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TPGS-750-M: A Second-Generation Amphiphile for Metal-Catalyzed Cross-Couplings in Water at Room Temperature

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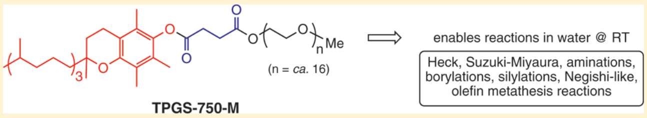
S Supporting Information



TPGS-750-M

ABSTRACT: An environmentally benign surfactant (TPGS-750-M), a diester composed of racemic α-tocopherol, MPEG-750, and succinic acid, has been designed and readily prepared as an effective nanomicelle-forming species for general use in metal-catalyzed cross-coupling reactions in water. Several "name" reactions, including Heck, Suzuki—Miyaura, Sonogashira, and Negishi-like couplings, have been studied using this technology, as have aminations, C—H activations, and olefin metathesis reactions. Physical data in the form of DLS and cryo-TEM measurements suggest that particle size and shape are key elements in achieving high levels of conversion and, hence, good isolated yields of products. This new amphiphile will soon be commercially available.

The notion of doing transition-metal-catalyzed organic synthesis in water only at ambient temperatures is oftentimes dismissed out of hand, as most uncharged organic molecules are simply insoluble. One approach that circumvents this limitation is the use of catalytic amounts of nanoparticles derived from amphiphiles that self-aggregate spontaneously in water, thereby providing a micellar environment within which organic substrates and catalysts may readily interact.[1] Such reactions are technically under homogeneous conditions, taking place within the lipophilic inner core of the micelle, while the water serves as the macroscopic medium that drives particle organization due to entropic factors.[2] With limited levels of surfactant present, concentrations of reactants are typically quite high, in which case reaction rates at room temperature can be competitive with those commonly seen at elevated temperatures in organic solvents.[3] One significant outgrowth of this phenomenon is that impurity profiles may be dramatically altered given the mildness of reaction conditions.

Over the past few years,[4] we have developed the concept of a "designer" surfactant in recognition of the fact that solvent effects can be crucial to the success of a reaction. Because the interior of a micelle serves in this capacity (i.e., as solvent), there is every reason to suspect that not all surfactants would be equally effective in metal-catalyzed cross-couplings. Moreover, from the green chemistry perspective,[5] the choice of amphiphile would ideally be, in the Anastas sense, "benign by design."[6] In other words, its use on any scale would have minimal environmental consequences and would ideally be recyclable.

As an initial entry into this area, we have reported a series of papers in which a first-generation surfactant, PTS (**1**; Figure 1),[7] was identified as a general nanomicelle-forming species that formed the basis of an enabling technology applied to several Pd- and Ru-catalyzed reactions performed in HPLC grade water at room temperature. Thus, several name reactions such as Heck,[8] Suzuki—Miyaura,[9] and Sonogashira[10] couplings could all be carried out in ≤5 wt % PTS/water at room temperature. Other Pd-catalyzed processes proceeded with comparable success, including aminations of aryl halides,[11] allylic aminations of alcohols,[12] and silylations of allylic ethers.[13] Several types of Ru-catalyzed metathesis reactions, including cross-[14] and ring-closing,[15] were shown to be quite amenable to this medium. Direct comparisons with existing commercially available (albeit far less expensive) amphiphiles demonstrated that surfactant makeup indeed matters and that in most if not all cases, PTS afforded as good or better results both in terms of yields and reaction rates.

Notwithstanding these successful applications, each surfactant is anticipated to have distinct characteristics, such as particle shape(s) (*e.g.*, spherical micelles, rods/worms, vesicles) and size, functionality (*e.g.*, a linear vs cyclic hydrocarbon interior),[1,2] as well as a specific hydrophilic—lipophilic balance (i.e., the relative amounts of its hydrophilic to lipophilic components).[16] These factors translate into observed variations in cross-coupling chemistry, although a full appreciation of the "rules" that precisely match a surfactant to a chosen reaction type remain elusive. In this report we disclose a new amphiphile, TPGS-750-M (**2**), that possesses several important advantages over PTS: (a) a newly engineered particle size that apparently better accommodates spacial needs of substrates/catalysts, leading to greater rates of couplings and therefore higher levels of conversion and resulting yields, and (b)

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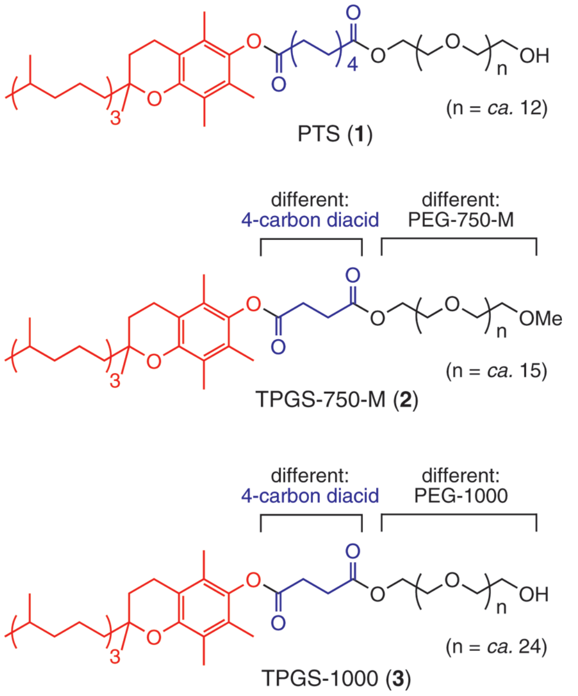
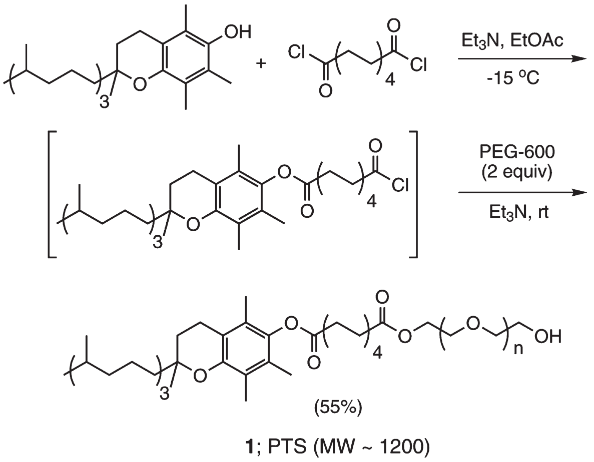
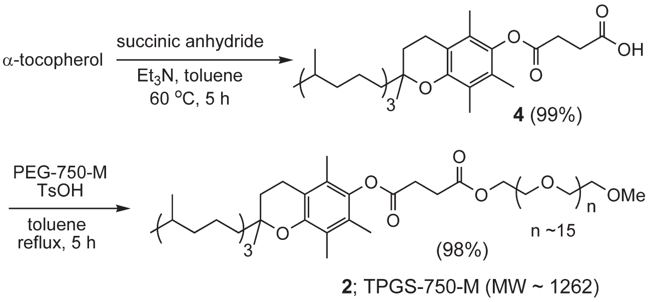


Figure 1. Structural comparisons between PTS, TPGS-750-M, and TPGS-1000.

Scheme 1. Literature Method To Prepare PTS[7]



Scheme 2. Synthesis of TPGS-750-M



a newly streamlined synthesis relative to that used to make PTS, which offers considerable promise for general utility in transition-metal-based catalysis. Thus, the overall goal was to provide a second-generation surfactant, one that offers the community methodology for metal-catalyzed couplings that take place as efficiently or more so relative to those in PTS/water, while simultaneously possessing a much-improved economic profile with respect to its preparation.

