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Surfactant Technology: With New Rules, Designing New Sequences Is Required!

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ABSTRACT: With a growing toolbox of surfactant-mediated chemistry in water and an increased number of scaled-up transformations has come tremendous learning [for example, see: Lipshutz, B. H.; et al. *The Hydrophobic Effect Applied to Organic Synthesis: Recent Synthetic Chemistry “in Water”*. *Chem. - Eur. J.* **2018**, 24 (26), 6672–6695]. These opportunities now reside within a few expert groups, and while all of the details are far from fully understood or still under development, substantial know-how has been gained in both reaction process and synthesis design. Herein we share some of the fundamental principles inherent to micellar catalysis and illustrate them on a particularly challenging case involving a Suzuki–Miyaura cross-coupling. The complete structures of the active pharmaceutical ingredient (API) and the intermediates are not fully disclosed for confidentiality reasons but can nevertheless serve as illustrative of the importance of factors that, unlike traditional chemistry in organic solvents, can be crucial to a successful outcome (e.g., lipophilicity). The API used as an example for this discussion bears significant commonality with a large number of other targets associated with the formation of a biphenyl array as well as the presence of an amide and products resulting from nucleophilic aromatic substitutions (S_NAr). Hence, we look to utilize these prior learnings and can now rapidly apply them to the design of optimal conditions for several other important transformations.

KEYWORDS: chemistry in water, surfactant, micelles, sustainability, design of synthesis, scale-up

In the course of developing a route to one of our drug substance candidates, we were faced with the task of generating a challenging biaryl nucleus. In addition, the targeted active pharmaceutical ingredient (API) required a very commonly encountered amide bond formation and nucleophilic aromatic substitutions, some of the most general functionalities encountered in APIs.¹ Over the years we have built a toolbox of chemistry in water-containing surfactants, whether vitamin E-derived^{2–8} or more recently proline-derived,^{9–12} to address such transformations, and hence, we

envisioned that this technology could serve as an excellent opportunity to tackle these reactivity and selectivity challenges. We very early recognized the benefits associated with such chemistry, which go far beyond mere environmental advances.¹³ Indeed, the mild conditions associated with their use enable exquisite selectivities at minimal cost in terms of catalyst especially. This all contributes to remarkable productivity (or economic benefit) and, more interestingly, opens up new scientific opportunities.

Thorough retrosynthetic analysis (Scheme 1) revealed a handful of options, with substantial variations in the order of steps to be followed. Careful experimental evaluation of these options actually allowed us to design several sequences. All of them share a common feature in the need for a Suzuki–Miyaura cross-coupling as the key and clearly most challenging step. While the basic raw materials would remain the same for all of the approaches, the assembly order and the choice of nucleophilic and electrophilic partners could be varied. It was particularly interesting to see the substantial impact observed as a function of each choice, as illustrated ultimately through Schemes 2 to 5.

In the first approach, the essential Suzuki–Miyaura cross-coupling was performed with amphoteric species **1** and bromoaniline **2** (Scheme 2, reaction 1). This transformation as shown is severely lacking in selectivity when run in any classical organic solvent, presumably because of the rather elevated temperature required (80 °C) to ensure reaction conversion. A 50% excess of expensive pinacol boronate **1** was required as well in this regard, and this led to a substantial amount of polysubstituted impurities (multiple oligomers observed, especially the disubstituted impurity **3'**). Switching to the milder micellar conditions using designer surfactant technology (in this case, TPGS-750-M in water) immediately resulted in improved selectivity (Scheme 2, reaction 2). Interestingly, the stoichiometry of the two coupling partners could be reduced from 1.5:1 to 1:1, as could the Pd catalyst loading from 3.5 to 0.5 mol %, significantly reducing the cost. In addition, thanks to the reduced levels of side products and impurities, the product could be directly crystallized, which led

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Scheme 1. Targeted API and Envisioned Building Blocks

Scheme 2. Suzuki Cross-Coupling Reactions between Amphoteric Species 1 and Bromoaniline 2 (1) in Organic Solvent and (2) in TPGS-750-M/H₂O Scheme 3. Suzuki Cross-Coupling Reaction Starting from Iodopyridine 5 in TPGS-750-M/H₂O Scheme 4. Suzuki Cross-Coupling Reaction Starting from a Substituted Iodopyridine in TPGS-750-M/H₂O

to significant productivity enhancement. However, all efforts to further improve the selectivity proved unsuccessful.

