* 2006, **47**, 1295–1298; (e) M. Carril, R. SanMartin, E. Domínguez, I. Tellitu, *Tetrahedron,* 2007, **63**, 690–702; (f) J. F. Guastavino, R. A. J. Rossi, *Org. Chem*., 2012, **77**, 460–472; (g) M. Hellal, S. Singh, G. D. Cuny, *J. Org. Chem*., 2012, **77**, 4123–4130.
2 (a) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc*., 1997, **119**, 11108–11109; (b) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc*., 1997, **119**, 12382–12383; (c) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem., Int. Ed*., 1997, **36**, 1740–1742.
3 (a) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res*., 2003, **36**, 234–245; (b) F. Bellina, R. Rossi, *Chem. Rev*., 2010, **110**, 1082–1146; (c) C. C. C. Johansson, T. J. Colacot, *Angew. Chem., Int. Ed.,* 2010, **49**, 676–707; (d) G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.,* 2002, **41**, 953-956; (e) Y.-J. Hao, X.-S. Hu, Y. Zhou, J. Zhou, J.-S. Yu, *ACS Catal*., 2020, **10**, 955–993.
4 In the case of α-arylations of ketones in water using 5 wt % PTS as surfactant, see: M. Lessi, T. Masini, L. Nucara, F. Bellina, R. Rossi, *Adv. Synth. Catal*., 2011, **353**, 501–507. In the case of α-arylations of α-phenyl substituted nitriles in water using 3 wt % PS-750-M as surfactant, see: M. Bihani, T. N. Ansari, L. Finck, P. P. Bora, J. B. Jasinski, B. Pavuluri, D. K. Leahy, S. Handa, *ACS Catal.,* 2020, **10**, 6816–6821. For α-arylations of nitroalkanes in water using surfactant, see: J. Brals, J. D. Smith, F. Ibrahim, F. Gallou, S. Handa, *ACS Catal*., 2017, **7**, 7245–7250. In the case of C-H activated arylations of indoles in micellar media, see: G. N. Vaidya, S. Fiske, H. Verma, S. K. Lokhande, D. Kumar, *Green Chem*., 2019, **21**, 1448–1454.
5 (a) B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, R. D. Gaston, R. C. Gadwood, *J. Org. Chem.,* 2011, **76**, 4379–4391; (b) B. H. Lipshutz, *J. Org. Chem.,* 2017, **82**, 2806–2816; (c) B. H. Lipshutz, *Johnson Matthey Technology Review,* 2017, **61**, 196–202; (d) M. P. Andersson, F. Gallou, P. Klumphu, B. S. Takale, B. H. Lipshutz, *Chem. Eur. J*., 2018, **24**, 6778–6786.
6 S. Handa, M. P. Andersson, F. Gallou, J. Reilly, B. H. Lipshutz, *Angew. Chem. Int. Ed*., 2016, **55**, 4914–4918.
7 B. H. Lipshutz, D. W. Chung, B. Rich, *Adv. Synth. Catal*., 2009, **351**, 1717–1721.
8 L. V. Desai, D. T. Ren, T. Rosner, *Org. Lett*., 2010, **12**, 1032–1035.
9 https://www.kitco.com/charts/livepalladium.html (accessed April 13, 2021).
10 M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc*., 1999, **121**, 1473–1478.
11 T. Sperger, F. Schoenebeck, *Synthesis,* 2018, **50**, 4471–4475.
12 (a) K. D. Hesp, R. J. Lundgren, M. Stradiotto, *J. Am. Chem. Soc.,* 2011, **133**, 5194–5197. (b) P. G. Alsabeh, M. Stradiotto, *Angew. Chem., Int. Ed*., 2013, **52**, 7242–7246.
13 C. M. Gabriel, M. Parmentier, C. Riegert, M. Lanz, S. Handa, B. H. Lipshutz, F. Gallou, *Org. Process Res. Dev*., 2017, **21**, 247–252.
14 http://ccc.chem.pitt.edu/wipf/MechOMs/evans_pKa_table.pdf
15 N. A. Isley, S. Dobarco, B. H. Lipshutz, *Green Chem*., 2014, **16**, 1480-1488.
16 https://www.chemicalbook.com/ChemicalProductProperty_EN_CB4504344.htm
17 (a) J. P. Stambuli, R. Kuwano, J. F. Hartwig, *Angew. Chem., Int. Ed*., 2002, **41**, 4746–4748. (b) T. J. Colacot, *Platin. Met. Rev*., 2009, **53**, 183–188. (c) T. Sperger, C. Stirner, F. Schoenebeck, *Synthesis,* 2016, **49**, 115–120. (d) C. C. C. Johansson Seechurn, T. Sperger, T. G. Scrase, F. Schoenebeck, T. J. Colacot, *J. Am. Chem. Soc.,* 2017, **139**, 5194–5200. (e) I. Kalvet, K. Deckers, I. Funes-Ardoiz, G. Magnin, T. Sperger, M. Kremer, F. Schoenebeck, *Angew. Chem., Int. Ed*., 2020, **132**, 7795–7799.
18 D. C. Rideout, R. Breslow, *J. Am. Chem. Soc*., 1980, **102**, 7816–7817.
19 N. R. Lee, M. Cortes-Clerget, A. B. Wood, D. J. Lippincott, H. Pang, F. A. Moghadam, F. Gallou, B. H. Lipshutz, *ChemSusChem*, 2019, **12**, 3159–3165.
20 https://pubchem.ncbi.nlm.nih.gov/compound/Polyoxyethylene-_23_-lauryl-ether
21 E. Marelli, Y. Renault, S. V. Sharma, S. P. Nolan, R. J. M. Goss, *Chem. Eur. J*., 2017, **23**, 3832–3836.
22 Aryl dehalogenation in the presence of dialkyl ketones resulting from the Pd(I) pre-catalyst was also observed when Pd(II) salts, such as Pd[dtbpf]Cl_2, were used.
23 (a) F. Churruca, R. SanMartin, I. Tellitu, E. Domínguez*, Org. Lett.,* 2002, **4**, 1591–1594. (b) F. Churruca, R. SanMartin, M. Carril, I. Tellitu, E. Domínguez, *Tetrahedron,* 2004, **60**, 2393–2408. (c) G. Danoun, A. Tlili, F. Monnier, M. Taillefer, *Angew. Chem., Int. Ed.,* 2012, **51**, 12815–12819.
24 R. A. Sheldon, *Green Chem*., 2007, **12**, 1261-1384.
25 S. Phillips, D. Holdsworth, P. Kauppinen, C. MacNamara, *Johnson Matthey Technol. Rev*., 2016, **60**, 277–286.
26 N. Akporji, R. R. Thakore, M. Cortes-Clerget, J. Andersen, E. Landstrom, D. H. Aue, F. Gallou, B. H. Lipshutz, *Chem. Sci.,* 2020, **11**, 5205–5212.

ToC graphic



α-Arylations can be run under micellar catalysis conditions using a Pd(I) pre-catalyst together with KO-*t*-Bu as base. Sequences using this coupling along with as many as four additional steps can be carried out in a 1-pot fashion, all in water.