RESULTS AND DISCUSSION

TPGS versus PTS: Distinguishing Features. In search of a more economically practical alternative to PTS,[7] the structurally similar platform found in commercially available amphiphile TPGS-1000[17] (**3**) emerged as an appealing option for potential refinements. Like PTS, this related surfactant possesses α-tocopherol as its main lipophilic component, but differs in the length of its diester linker and appended PEG chain. Thus, in place of the longer (10-carbon) sebacic acid residue that joins PEG-600 to the hydrophobic vitamin E portion of PTS, TPGS-1000 has a shorter (and significantly less expensive) 4-carbon succinic acid linker. Not only is the preparation of the initial adduct, vitamin E succinate, a virtually quantitative reaction, this intermediate is also commercially available.[18] Since the vitamin E portion, by far, is the most costly of the three ingredients that would make up any surfactant of this type, the efficient use of this component is especially noteworthy and significantly enhances the economic appeal of TPGS-750-M over PTS. As illustrated in Scheme 1, the existing route to PTS is less than half as efficient, owing to the lack of regiocontrol in using sebacoyl chloride as the diester precursor. As expected, the diacid chloride route generates extensive byproduct formation due to uncontrolled couplings at each end, and ultimately, the desired PTS portion of the reaction mixture requires very specific protocols to realize purity levels needed for use in green chemistry. TPGS analogues, however, regardless of PEG units, benefit considerably from the succinic anhydride route, where unquestionably the first step leads to the single ring-opening half acid ester **4** (Scheme 2).[19]

The second important structural change made in the TPGS series that further streamlines syntheses of such "designer" surfactants (i.e., analogues of TPGS-1000) is use of a monomethylated poly(ethylene glycol) (MPEG), rather than the corresponding PEG diol. That is, given their similar cost structure, an MPEG monoalcohol as nucleophilic partner en route to the corresponding diesters **3** obviates double-ended diesterification, commonly seen with PTS due to residual sebacoyl chloride and the use of diol PEG-600. Hence, not only is the gross structural feature of a TPGS analogue readily distinguished from PTS, the workup required due to impurity profile differences between these amphiphiles is markedly different as well.

Another important distinction between PTS (containing a 10-carbon linker and PEG-600) and surfactants in the TPGS series (with a 4-carbon linker and PEG-1000) is that TPGS is more weighted toward its hydrophilic component, i.e., it has a far higher hydrophilic lipophilic balance (HLB) of 13 versus 10 for PTS.[14] Longer PEG chains have also been found to decrease nanoparticle size and to change particle shape; hence, the nanoenvironment available to a given set of reactants and catalyst can vary (Table 1), as do the observed experimental results. Dynamic light scattering (DLS)[20] data indicate that PTS forms on average ca. 24 nm particles,[4] whereas modified PTS made with PEG-1000 (i.e., PTS-1000) leads to 7 nm micelles. On the other

Table 1. Average Diameter of Surfactants in Water

amphiphile	average diameter (nm)[a]
PTS with PEG-600 (**1**)	24
PTS with PEG-1000	7
TPGS-1000 (**3**)	13
TPGS-750-M (**2**)	53
TPGS-550-M	65

[a] Determined by dynamic light scattering (DLS).

hand, TPGS-1000 forms 13 nm micelles in water that would be expected to increase in size as the PEG chain is shortened. The newly synthesized TPGS analogues, 550-M, and 750-M, indeed formed far larger particles, a potentially good omen for their use in cross-coupling reactions in water.

Designing a Better Micelle for Cross-Couplings. Although surfactants PTS, TPGS-750-M, and TPGS-1000 appear to be very similar in structural makeup, the extent of the cross-couplings occurring within each of their spontaneously formed nanoparticles in water can be quite varied. Hints that size and nature of the particles formed can be important factors come from DLS data. However, these numbers represent average values and offer little insight into individual particle shape or size. On the other hand, cryo-TEM analysis[21] is extremely useful for this purpose, and hence, these experiments were performed on each of these three surfactants (Figure 2). Cryo-TEM data on PTS show that it is composed of two types of nanoparticles: 8–10 nm spheres, and rods of highly variable lengths (A). By contrast, TPGS-1000 (C) appears to form only spherical particles (13 nm). The change to shorter PEG lengths by using MPEG-550 and -750 (thereby leading to surfactants TPGS-550-M, and -750-M) altered particle size significantly, with DLS data suggestive of particles averaging 53–65 nm. Relative to PTS and TPGS-1000, TPGS-750-M led to a higher percentage of larger rod-like particles (B). Among the three lower homologues in the TPGS series, TPGS-750-M gave the most synthetically useful cross-couplings (*vide infra*). Thus, while it is far from obvious why larger nanoparticles (spherical or otherwise) offer as good or better quality cross-couplings relative to PTS, it appears that micelles on the order of 50+ nm best accommodate the components associated with Pd- and Ru-catalyzed couplings described to date.

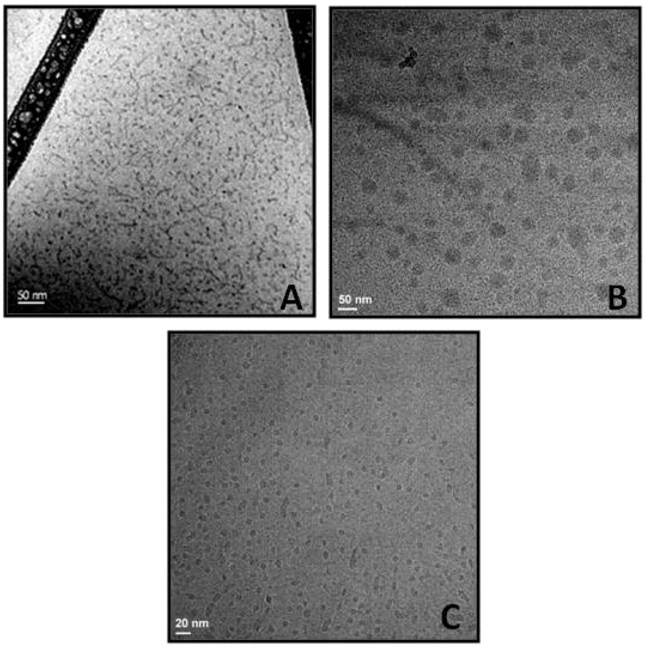


Figure 2. Cryo-TEM image of (A) aqueous PTS **1** (50 nm scale), (B) TPGS-750-M (50 nm scale), and (C) TPGS-1000 (20 nm scale).

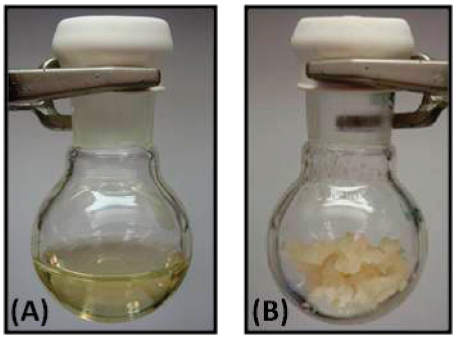


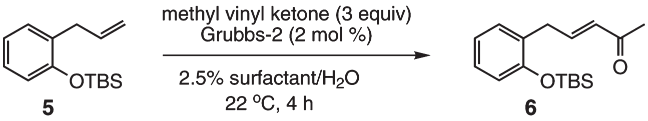
Figure 3. (A) Neat PTS; (B) neat TPGS-750-M.

Synthesis of TPGS Analogues: Spotlight on TPGS-750-M. To meld the convenience of preparing surfactants in the TPGS series with the established chemical versatility of PTS,[4] the HLB of commercially available TPGS-1000 was tuned by balancing the length of its PEG chain. Accordingly, TPGS variants with MPEG molecular weights of approximately 550 (n = *ca.* 11) and 750 (n = *ca.* 15) were synthesized via the straightforward two-step route outlined in Scheme 2. Under optimized conditions on a laboratory scale of <10 g, as illustrated for TPGS-750-M, each of the two steps affords a nearly quantitative yield of the desired product. Ring-opening of succinic anhydride (1.5 equiv) by α-tocopherol in warm toluene (0.5 M) takes place smoothly in 5 h. The resulting acid is then put through a standard workup and filtration through silica gel to give known white solid **4**.[22] Treatment of ester **4** with MPEG-750 in the usual way (cat. TsOH, toluene, Δ, Dean–Stark trap) gave the desired, previously unknown amphiphile **2** as a waxy solid (Figure 3B). This sequence could be smoothly scaled to >170 g, with comparable yields for each step (97% and 98%, respectively). In a similar fashion, both TPGS-600 and TPGS-550-M were prepared as viscous liquid materials. All could be stored indefinitely in vials at ambient temperatures.