Switching the polarities of the coupling partners led to the next breakthrough. Starting from the more reactive iodopyridine 5, the reaction could be performed under ideal

stoichiometric conditions (1:1 in electrophile and nucleophile), thus minimizing the formation of undesired pseudo-regioisomers and oligomers. The targeted product 3 was obtained in excellent isolated yield (95%) with greatly enhanced selectivity (<2% oversubstitution to 3'). Interest-

Scheme 5. Variation of the Catalyst for the Suzuki Cross-Coupling Reaction Starting from Benzamide Boronate Ester 8

Table 1. PMI and Cost Estimation of Variations in Reaction Conditions Associated with the Coupling in Schemes 2 to 5 (Reactions 1 to 7)

reaction	yield (%) ^a	chemical yield (%)	oversubstitution (cpd 3') (%)	T (°C)	catalyst (mol %)	PMI ^b /PMI _{water} /PMI _{solvent}	cycle time (%)	cost (%) ^c
1	50	75	15	80	Pd(dppf)Cl_2 (3.5)	203/23.5/152	220	550
2	60	80	8	40	Pd(dtbpf)Cl_2 (0.5)	62/23.5/33.5	100	100
3	95	98	2	60	Pd(dtbpf)Cl_2 (0.2)	40/16/19	90	58
4	95	98	<2	45	Pd(dtbpf)Cl_2 (0.2)	40/16/19	90	58
5	>95	>98	<0.5	20	Pd(dtbpf)Cl_2 (0.5)	35.5/13/16.5	88	55
6	87	89	<0.5	20	Pd(dtbpf)Cl_2 (0.1)	40/16/19	95	57
7	>95	>98	<0.5	20	Pd(OAc)_2 , Handaphos (0.1)	35.5/13/16.5	82	59

^aIsolated yields. ^bPMI = process mass intensity.^{15,16} ^cSum of raw materials, manufacturing, and waste disposal costs.

ingly, the loading of the same palladium catalyst could be further reduced from 0.5 to 0.2 mol % (Scheme 3).

Following this lead, we hypothesized that blocking the reactive functionality of the pyridine moiety by submitting it first to the ultimately necessary $\text{S}_{\text{N}}\text{Ar}$ reaction might further reduce the potential for oversubstitution (Scheme 4). While we unfortunately did not observe this outcome but rather stayed with a similar oversubstitution yield of 2%, we observed quite unexpectedly that the pyridyl iodide gained in reactivity, requiring only gentle warming to 45 °C instead of 60 °C. This subtle difference turned out to be crucial in finalizing the reaction partner ultimately used in the overall sequence.

Continued substitution on the various fragments eventually led to the best synthetic outcome, which turned out to be achieved by capping of the aniline boronate ester with the (ultimately necessary) benzamide functionality (compound 8). When a 0.5 mol % loading of the same catalyst was used at room temperature, the biaryl product was isolated in 95% yield with virtually no oversubstitution, presumably as a result of the high steric demand of a second coupling. Reducing the catalyst loading to 0.1 mol % led to a slight decrease in isolated yield (87%), likely due to a slower reaction. Alternatively, the same outcome was achieved using an additional 10% excess of boronate. The best results were obtained when a 1000 ppm (0.1 mol %) loading of the ligand HandaPhos¹⁴ was employed in combination with the catalyst precursor Pd(OAc)_2 (Scheme 5), leading to 9 in 95% isolated yield.

DISCUSSION

In all of the experiments, reactions were pushed to sufficient conversion within a maximum of 24 h of reaction time. The crude materials were processed in the appropriate manner (i.e., direct crystallization or an initial crystallization of a salt followed by a second crystallization of the free form) to generate material leading to a drug substance of proper quality.