Cross-Couplings in Aqueous TPGS-750-M. To compare and contrast these newly designed amphiphiles for promoting cross-couplings in water relative to those previously studied using commercially available PTS[23] (**1**) and TPGS-1000,[24] two olefin metathesis reactions were initially examined (Table 2). Both olefin cross- and ring-closing metathesis proceed smoothly in 2.5 wt % PTS/water (entries 1, 6) and in TPGS-750-M (entries 4, 9), although notably inferior results are seen in both cases using 2.5 wt % TPGS-1000/water (entries 5, 10). With methyl vinyl ketone and olefin **5**, in the presence of the second generation Grubbs catalyst, product **6** was formed to the extent of 64% conversion after 4 h at room temperature in PTS/H_2O, whereas in aqueous TPGS-1000 under otherwise identical conditions only 35% conversion had occurred (entry 5). The best result (74%) was observed using TPGS-750-M (entry 4). Diene **7** also underwent ring-closing metathesis in PTS to produce an 85% isolated yield of seven-membered ring product **8** (entry 6), whereas in micellar TPGS-1000 only a 40% level of conversion was noted (entry 10). For both test reactions, all three of the new

Table 2. Screening of Surfactants: Representative Olefin Metathesis Reactions in Water

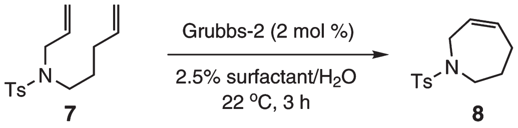
Cross Metathesis:



entry	surfactant	conv. [%][a]
1	PTS	64
2	TPGS-550-M	50
3	TPGS-600	60
4	TPGS-750-M	74
5	TPGS-1000	35

[a] Determined by ^{1}H NMR.

Ring-Closing Metathesis:



entry	surfactant	yield [%][b]
6	PTS	85
7	TPGS-550-M	70
8	TPGS-600	75
9	TPGS-750-M	88
10	TPGS-1000	40

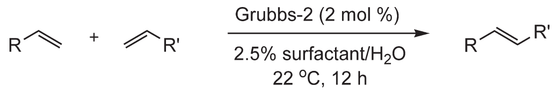
[b] Isolated yield of chromatographically pure materials.

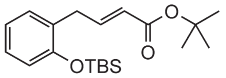
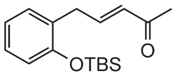
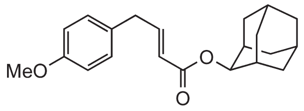
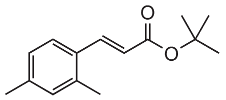
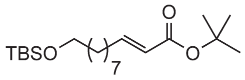
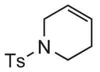
TPGS variants gave results that were significantly superior to those of TPGS-1000. The best results were obtained using TPGS-750-M (entries 4, 9), affording results that are equal or superior to those obtained using PTS.

To examine the generality of TPGS-750-M, a broader survey of olefin metathesis reactions was carried out. As shown in Table 3, reactions conducted in 2.5% TPGS-750-M/water gave, in all examples, yields equal to or slightly better than those obtained in PTS/water. These results were especially encouraging in that they demonstrated the potential for TPGS-750-M to replace PTS on two key fronts: (1) equal or superior efficiency in reactions, and (2) far greater efficiency in its preparation. Importantly, TPGS-750-M can be directly substituted for PTS under already established protocols,[4] without additional optimization.

An interesting and potentially very useful experimental observation was made from a reaction in which the pH of the aqueous phase had been lowered to between 2 and 3 by virtue of the addition of small amounts of $KHSO_4$ (0.02 M). As had been shown previously by Grubbs and co-workers, ring-opening metathesis polymerization (ROMP) reactions in aqueous acid are accelerated as a result of protonation of the catalyst-containing phosphine moiety, thereby freeing a coordination site on Ru.[25] By simply using PTS or TPGS-750-M in the presence of this salt, rates of olefin metathesis reactions using even a challenging partner in methyl vinyl ketone were significantly enhanced (Table 4).

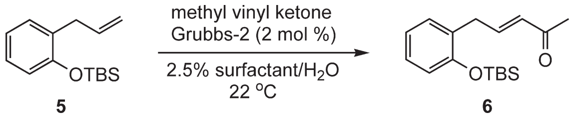
Table 3. Cross- and Ring-Closing Metathesis Reactions in PTS versus TPGS-750-M in Water



Entry	Product	PTS yield (%)[a]	**TPGS-750-M** yield (%)[a]
1		88	91
2		70	74
3		78	82
4		72	74
5		95	95
6[b]		99	99

[a] Isolated yield of chromatographically pure materials. [b] Reaction run for 3 h.

Table 4. Effect of pH on Olefin Metathesis Reactions



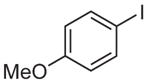
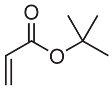
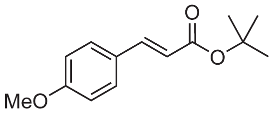
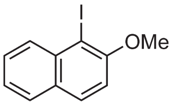
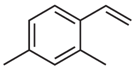
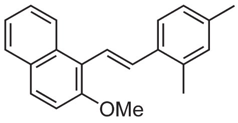
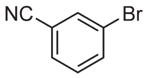
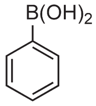
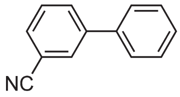
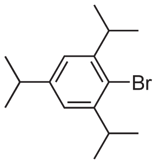
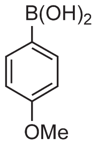
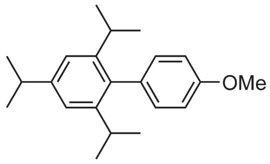
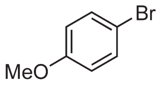
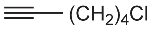
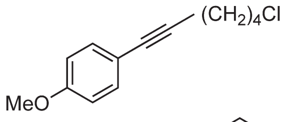
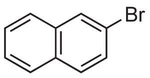
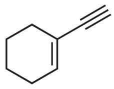
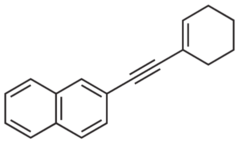
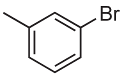
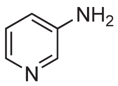
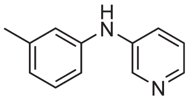
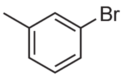
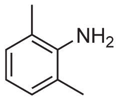
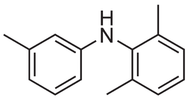
surfactant	time (h)	yield (%)[a]
TPGS-750-M	12	74
0.02 M $KHSO_4$ TPGS-750-M	4	93
0.02 M $KHSO_4$ PTS	4	91

[a] Isolated yield of chromatographically pure materials.

Although results for Ru-catalyzed metathesis reactions were encouraging, a more extensive study for comparison purposes between amphiphiles involving Pd-catalyzed cross-couplings was undertaken. These transformations included Heck, Suzuki—Miyaura, and Sonogashira couplings, as well as Buchwald-Hartwig aminations. Results are shown in Table 5 and clearly suggest that the more conveniently accessed surfactant TPGS-750-M relative to PTS promotes the same variety of valued C—C bond-forming reactions under identical conditions: in water at room temperature.

Heck couplings with aryl iodides (entries 1, 2) have been previously studied in PTS/water,[8] requiring typically high

Table 5. Pd-Catalyzed Cross-Couplings with TPGS-750-M and PTS in Water at Room Temperature

Entry	Aryl Halide	Partner	Product	PTS yield (%)[a]	**TPGS-750-M** yield (%)[a]
	Heck[b]				
1				96	97
2				92	95
	Suzuki-Miyaura[c]				
3				78	93
4				76	88
	Sonogashira[d]				
5				55	66
6				84	99
	Buchwald-Hartwig[e]				
7				83	98
8				81	93

[a] Isolated yield of chromatographically pure materials. [b] Reactions carried out for 4−12 h using aryl iodide (1 equiv), acrylate or styrene (2 equiv), triethylamine (3 equiv), catalyst $Pd(P(t\text{-}Bu)_3)_2$ (2 mol %), and 5 wt % of surfactant/H_2O. [c] Reactions carried out for 2−24 h using aryl bromide (1 equiv), arylboronic acid (1.5−2 equiv), triethylamine (3 equiv), catalyst $PdCl_2$(dtbpf) (2 mol %), and 2 wt % of surfactant/H_2O. [d] Reactions carried out for 21−25 h using aryl bromide (1 equiv), alkyne (1.5 equiv), triethylamine (2 equiv), catalyst $Pd(CH_3CN)_2Cl_2$ (1 mol %), X-Phos (2.5 mol %), and 3 wt % of surfactant/H_2O. [e] Reactions carried out for 19−20 h using aryl bromide (1 equiv), aryl amine (1.2 equiv), KO-*t*-Bu (1.5 equiv), catalyst [(π-allyl)PdCl]$_2$ (0.5 mol %), cBRIDP (2 mol %), and 2 wt % of surfactant/H_2O.

surfactant loading (15 wt %) when using $PdCl_2$(dtbpf) as catalyst (Figure 4). Subsequent catalyst screening revealed that PTS loading could be dropped to 5% by switching to $Pd(P(t\text{-}Bu)_3)_2$ as the source of palladium.[26] Trials revealed that this reduced loading could be maintained with TPGS-750-M/H_2O, and slightly higher yields could be obtained as compared to those using PTS. Similarly, improved yields for Suzuki−Miyaura cross-couplings could be realized, for both straightforward (entry 3) and more sterically challenging (entry 4) substrate combinations with 2% aqueous TPGS-750-M under otherwise identical conditions (2 wt % PTS in water). A similar trend was seen with Sonogashira couplings in 3 wt % surfactant/water, with a moderately yielding substrate combination showing improvement (entry 5), and a coupling involving an enyne elevated to nearly quantitative yield (entry 6). Generation of unsymmetrical diarylamines in water also appears to benefit from a change in amphiphile from PTS to TPGS-750-M (entries 7, 8). The same aniline-forming reaction (entry 7) using TPGS-1000 led to only a 39% yield of the desired derivative versus a 98% yield using TPGS-750-M.

Perhaps the most remarkable result obtained using PTS technology was the development of a new zinc-mediated Negishi-like

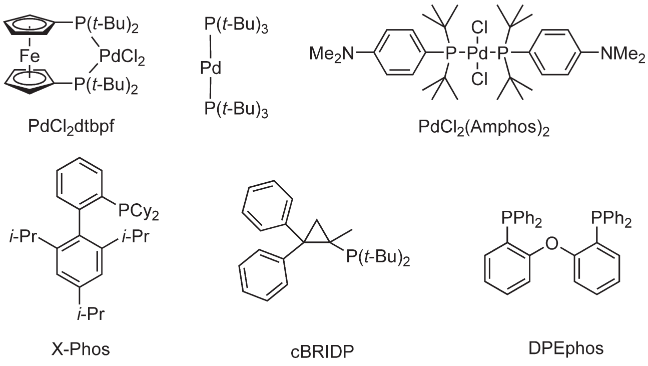
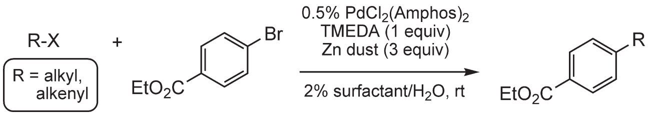
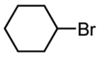
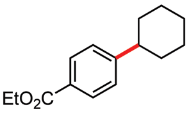
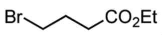
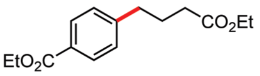
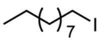
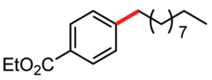
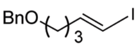
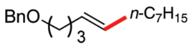
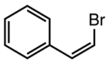
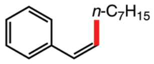
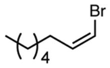
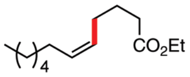


Figure 4. Palladium catalysts and ligands employed.

Table 6. Room Temperature Negishi-like Couplings with TPGS-750-M versus PTS in Water



Entry	R-X	Product	PTS yield (%)[a]	**TPGS-750-M** yield (%)[a]
1			51	75
2			48	71
3[b]			91	89
4			85 E/Z - >99/1	84 E/Z - >99/1
5			83 E/Z -77/23	90 E/Z - 88/12
6			74 E/Z - 96/4	87 E/Z - 99/1

[a] Isolated yield of chromatographically pure materials. [b] Using 1% Pd(Amphos)$_2$Cl$_2$, 4 equiv of Zn powder, and 5 equiv of TMEDA.

coupling between aryl and alkyl halides, performed in water at room temperature.[27] Although organozinc halides are notoriously moisture-sensitive,[28] they can be formed *in situ* on the surface of zinc dust or powder from an alkyl or vinylic halide, which then reacts with an aryl or vinylic halide under palladium catalysis within the hydrophobic core of a nanoparticle. In the presence of a stabilizing ligand for the transient RZnX, *e.g.*, tetramethylethylenediamine (TMEDA), this sequence takes place in an aqueous medium leading to a variety of primary and secondary alkyl-substituted aromatics and olefins. Crucial to success are the relative rates of organozinc halide formation, transmetalation to palladium, and aqueous protonation of RZnX, all controlled such that RZnX is not formed *in situ* too rapidly so as to avoid quenching by eventual exposure to the nanoparticle-surrounding water. The surfactant likely plays dual critical roles by both helping to insulate the nascent organozinc species from water, thereby extending lifetime, as well as by acting as a general solubilizing agent.

On the basis of several comparison examples (Table 6), TPGS-750-M appears to best accommodate the multiple species involved leading to competitive or superior yields of the coupling products relative to PTS under otherwise identical conditions. Primary and secondary alkyl halides, including both bromides and iodides, can serve as the organozinc halide precursor. A range of functionality, such as esters (entries 1−3), is likely to be tolerated under these mild conditions. In addition to aryl bromides as coupling partners (entries 1−3), alkenyl halides also work well in these reactions (entries 4−6). Interestingly, not only are the yields of cross-coupled products as good or better using aqueous TPGS-750-M, the levels of stereoretention are higher in this medium relative to those observed in PTS/water.

Another exciting development in the pursuit of new, more efficient, and atom-economical strategies in micellar catalysis focuses on C−H activation reactions of aromatic hydrogens.[29] While this class of reactions is appealing as a direct route to aryl substitution, the relative inertness of the sp^2 C−H bond in most aromatics has generally necessitated relatively harsh reaction conditions, including high temperatures and oftentimes strongly acidic media. Most strategies rely on directing groups to enhance reactivity, although where applicable, issues of regiocontrol and monosubstitution can arise.[30]

Prior studies in our laboratory in this timely arena showed that such chemistry occurs in water at room temperature, including the Fujiwara−Moritani reaction.[31] It was found that by using a commercially available cationic palladium catalyst, *ortho*-directed couplings of acrylate and anilide derivatives could, indeed, be performed in 2% PTS/water at ambient temperatures (Scheme 3, left). Akin to other reaction types described herein, the process was found to be easily adaptable to use of TPGS-750-M. Similarly, C−H arylation reactions of aryl ureas with aromatic iodides could also be achieved in water at room temperature, with the aid of a surfactant (Scheme 3, right). In this case, a cationic palladium species had to be generated *in situ*, necessitating use of HBF$_4$. While under optimized conditions the surfactant Brij 35 gave the highest yields (*e.g.*, 76% vs 68%), results with PTS were matched by TPGS-750-M.

Beyond metathesis and aromatic cross-coupling reactions, allylic substitution chemistry has also been developed in PTS/water and would benefit from adaptation to the more practical TPGS-750-M surfactant. Procedures that take advantage of micellar catalysis have led to use of less common allylic alcohols[12] and allylic ethers[13] as viable coupling partners. Developing conditions for reactions with these relatively inert substrates toward Pd catalysis is appealing in a number of ways: (1) it streamlines synthetic planning by minimizing prior derivatization; (2) it allows more readily stored (and often less expensive) precursors to be employed; and (3) it expands options in terms of orthogonal reactivity, improving opportunities for selectivity when there are multiple functionalities present that could potentially participate in a Pd-catalyzed reaction.

In the case of a model allylic alcohol (Table 7, entry 1), it was found that a palladium-catalyzed amination reaction could be effected in 2% PTS/water at room temperature in the presence of methyl formate, an additive that apparently enhances the leaving-group ability of the allylic alcohol (although not by prior transesterification).[12] These mild conditions, when utilized with TPGS-750-M as surfactant, gave the same product in competitive

Scheme 3. C−H Activation Reactions: PTS versus TPGS-750-M in Water at Room Temperature

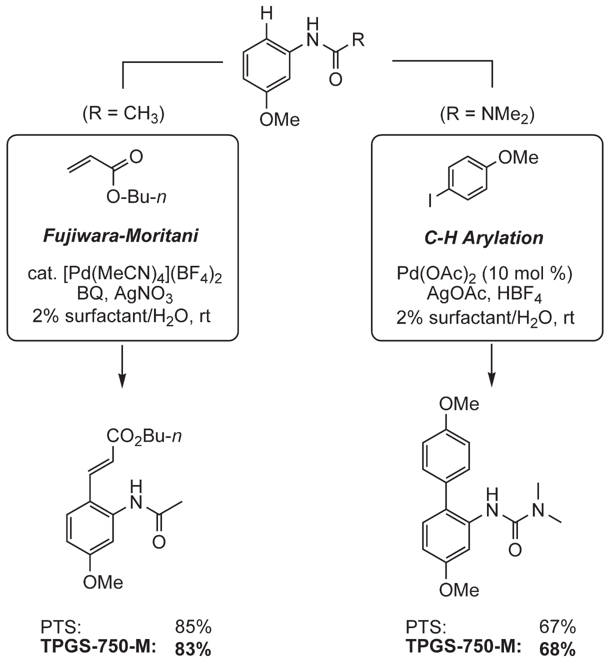
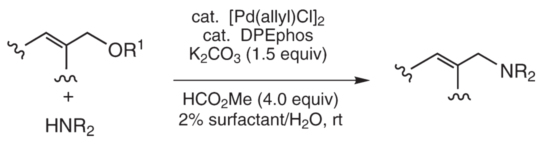
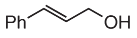
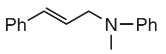
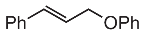
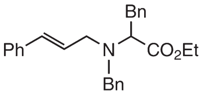
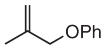
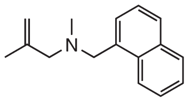
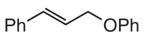
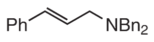