Our historical data had shown that a purity of >97% would systematically guarantee such quality, and these data were used to set specifications at this stage. The environmental impact was expressed in terms of the process mass intensity (PMI), a recognized metric that has been widely adopted within the industry.¹⁷ It represents the amount of overall chemicals utilized to prepare 1 kg of product. Cycle time is used to express the overall time required from the start of the process to the end, cleaning excluded. Costs are reported as raw material costs (sum of all goods utilized in the process), manufacturing costs (manpower and equipment amortization for a given site as set by internal markers), and overall costs. Our internal costing tools were utilized in all of the calculations to ensure consistency. All of the results are normalized to 100% on the basis of the first process performed using an aqueous surfactant solution (Table 1, entry 2). The original process in organic solvent (Table 1, entry 1) dramatically suffered from mediocre selectivity, which required a first crystallization of 3 as a salt followed by free-basing and subsequent crystallization of the free form. This ultimately led to a poor PMI and high overall costs associated with this labor-intensive process. Switching to our first surfactant-enabled process¹⁸ (Table 1, entry 2) already led to significant improvements, reducing the PMI by more than 3-fold, the cycle time by more than 2-fold, and the costs by more than 3-fold. It is interesting to further understand the impact of this technology on the last of these parameters, cost.¹⁹ Clearly, a more than 2-fold improvement in the overall raw material cost was realized, mostly due to the reduced catalyst loading and to the improved stoichiometry of the cross-coupling partners (only a 10% excess of the boronate ester), while the labor cost was cut by more than 5-fold. These ratios will obviously change depending on the specific raw materials and on the site utilized for production, but these two components will always have to be considered. It is also important to add that our tools include high waste disposal costs to optimally influence best practices and waste

minimization. A remarkable impact on the PMI in particular was observed when the isolated yield could be reliably increased to $\geq 95\%$ (entries 3–5). The cycle time was only marginally improved, as the processes essentially remained the same, with only faster crystallization and isolation of the solids. Costs were simulated as well and remained again very similar in all three cases. Interestingly, enabling the cross-coupling with lower catalyst loading (entry 6) did not significantly improve the PMI or cycle time. The major reason was the slightly lower isolated yield, which required longer processing time to afford material of suitable quality and more boronate to reach full conversion. HandaPhos (Table 1, entry 7) was determined to be the most effective ligand, giving the optimal PMI and cycle time.^{17,19} One additional critical benefit to the technology is the reduction in the amounts of excess boronate esters needed, which are of limited stability. Indeed, the mild conditions associated with this micellar approach ultimately allow for use of the ideal 1:1 stoichiometry. With coupling partners of high complexity, it becomes very important to get as close to this ratio as possible. This requirement is particularly well recognized in the context of natural product synthesis and applies to any set of complex targets, especially when being made at scale.^{20,21} Moreover, reducing excesses of reaction partners ultimately requires less effort in handling the crude reaction mixture en route to purified products.²²

In almost all of our applications of the surfactant technology on scale, we have observed a significant benefit of adding small quantities of an organic cosolvent.²³ In the above-discussed case, THF was the cosolvent of choice that would enable the proper physical properties of the bulk reaction medium and facilitate the overall process. It served for example as the medium that facilitated the addition of the boronate ester, thus avoiding a tedious solid addition. It must be noted that the cosolvent is distilled at the end of the reaction to facilitate and increase the recovery of the product, which would otherwise be partitioned between the organic and aqueous phases. Besides, its easy removal under gentle warming and reduced pressure enables recovery of the solvent and further facilitates containment of the TPGS-750-M in a single phase for easier disposal. We will soon report a full account of this part of the process.

Interestingly, when it comes to water, we observed that the simple switch of the medium from an organic solvent to bulk water led to the same PMI for water for the process (entries 1 and 2). That is, the total amount of water utilized throughout the process per kilogram of product stayed constant. When the process was further designed (entries 3 to 7), the PMI for water then significantly decreased by 45% under our best conditions. This apparently counterintuitive observation that less water is needed for processes that occur in bulk water is actually a fundamental benefit of micellar-enabled chemistry, which typically occurs with high selectivities and at high concentrations.²⁴

COMPUTATIONAL INVESTIGATIONS

In order to gain insight into the observed changes in activity and selectivity as evidenced by the outcomes associated with the key coupling shown in Schemes 2 to 5, we conducted density functional theory calculations using the COSMO-RS implicit solvent model.²⁵ We used the Turbomole program, version 7.5²⁶ with the BP functional,^{27,28} the TZVP basis set,²⁹ and the COSMO implicit solvent model³⁰ with infinite dielectric constant (a requirement for COSMO-RS calculations).