Table 7. Aminations of Allylic Alcohols and Ethers in Water at Room Temperature



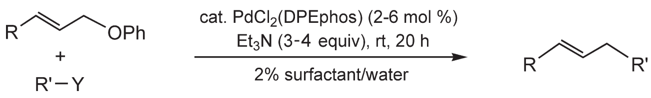
entry	allylic partner	product	PTS yield (%)[a]	TPGS-750-M yield (%)[a]
1			94	92
2			91	95
3			81	80
4			99	93

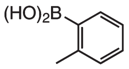
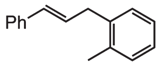
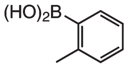
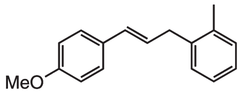
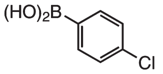
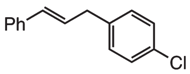
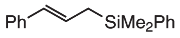
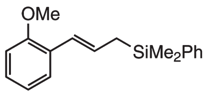
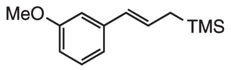
[a] Isolated yield of chromatographically pure materials.

yield. A related amination developed for allylic phenyl ethers[32] also translated well from PTS to TPGS-750-M (entries 2−4). Although C−N bond formation proceeds smoothly under conditions similar to those used for aminations of allylic alcohols, allylic ethers are far less prone to react relative to allylic carbonates and acetates under typical Pd-catalyzed allylation conditions.

Couplings of allylic phenyl ethers with either boronic acids (Table 8, entries 1−3)[33] or silanes[13] (entries 4−6) in water at room temperature have also been developed. These protocols were readily subject to replacement of PTS with TPGS-750-M as surfactant, as similar yields were achieved under otherwise identical conditions.

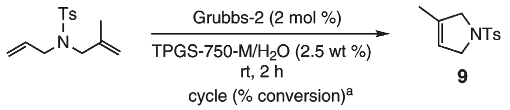
Table 8. Additional Reactions of Allylic Phenyl Ethers in Water



entry	partner	product	PTS yield (%)[a]	TPGS-750-M yield (%)[a]
1			99	99
2			82	84
3[b]			74	75
4	PhMe$_2$Si−SiMe$_2$Ph		91	91
5	PhMe$_2$Si−SiMe$_2$Ph		87	89
6	TMS−TMS		90	88

[a] Isolated yield of chromatographically pure materials. [b] Using catalyst PdCl$_2$(dtbpf) (6 mol %).

Table 9. Recycling of TPGS-750-M



cycle							
1	2	3	4	5	6	7	8
>99	>99	>99	>99	>99	>99	99	99

[a] Determined by ^{1}H NMR spectroscopy.

Recycling TPGS-750-M. By design, the preferred solubility of TPGS-750-M in water, as opposed to common organic solvents used for extraction (*e.g.*, hydrocarbons, Et$_2$O, and EtOAc), allows for recycling of the aqueous phase. A ring-closing metathesis reaction was studied, where each cycle was followed by a standard in-flask extraction of the product using minimal amounts of Et$_2$O (3 times), after which fresh substrate and catalyst were introduced. As illustrated in Table 9, after eight recycles, essentially complete conversion to the desired trisubstituted olefinic product **9** can be realized.

CONCLUSION

A new "designer" surfactant, TPGS-750-M, an unsymmetrical diester of succinic acid, has been prepared very efficiently in two steps and shown to form nanomicelles in water. These particles readily accommodate a variety of substrates and catalysts leading to efficient Pd- and Ru-catalyzed cross-couplings at room temperature. In the many cases studied and described herein, second-generation TPGS-750-M is oftentimes a superior choice to first-generation surfactant PTS, usually insofar as both yields are concerned, and especially in terms of economics of preparation and levels of purity.[34]

■ EXPERIMENTAL SECTION

DL-α-Tocopherol Succinate (4), <10 g Scale. To a solution of DL-α-tocopherol (4.30 g, 10.00 mmol) and succinic anhydride (1.50 g, 15.00 mmol) in toluene (20 mL) was added Et_3N (0.35 mL, 2.50 mmol) at 22 °C with stirring, and the stirring was continued at 60 °C for 5 h. Water was added to the reaction mixture, which was then extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl (3 × 50 mL) and water (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* affording a yellow liquid, which was purified by flash column chromatography on silica gel eluting with a 10% EtOAc/hexane to 35% EtOAC/hexanes gradient to afford DL-α-tocopherol succinate (5.25 g, 99%) as a white solid, mp 68−71 °C, lit.[22] mp 64−67 °C. IR (neat) 2926, 1757, 1714, 1576, 1463, 1455, 1415, 1377, 1251, 1224, 1151, 1110, 1078, 926 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (t, $J = 6.8$ Hz, 2H), 2.84 (t, $J = 6.8$ Hz, 2H), 2.59 (t, $J = 6.8$ Hz, 2H), 2.09 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.85−1.71 (m, 2H), 1.56−1.50 (m, 3H), 1.43−1.05 (m, 21H), 0.88−0.84 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 171.0, 149.7, 140.7, 126.9, 125.1, 123.2, 117.6, 75.2, 39.6, 37.8, 37.7, 37.6, 37.5, 33.0, 32.9, 31.3, 29.2, 28.8, 28.2, 25.0, 24.6, 24.0, 22.9, 22.8, 21.2, 20.8, 19.95, 19.88, 13.0, 12.2, 12.0; MS (ESI) m/z 554 (M + Na); HRMS (ESI) calcd for $C_{33}H_{54}O_5Na$ $[M + Na]^+$ 553.3869, found 553.3876.

TPGS-750-M (2). A mixture containing DL-α-tocopherol succinate (2.97 g, 5.60 mmol), poly(ethylene glycol) monomethylether-750 (4.00 g, 5.33 mmol) and *p*-TsOH (0.15 g, 0.79 mmol) in toluene (20 mL) was refluxed for 5 h using a Dean−Stark trap. After cooling to rt, the mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ (3 × 50 mL), brine (2 × 30 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford the title compound (6.60 g, 98%) as a waxy solid. IR (neat) 2888, 1755, 1739, 1465, 1414, 1346, 1281, 1245, 1202, 1109, 947, 845 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28−4.26 (m, 2H), 3.71−3.54 (m, PEG), 3.38 (s, 3H), 2.93 (t, $J = 7.2$ Hz, 2H), 2.79 (t, $J = 7.2$ Hz, 2H), 2.58 (t, $J = 6.8$ Hz, 2H), 2.08 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.84−1.70 (m, 2H), 1.55−1.04 (m, 24H), 0.87−0.83 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 170.9, 149.5, 140.6, 126.7, 125.0, 123.0, 117.4, 94.5, 75.1, 72.0, 70.64, 70.56, 69.1, 64.0, 59.0, 39.4, 37.6, 37.5, 37.4, 37.3, 32.8, 32.7, 31.1, 29.2, 28.9, 28.0, 24.8, 24.5, 22.8, 22.7, 21.1, 20.6, 19.8, 19.7, 13.0, 12.1, 11.8; MS (ESI) m/z 1272 (M + Na).

DL-α-Tocopherol Succinate (4), >150 g Scale. DL-α-Tocopherol (66.4 g, 154.1 mmol) and methylene chloride (300 mL) were charged under nitrogen into a 1 L single necked round-bottom flask that had been oven-dried and cooled under vacuum. Succinic anhydride (23.1 g, 231 mmol) was added to the clear yellow solution followed by the addition of 4-dimethylaminopyridine (9.4 g, 77.1 mmol) and finally triethylamine (21.5 mL, 154 mmol). The reaction mixture was stirred at 23 °C overnight during which time the reaction mixture became a dark purplish solution. HPLC and TLC (3:7 EtOAc/hexanes, $R_f = 0.3$) indicated the reaction was complete. The reaction mixture was poured into a 1 L separatory funnel, and the flask was rinsed with methylene chloride (300 mL). The organic layer was washed with 1 M HCl (160 mL) (× 3), water (100 mL) (× 2), and saturated aqueous sodium chloride solution (250 mL). The organic layer was dried over Na_2SO_4 and filtered, and the solvent was emoved *in vacuo* affording a dark, viscous oil. The oil was poured onto a pad of silica gel (600 g in a 1.2 L filter funnel) and then eluted first with methylene chloride (1.5 L) (to remove impurity) followed by elution with 1:1 EtOAc/hexanes (3 L). Concentration of the solvent *in vacuo* followed by storage under high vacuum overnight affords 82.56 g of a faintly yellow semisolid containing 4 wt % EtOAc (79.26 g actual, 96.9%). NMR ($CDCl_3$) was consistent with the desired product. Used as is for the next reaction.

TPGS-750-M (2). DL-α-Tocopherol succinate (79.26 g, 149.3 mmol) was dissolved in toluene (560 mL, 5.3 mol) in a 1 L 3-necked round-bottom flask under a stream of nitrogen. MPEG 750 (104.5 g, 141.9 mmol) was added to the reaction mixture followed by the addition of *p*-toluenesulfonic acid monohydrate (3.01 g, 15.8 mmol) which caused a slight lightening of the solution. The flask was fitted with a Dean−Stark trap (receiver filled with toluene) and a condenser. The reaction mixture was heated to reflux for 5 h. HPLC indicates that starting material still remains. The reaction mixture was cooled to room temperature, additional MPEG-750 (5.00 g, 6.78 mmol) was added, and the reaction was heated to reflux for an additional 5 h. HPLC indicated that almost all of the starting material was gone. The reaction mixture was cooled to room temperature and concentrated on a rotary evaporator to afford a viscous dark brown oil. The oil was passed through a pad of basic aluminum oxide (600 g in a 0.2 L filter funnel) eluting with methylene chloride (3 L). The solvent was removed *in vacuo* to afford a faintly yellow waxy solid. The material was placed under high vacuum keeping the material at 50 °C (the waxy solid liquefies at this temperature) until removal of the residual toluene and methylene chloride was complete. After cooling and resolidification, 174.11 g (98.2%) of material was obtained that was identical in all aspects (HPLC, ^{1}H NMR, ^{13}C NMR) with the sample prepared on a smaller scale.

General Procedure for Cross Metathesis (Table 3). Alkene (0.50 mmol), acrylate (1.00 mmol)/ketone (1.50 mmol), and Grubbs-2 catalyst (8.5 mg, 0.010 mmol) were sequentially added into a Teflon-coated stir-bar-containing Biotage 2−5 mL microwave reactor vial at rt, and then the vial was sealed with a septum. An aliquot of TPGS-750-M/H_2O (1.0 mL; 2.5% TPGS-750-M by weight; all cross-coupling reactions were conducted at 0.5 M unless stated otherwise) was added via syringe, and the resulting solution was allowed to stir at rt for 12 h. The homogeneous reaction mixture was then diluted with EtOAc (2 mL) and filtered through a bed of silica gel, and the bed was further washed (3 × 5 mL) with EtOAc to collect all of the cross-coupled material. The volatiles were removed *in vacuo* to afford the crude product that was subsequently purified by flash chromatography on silica gel.

(*E*)-*tert*-Butyl 4-(2-(*tert*-Butyldimethylsilyloxy)phenyl)-2-butenoate (Table 3, entry 1). The representative procedure above was followed using *tert*-butyl(2-allylphenoxy)dimethylsilane (124 mg, 0.50 mmol), *tert*-butyl acrylate (128 mg, 1.00 mmol), and Grubbs-2 catalyst (8.5 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless oil (158 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.10 (m, 2H), 7.00 (dt, $J = 15.6$, 6.4 Hz, 1H), 6.91 (dt, $J = 7.6$, 1.2 Hz, 1H), 6.82 (dd, $J = 8.0$, 0.8 Hz, 1H), 5.68 (dt, $J = 15.6$, 1.6 Hz, 1H), 3.48 (dd, $J = 6.4$, 1.6 Hz, 2H), 1.46 (s, 9H), 1.01 (s, 9H), 0.25 (s, 6H).[14]

(*E*)-5-(2-(*tert*-Butyldimethylsilyloxy)phenyl)pent-3-en-2-one (Table 3, entry 2). The representative procedure above was followed using *tert*-butyl(2-allylphenoxy)dimethylsilane (124 mg, 0.50 mmol), methyl vinyl ketone (106 mg, 1.50 mmol), and Grubbs-2 catalyst (8.5 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless oil (107 mg, 74%). IR (neat) 3062, 3034, 2932, 2894, 2859, 1699, 1676, 1626, 1599, 1582, 1492, 1472, 1452, 1422, 1390, 1361, 1254, 1182, 1108, 1043, 982, 929 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (td, $J = 7.6$, 1.6 Hz, 1H), 7.11 (dd, $J = 7.6$, 1.6 Hz, 1H), 6.95 (dt, $J = 16.0$, 6.4 Hz, 1H), 6.92 (td, $J = 7.6$, 1.2 Hz, 1H), 6.84 (dd, $J = 7.6$, 1.2 Hz, 1H), 6.03 (dt, $J = 16.0$, 1.6 Hz, 1H), 3.54 (dd, $J = 6.4$, 1.6 Hz, 2H), 2.24 (s, 3H), 1.01 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 153.7, 146.8, 132.0, 130.7, 128.4, 128.1, 121.4, 118.6, 33.7, 26.9, 25.9, 18.4, −4.0; EI-MS m/z (%) 275

(M − CH_3^+, 2), 233 (M − $C_4H_9^+$, 100), 215 (20), 151 (8), 75 (42); HRMS (EI) calcd for $C_{13}H_{17}O_2Si$ [M − C_4H_9]$^+$ 233.0998, found 233.1006.

(*E*)-2-Adamantyl 4-(4-methoxyphenyl)-2-butenoate (Table 3, entry 3). The representative procedure was followed using 4-allylanisole (74 mg, 0.50 mmol), 2-adamantyl acrylate (206 mg, 1.00 mmol), and Grubbs-2 catalyst (8.5 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a colorless oil (134 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.08 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 5.84 (dt, J = 15.2, 1.2 Hz, 1H), 4.99 (br s, 1H), 3.80 (s, 3H), 3.47 (dd, J = 6.8, 1.2 Hz, 2H), 2.05−2.01 (m, 4H), 1.90−1.74 (m, 8H), 1.58−1.56 (m, 2H).[14]

(*E*)-*tert*-Butyl 3-(2,4-Dimethylphenyl)acrylate (Table 3, entry 4). The representative procedure was followed using 2,4-dimethyl-1-vinylbenzene (66 mg, 0.50 mmol), *tert*-butyl acrylate (128 mg, 1.00 mmol), and Grubbs-2 catalyst (8.5 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 2% EtOAc/hexanes) afforded the product as a colorless oil (86 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 15.6 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.03−7.01 (m, 2H), 6.29 (d, J = 15.6 Hz, 1H), 2.42 (s, 3H), 2.34 (s, 3H), 1.55 (s, 9H).[14]

(*E*)-*tert*-Butyl 11-(*tert*-Butyldimethylsilyloxy)-2-undecenoate (Table 3, entry 5). The representative procedure was followed using *tert*-butyl(dec-9-enyloxy)dimethylsilane (135 mg, 0.50 mmol), *tert*-butyl acrylate (128 mg, 1.00 mmol), and Grubbs-2 catalyst (8.5 mg, 0.01 mmol). Column chromatography on silica gel (eluting with 2% EtOAc/hexanes) afforded the product as a colorless oil (176 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (dt, J = 15.6, 7.2 Hz, 1H), 5.73 (dt, J = 15.6, 1.2 Hz, 1H), 3.61 (t, J = 7.2 Hz, 2H), 2.17 (qd, J = 7.2, 1.2 Hz, 2H), 1.52−1.42 (m, 4H), 1.48 (s, 9H), 1.32−1.30 (m, 8H), 0.90 (s, 9H), 0.05 (s, 6H).[14]

General Procedure for Ring-Closing Metathesis (Table 3). Diene (0.20 mmol) and Grubbs-2 catalyst (3.4 mg, 0.004 mmol) were both added into a Teflon-coated stir-bar-containing Biotage 2−5 mL microwave reactor vial at rt, and the vial was sealed with a septum. An aliquot of TPGS-750-M/H_2O was added via syringe (2.0 mL; 2.5% TPGS-750-M by weight; all RCM reaction were conducted at 0.1 M unless stated otherwise), and the resulting solution was allowed to stir at rt for 3 h. The homogeneous reaction mixture was then diluted with EtOAc (2 mL) and filtered through a bed of silica gel, and the bed was further washed (3 × 5 mL) with EtOAc to collect all of the cyclized material. The volatiles were removed *in vacuo* to afford the crude product, which was subsequently purified by flash chromatography using silica gel.