All of the COSMO-RS calculations were performed using COSMOtherm, version 19.0, and the BP_TZVP_19 parametrization. This allows for analysis of thermodynamic properties such as solubility, partitioning, interfacial tension,³¹ and reaction free energies in a two-phase system such as exists with TPGS-750-M-derived nanomicelles in an aqueous medium. We focused on capturing major trends with respect to changes in the reaction medium and reactant chemistry. The oxidative addition is the first step in the Suzuki–Miyaura reaction (Figure 1), and we have found previously that the

Figure 1. Generic mechanism for (hetero)aryl–(hetero)aryl Suzuki–Miyaura cross-coupling.

reaction energy for that step correlates well with observed activity.¹⁴ This suggests that the transition state for the oxidative addition, a dissociation reaction, is strongly correlated with the reaction energy. Linear free energy relationships for heterogeneous catalysis of dissociation reactions show that the energy of the transition state is proportional to the reaction energy (the energy of the dissociated state).³² The proportionality constant is ~ 0.9 with an offset that for metals depends on the catalytic site geometry, where atomic steps are more reactive than flat terraces.

Regardless of the ligand chelated to the Pd center, a similar reaction mechanism for the oxidative addition of all halides is expected, so we used the known correlation from heterogeneous catalysis with an offset of 150 kJ/mol for the oxidative addition step and an offset of 100 kJ/mol for the rest of the reaction, represented by TS₂. Linear free energy relationships have been demonstrated to hold also for the Suzuki–Miyaura reaction,³³ although they are not yet proven for transition states. We are aiming to capture main trends and not quantitatively reproduce experiments. In order to better compare the reactions, we performed all of the calculations using the HandaPhos ligand, as we have established the correlation between the activity and the oxidative reaction energy for chemistry using this ligand. The corrections from translational, vibrational, and rotational entropy were taken to be the same as for our model HandaPhos reaction.¹⁴ Although small differences are expected, the main entropy contribution to the reaction energy in a coupling reaction is due to the loss of entropy from the decreased number of particles on the product side, and with similar sizes of reactants, similar contributions can be expected. Further investigations will

compare reactions using different ligands and with rigorous calculation of entropy contributions, but we note that the activity for the 1,1'-bis(di-*tert*-butylphosphino)ferrocene (dtbpf) ligand was almost as good as that for HandaPhos, comparing reactions 5–7 in Table 1.

The partition coefficients for all of the components (aryl or heteroaryl halide $\text{Ar}^1\text{-X}$, boronic acid or boronate ester $\text{Ar}^2\text{-B(OR)}_2$, and the (HandaPhos)Pd catalyst) were calculated for the three-phase model micellar system,²⁵ i.e., between water, the water-containing PEG phase, and the lipophilic vitamin E cores. All of the organic compounds with the exception of the (HandaPhos)Pd catalyst had favorable partitioning into the PEG phase, and the (HandaPhos)Pd partition coefficient toward the vitamin E cores relative to the PEG phase was only $\log(P) = 0.27$, which is so close to 0 that the partitioning is almost 1:1. Therefore, we chose the water-containing PEG phase as a model for reactions in the micellar medium (33 mol % water, 62 mol % PEG, and 5% vitamin E).

We calculated the reaction energies for the oxidative addition steps as well as for the overall Suzuki–Miyaura reaction according to the following equations:

oxidative addition:

overall:

There was a surprisingly small difference in the reaction energy for the same reaction in three different solvents: toluene, THF, and the model PEG phase. The maximum difference was only 2.2 kJ/mol, which is in the range of typical COSMO-RS accuracies. This means that the activity (based on transition state energy) is actually not expected to be that different in different media. Because we observed a large increase in activity in going from reaction 1 to reaction 2 (i.e., from toluene to TPGS-750-M; Scheme 2 and Table 1, entries 1 and 2), as is commonly observed upon switching to aqueous micelles as the reaction medium, the change in solvent chemistry seems not to affect the reaction pathway in a major way. The activity enhancement could instead come from increased local concentrations.^{34–36} The remaining calculations, therefore, were performed in the model PEG phase. The fact that the differences between various solvents were so small made us choose not to include the effect of the THF cosolvent in the calculations. The reaction energy for our reference reaction in Nok surfactant³⁷ instead of TPGS-750-M surfactant differed by only 0.5 kJ/mol.