1-Tosyl-1,2,5,6-tetrahydropyridine (Table 3, entry 6). The representative procedure was followed using *N*-allyl-*N*-(but-3-enyl)-4-methylbenzenesulfonamide (53 mg, 0.20 mmol) and Grubbs-2 catalyst (3.4 mg, 0.004 mmol). Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a white solid (47 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.77−5.72 (m, 1H), 5.63−5.58 (m, 1H), 3.58−3.55 (m, 2H), 3.16 (t, J = 6.0 Hz, 2H), 2.42 (s, 3H), 2.24−2.18 (m, 2H).[35]

1-Tosyl-2,5,6,7-tetrahydro-1*H*-azepine (Table 3, entry 7). The representative procedure was followed using *N*-allyl-4-methyl-*N*-(pent-4-enyl)benzenesulfonamide (56 mg, 0.20 mmol) and Grubbs-2 catalyst (3.4 mg, 0.004 mmol). Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a white solid (44 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.79−5.74 (m, 1H), 5.67−5.62 (m, 1H), 3.83−3.82 (m, 2H), 3.38 (t, J = 6.0 Hz, 2H), 2.42 (s, 3H), 2.20−2.15 (m, 2H), 1.82−1.76 (m, 2H).[36]

General Procedure for Heck Coupling (Table 5). The catalyst Pd[P(t-Bu)$_3$]$_2$ (5.1 mg, 0.01 mmol) and aryl iodide (0.50 mmol) were added under argon into a 5.0 mL microwave vial equipped with a large stir bar and Teflon-lined septum. An aliquot of TPGS-750-M/H_2O solution (1.0 mL; 5.0% TPGS-750-M by weight), triethylamine (208 μL, 1.50 mmol), and acrylate/styrene (1.0 mmol) were added by syringe, and the resulting mixture was allowed to stir at rt for 4−12 h. The homogeneous reaction mixture was then diluted with EtOAc (2 mL) and filtered through a bed of silica gel, and the bed was further washed (3 × 5 mL) with EtOAc to collect all of the coupled material. The volatiles were removed *in vacuo* to afford the crude produc, which was subsequently purified by flash chromatography on silica gel.

(*E*)-*tert*-Butyl 3-(4-Methoxyphenyl)acrylate (Table 5, entry 1). Following the general procedure using 4-methoxyiodobenzene (117 mg, 0.50 mmol) and *tert*-butyl acrylate (145 μL, 1.00 mmol), the reaction was stirred for 4 h at rt. Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless oil (113 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 16.0 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.25 (d, J = 16.0 Hz, 1H), 3.84 (s, 3H), 1.54 (s, 9H).[37]

(*E*)-1-(2,4-Dimethylstyryl)-2-methoxynaphthalene (Table 5, entry 2). Following the general procedure using 1-iodo-2-methoxynaphthalene (142 mg, 0.50 mmol) and 2,4-dimethylstyrene (132 μL, 1.0 mmol), the reaction was stirred for 12 h at rt. Column chromatography on silica gel (eluting with 5% EtOAc/hexanes) afforded the product as a tan semisolid (137 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.7 Hz, 1H), 7.81 (t, J = 7.8 Hz, 2H), 7.68 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.40−7.30 (m, 4H), 7.10 (d, J = 8.2 Hz, 1H), 7.05 (s, 1H), 3.98 (s, 3H), 2.40 (s, 3H), 2.37 (s, 3H).[8]

General Procedure for Suzuki−Miyaura Coupling (Table 5). Arylboronic acid (0.50−1.00 mmol), aryl bromide (0.50 mmol), and Pd(dtbpf)Cl_2 (6 mg, 0.01 mmol) were added to a reaction tube equipped with a magnetic stir bar. Under a positive flow of argon while stirring, surfactant solution (1.0 mL, 2 wt % TPGS-750-M in water), and Et_3N (0.21 mL, 1.5 mmol) were added by syringe and stirred vigorously for 2−24 h. The reaction mixture was then diluted with brine and extracted with EtOAc. The solution obtained was dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel to afford the title compounds.

3-Phenylbenzonitrile (Table 5, entry 3). Following the general procedure using 3-bromobenzonitrile (91 mg, 0.5 mmol) and phenylboronic acid (91 mg, 0.75 mmol), the reaction was stirred for 2 h at rt. Column chromatography on silica gel (eluting with 20% CH_2Cl_2/hexanes) afforded the product as a slightly yellow oil (83 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.79 (m, 2H), 7.62−7.38 (m, 7H).[38]

4-Methoxy-2′,4′,6′-tri-isopropylbiphenyl (Table 5, entry 4). Following the general procedure using 4-methoxy-phenylboronic acid (152 mg, 1.00 mmol) and 2,4,6-tri-iso-propylbromobenzene (126 μL, 0.50 mmol) the reaction was stirred for 24 h at rt. Column chromatography on silica gel (eluting with 5% CH_2Cl_2/hexanes) afforded the product as a white solid (137 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.7 Hz, 2H), 7.13 (s, 2H), 7.01 (d, J = 8.7 Hz, 2H), 3.92 (s, 3H), 3.01 (sept, J = 6.9 Hz, 1H), 2.73 (sept, J = 6.9 Hz, 2H), 1.38 (d, J = 6.9 Hz, 6H), 1.15 (d, J = 6.9 Hz, 12H).[39]

General Procedure for Sonogashira Coupling (Table 5). The catalyst Pd(CH_3CN)$_2Cl_2$ (1.3 mg, 0.005 mmol) and XPhos (6.2 mg, 0.013 mmol) were added under argon into a 5.0 mL microwave vial equipped with a large stir bar and Teflon-lined septum. An aliquot of TPGS-750-M/H_2O (1.0 mL; 3.0% TPGS-750-M by weight) solution, triethylamine (140 μL, 1.00 mmol), aryl bromide (0.50 mmol), and alkyne (0.75 mmol) were added by syringe, and the resulting solution was allowed to stir at rt for 21−25 h. The homogeneous reaction mixture was then diluted with EtOAc (2 mL),and filtered through a bed of silica gel, and the bed was further washed (3 × 5 mL) with EtOAc to collect all of the coupled material. The volatiles were removed *in vacuo* to afford the crude product, which was subsequently purified by flash chromatography on silica gel.

1-(6-Chlorohex-1-ynyl)-4-methoxybenzene (Table 5, entry 5). Following the general procedure using 4-bromoanisole (60 mg, 0.48 mmol) and 6-chloro-1-hexyne (90 μL, 0.74 mmol), the reaction was stirred for 25 h at rt. Column chromatography on silica gel (eluting with 1% EtOAc/hexanes) afforded the product as a pale yellow oil (70 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 3.62 (t, J = 6.6 Hz, 2H), 2.45 (t, J = 7.0 Hz, 2H), 2.02−1.94 (m, 2H), 1.81−1.71 (m, 2H).[10]

2-(Cyclohexenylethynyl)naphthalene (Table 5, entry 6). Following the general procedure using 2-bromonaphthalene (103 mg, 0.50 mmol) and 1-ethynylcyclohex-1-ene (100 μL, 0.85 mmol), the reaction was stirred for 21 h at rt. Column chromatography on silica gel (eluting with 1% EtOAc/hexanes) afforded the product as an off-white solid (115 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.82−7.76 (m, 3H), 7.50−7.45 (m, 3H), 6.29−6.27 (m, 1H), 2.30−2.26 (m, 2H), 2.21−2.16 (m, 2H), 1.75−1.62 (m, 4H).[10]

General Procedure for Buchwald−Hartwig Amination (Table 5). The catalyst [(π-allyl)PdCl]$_2$ (2.1 mg, 0.006 mmol), ligand cBRIDP (Takasago; 7.6 mg, 0.022 mmol), KO-*t*-Bu (184 mg, 1.56 mmol), and amine (1.20 mmol) were added under argon into a 5.0 mL microwave vial equipped with a large stir bar and Teflon lined septum. An aliquot of TPGS-750-M/H_2O (1.0 mL; 2.0% TPGS-750-M by weight) solution and aryl bromide (1.00 mmol) were added by syringe, and the resulting solution was allowed to stir at rt for 19−20 h. The homogeneous reaction mixture was then diluted with EtOAc (2 mL) and filtered through a bed of silica gel, and the bed was further washed (3 × 5 mL) with EtOAc to collect all of the coupled material. The volatiles were removed *in vacuo* to afford the crude product that was subsequently purified by flash chromatography on silica gel.