We next performed a systematic set of calculations for reactions 2, 3, and 4 (Schemes 2 to 4 and Table 1, entries 2–4), where we tested $\text{X} = \text{Cl}$, Br , and I for all three systems. Figure 2 shows the reactions as depicted in the paper, and Figure 3 shows the trends for each reaction when the halide was changed. Figure 2 shows that the reaction energy for the oxidative addition step is different for the three reactions and that the difference is about 50 kJ/mol, which is significantly larger than the solvent effects. All three reaction energies are compared to the reaction energy of the reference reaction we previously modeled in our early disclosures on the HandaPhos ligand (reaction 25 in ref 38),³⁹ which was found to be very active experimentally. Without any knowledge about the optimum value other than it should be close to that of our chosen reference reaction, reactions 2–4 should show good

Figure 2. Schematic free energy diagram for the Suzuki–Miyaura reactions studied in the paper. The first transition state (TS_{OxAd}) is for the oxidative addition, and the intermediate is the product of the oxidative reaction step, i.e., the dissociated halide bound to the Pd catalyst. The second transition state (TS_2) is for the rest of the reaction cycle in Figure 1, which comprises both the transmetalation and reductive elimination steps. Both transition states were calculated via assumed linear free energy relationships with the reaction energy.

Figure 3. Schematic free energy diagram for the Suzuki–Miyaura reactions studied in the paper, for $\text{X} = \text{Cl}$, Br , and I in each reaction. The first transition state (TS_{OxAd}) is for the oxidative addition, and the intermediate is the product of the oxidative reaction step, i.e., the dissociated halide bound to the Pd catalyst. The second transition state (TS_2) is for the rest of the reaction cycle in Figure 1, which comprises both the transmetalation and reductive elimination steps. Both transition states were calculated via assumed linear free energy relationships with the reaction energy.

activity and yield, which is consistent with the low catalyst loadings required.

The most reactive halides, such as 2,6-dichloro-4-iodopyridine (5), will according to our estimates have a low barrier for the oxidative addition step (low barrier for the first transition state), but could suffer from a more difficult transmetalation or reductive elimination step (second transition state). This is because the reaction energy of the oxidative addition drops more than the reaction energy of the whole reaction. The trend observed in Figure 2 becomes clearer when it is compared to the results in Figure 3. As the reactivity increases in going from Cl to Br to I , the oxidative addition barrier decreases, whereas the reaction energy for the whole Suzuki–Miyaura cross-coupling reaction increases, which in turn leads to a higher barrier for the remaining steps after the oxidative addition. This could result in shifting the rate-determining step toward the later stages of the reaction, which in turn could stabilize the oxidative addition intermediate over the nonreacted halide. This stabilization of the oxidative reaction intermediate relative to reactants and products effectively reduces the amount of free catalyst (most becomes bound with the iodide), which

should vastly reduce the probability of dimer formation, here requiring a free catalyst.

When the nucleophile was introduced on the halide (i.e., in going from reaction 3 to reaction 4), we observed an increase in reactivity due to the lower reaction temperature required for this transformation. This observation of increased efficiency can be explained by our calculations, as the oxidative addition reaction energy for reaction 4 is closer to the reference reaction energy than is that associated with reaction 3 (Figure 2), further supporting our assumption that the chosen reference reaction is close to an optimum value.

We also systematically investigated the selectivity of the reactions, which was found to be poor for reaction 2 but much improved for reactions 3 and 4. To do so, we calculated the oxidative addition reaction energy as well as the overall reaction energy for forming the first oligomer from the products of reactions 2–4 via a new Suzuki–Miyaura cross-coupling cycle. The results are shown in Figure 4. For reaction

Figure 4. Schematic free energy diagram for the Suzuki–Miyaura reactions studied in the paper, comparing monomer formation (blue) to subsequent product reaction (red). The first transition state (TS_{OxAd}) is for the oxidative addition, and the intermediate is the product of the oxidative reaction step, i.e., the dissociated halide bound to the Pd catalyst. The second transition state (TS_2) is for the rest of the reaction cycle in Figure 1, which comprises both the transmetalation and reductive elimination steps. Both transition states were calculated via assumed linear free energy relationships with the reaction energy.

2, the reaction energies for product formation and subsequent product reaction are very similar. This means that it is quite likely that the product, which contains a halide entity, continues to react after being formed, leading to poor selectivity and an increased amount of oversubstitution. By contrast, for reactions 3 and 4, as a result of the changed reactant chemistry, monomer formation is clearly favored over subsequent product reaction. For reaction 3, the catalyst blocking could contribute to the selectivity as discussed in the previous section, as the product reaction has a reaction energy close to the “reference” value. For reaction 4, product formation is close to the “reference” value, while the product reaction barrier is larger, so the reaction is likely to be kinetically hindered.

■ COMPLETION OF THE SYNTHESIS

With these results in hand, we developed two approaches in which the key cross-coupling step occurred in water as the bulk reaction medium. In the first variant (Scheme 6), we started from commercially available 2,6-dichloropyridine, which was selectively functionalized at position 4 using an iridium-catalyzed selective borylation developed by Hartwig,⁴⁰ resulting in boronate ester **1** in 80% isolated yield. Although highly efficient and selective, the cost of the precious metal

required us very early on to minimize the iridium loading. We eventually developed a robust protocol that would proceed with as little as 0.01 mol % iridium catalyst, resulting in 80% isolated yield of the boronate ester. This ester participated in a Suzuki–Miyaura cross-coupling to afford the biaryl product **3** in 60% yield. The two chlorides were then selectively displaced sequentially via two nucleophilic aromatic substitutions, requiring DMSO as the bulk medium, to give product **10** in 72% overall yield (85% each step). All attempts to carry out the transformations in aqueous TPGS-750-M resulted in mediocre yields, mostly because of the high temperatures required for this combination possessing low reactivity. Aniline **2** was formed using a mild carbonyl iron powder (CIP) reduction of the corresponding bromonitrobenzene in a process that had proven smooth and highly selective (98% yield).⁴¹ The sequence ended with the capping of the aniline with a heteroaryl system, giving product **11** in 90% isolated yield. Interestingly, it must be pointed out that the surfactant conditions enabled the use of the free hydroxyl group present in the second nucleophile, whereas all more standard organic conditions failed to deliver productive chemoselectivity in our hands.⁴² A 30% overall yield was thus obtained for this route.

The second approach (Scheme 7) relied on the same CIP reduction of the nitrobenzene in 2 wt % TPGS-750-M/ H_2O , leading to aniline **2** in close to quantitative yield while leaving the bromide untouched.⁴¹ The pinacol boronate ester was installed via a Miyaura protocol in water using a 2 mol % loading of $Pd(dtbpf)Cl_2$ and a minimal (10%) excess of B_2pin_2 to yield the cross-coupling partner **4** in 90% yield.⁴³

Capping of aniline **4** was achieved via activation of carboxylic acid **12** with oxalyl chloride in THF, with gentle distillation upon completion to reduce the volume and remove volatile byproducts, followed by slow dosing onto the aniline stirred in a 2 wt % aqueous solution containing TPGS-750-M. The resulting fully functionalized boronate ester **8** was isolated by crystallization in 85% yield with >98% purity. The 2,6-dichloropyridine was selectively iodinated at position 4 using *N*-iodosuccinimide in the surfactant solution⁴⁴ and subsequently monosubstituted in an S_NAr reaction on chloropyridine **5** using the appropriate nucleophile in a 1:4 THF/2 wt % TPGS-750-M/ H_2O mixture. The product was obtained with high purity (>98%) after recrystallization from aqueous acetic acid. These substrates **6** and **8** were found to be the best coupling partners in our hands, as described above. The sequence ended with another S_NAr reaction that proceeded smoothly under mild conditions and delivered the target compound **11** in good yield (85%). The presence of a free hydroxyl group in this second nucleophile indeed required gentle conditions so as to minimize cleavage of the amide bond and proceeded best in 2 wt % TPGS-750-M/ H_2O . An overall yield of 42% was obtained for this route.

In both cases, the enablement of the catalysis with low levels of transition metal catalyst allowed for sufficient depletion of residual palladium to well below 10 ppm at the API stage via simple crystallization along the synthetic routes without any additional scavenging technique.

■ CONCLUSION

We have demonstrated that judicious optimization of both the nature of the chemistry to be applied and the physical properties of all of the components of the reactive system can lead to the best synthetic outcome, maximizing an aqueous surfactant-enabled approach. Our observations were correlated

Scheme 6. Variant 1 of the Synthesis of the API

Scheme 7. Variant 2 of the Synthesis of the API

with quantum-mechanical calculations to rationalize the behavior of each of the reaction components in the medium. When suitably designed, exquisite selectivities and performance could be observed, leading to significant benefits in terms of yield, cost, and environmental footprint. More practically, these benefits include a significant decrease in catalyst loading with increases in selectivity and yield, all leading to improvements in the overall productivity.

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Notes

The authors declare no competing financial interest.

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reaction conditions: (HandaPhos)Pd (1000 ppm), 2 wt % TPGS-750-M/H₂O, Et₃N, rt, 18 h

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