***N*-(*m*-Tolyl)-3-aminopyridine (Table 5, entry 7).** Following the general procedure using 3-bromotoluene (121 μL, 1.00 mmol) and 3-aminopyridine (113 mg, 1.20 mmol), the reaction was stirred for 20 h at rt. Column chromatography on silica gel (eluting with 40% EtOAc/hexanes) afforded the product as an off-white solid (180 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (br s, 1H), 8.17 (br s, 1H) 7.41 (dd, J = 8.4, 1.6 Hz, 1H), 7.21−7.17 (m, 2H), 6.91 (s, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 7.2 Hz, 1H), 5.81 (br s, 1H), 2.33 (s, 3H).[40]

2,6-Dimethyl-*N*-(*m*-tolyl)aniline (Table 5, entry 8). Following the general procedure using 3-bromotoluene (121 μL, 1.00 mmol) and 2,6-dimethylaniline (148 μL, 1.20 mmol), the reaction was stirred for 19 h at rt. Column chromatography on silica gel (eluting with 30% EtOAc/hexanes) afforded the product as an off-white solid (196 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.09 (m, 3H), 7.06 (t, J = 7.6 Hz, 1H), 6.59 (d, J = 7.2 Hz, 1H), 6.36 (s, 1H), 6.32 (d, J = 8.0 Hz, 1H), 5.15 (br, 1H), 2.26 (s, 3H), 2.23 (s, 6H).[11]

General Procedure for Negishi Coupling (Table 6). In a 5 mL round-bottom flask under argon containing zinc dust/powder and $PdCl_2(Amphos)_2$ was added a solution of 2 wt % of TPGS-750-M. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) was added at rt followed by the addition of alkyl halide (2.0−3.0 mmol) and aryl or alkenyl bromide (1 mmol). The flask was stirred vigorously at rt for 12−48 h. The reaction mixture was then filtered through a plug of silica (10 g) and washed with diethyl ether (70 mL) into a 100 mL flask containing 2 g of silica. Solvents were removed under vacuum. The residue was loaded on silica gel and purified by flash chromatography to afford the product.

Ethyl 4-Cyclohexylbenzoate (Table 6, entry 1). Following the general procedure, using zinc dust (195 mg, 3 mmol), $PdCl_2(Amphos)_2$ (3.5 mg, 0.005 mmol), 2 wt % of TPGS-750-M (3 mL), TMEDA (116 mg, 1 mmol), bromocyclohexane (407 mg, 2.5 mmol), and ethyl bromobenzoate (229 mg, 1 mmol), the reaction was stirred for 48 h at rt. Column chromatography on silica gel (eluting with 1% Et_2O/petroleum ether) afforded the product (174 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 4.37 (q, J = 7.0 Hz, 2H), 2.56−2.55 (m, 1H), 1.87−1.84 (m, 4H), 1.43−1.38 (m, 9H).[41]

Ethyl 4-[(4-Ethoxycarbonyl)phenyl]butanoate (Table 6, entry 2). Following the general procedure, using zinc dust (195 mg, 3 mmol), $PdCl_2(Amphos)_2$ (3.5 mg, 0.005 mmol), 2 wt % of TPGS-750-M (3 mL), TMEDA (116 mg, 1 mmol), ethyl 4-bromobutanoate (390 mg, 2 mmol), and ethyl bromobenzoate (229 mg, 1 mmol), the reaction was stirred for 48 h at rt. Column chromatography on silica gel (eluting with 10% Et_2O/petroleum ether) afforded the product (187 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.35 (q, J = 7.5 Hz, 2H), 4.11 (q, J = 7.5 Hz, 2H), 2.69 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.95 (quint, J = 7.5 Hz, 2H), 1.37 (t, J = 7.5 Hz, 3H), 1.24 (t, J = 7.5 Hz, 3H).[42]

Ethyl 4-Decylbenzoate (Table 6, entry 3). Following the general procedure, using zinc powder (260 mg, 4 mmol), $PdCl_2(Amphos)_2$ (7 mg, 0.01 mmol), 2 wt % of TPGS-750-M (6 mL), TMEDA (580 mg, 5 mmol), iododecane (804 mg, 3 mmol), and ethyl bromobenzoate (229 mg, 1 mmol), the reaction was stirred for 36 h at rt. Column chromatography on silica gel (eluting with 1% Et_2O/petroleum ether) afforded the product (258 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 4.35 (q, J = 7.5 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 1.63−1.60 (m, 2H), 1.38 (t, J = 7.5 Hz, 3H), 1.27−1.25 (m, 14H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz) δ 166.9, 148.6, 129.7, 128.5, 128.1, 60.9, 36.2, 32.1, 31.8, 29.8, 29.7, 29.6, 29.5, 29.4, 22.9, 14.5, 14.3; HRMS ($C_{19}H_{30}O_2$) calcd 290.2246, found 290.2252.

(*E*)-((Dodec-4-en-1-yloxy)methyl)benzene (Table 6, entry 4). Following the general procedure, using zinc powder (260 mg, 4 mmol), $PdCl_2(Amphos)_2$ (7 mg, 0.01 mmol), 2 wt % of TPGS-750-M (6 mL), TMEDA (580 mg, 5 mmol), 1-iodoheptane (678 mg, 3 mmol), and (*E*)-(((5-iodopent-4-en-1-yl)oxy)methyl)benzene (302 mg, 1 mmol, Z/E = 1/99), the reaction was stirred for 16 h at rt. Column chromatography on silica gel (eluting with 5% EtOAc/petroleum ether) afforded the product (231 mg, 84%, Z/E = 1/99). ^{1}H NMR (400 MHz) δ 7.35−7.34 (m, 4H), 7.30−7.27 (m, 1H), 5.45−5.36 (m, 2H), 4.50 (s, 2H), 3.48 (t, J = 6.6 Hz, 2H), 2.08 (q, J = 6.7 Hz, 2H), 1.97 (q, J = 6.7 Hz, 2H), 1.68 (quint, J = 7.0 Hz, 2H), 1.35−1.27 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz) δ 138.9, 131.3, 129.6, 128.6, 127.9, 127.7, 73.1, 70.1, 32.8, 32.1, 29.9, 29.8, 29.4, 29.4, 29.4, 22.9, 14.4; HRMS ($C_{19}H_{30}O$) calcd 274.2297, found 274.2293.

1-((*Z*)-Non-1-enyl)benzene (Table 6, entry 5). Following the general procedure, using zinc powder (260 mg, 4 mmol), $PdCl_2(Amphos)_2$ (7 mg, 0.01 mmol), 2 wt % of TPGS-750-M (6 mL), TMEDA (580 mg, 5 mmol), 1-iodoheptane (678 mg, 3 mmol), and 1-((*Z*)-2-bromovinyl)benzene (183 mg, 1 mmol, Z/E = 99/1), the reaction was stirred for 16 h at rt. Column chromatography on silica gel (eluting with petroleum ether) afforded the product (182 mg, 90%, Z/E = 88/12). ^{1}H NMR (400 MHz) δ 7.34 (t, J = 7.7 Hz, 2H), 7.27 (d, J = 6.9 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 6.40 (brd, J = 11.7 Hz, 1H), 5.67 (dt, J = 11.7, 7.3 Hz, 1H), 2.34 (dq, J = 7.5, 1.5 Hz, 2H), 1.47−1.42 (m, 2H), 1.31−1.26 (m, 8H), 0.88 (t, J = 7.1 Hz, 3H).[43]

(*Z*)-Ethyl Dodec-5-enoate (Table 6, entry 6). Following the general procedure, using zinc powder (260 mg, 4 mmol), $PdCl_2(Amphos)_2$ (7 mg, 0.01 mmol), 2 wt % of TPGS-750-M (6 mL), TMEDA (580 mg, 5 mmol), (*Z*)-1-bromooct-1-ene (181 mg, 1 mmol, Z/E = 99/1), and ethyl 4-bromobutanoate (390 mg, 2 mmol), the reaction was stirred for 12 h at rt. Column chromatography on silica gel (eluting with 5% EtOAc/petroleum ether) afforded the product (196 mg, 87%, Z/E = 99/1). ^{1}H NMR (400 MHz) δ 5.43−5.30 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.28 (q, J = 7.6 Hz, 2H), 2.06 (q, J = 7.4 Hz, 2H), 2.00 (q, J = 7.7 Hz, 2H), 1.70−1.65 (m, 2H), 1.34−1.23 (m, 11H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz) δ 174.0, 131.3, 128.6, 60.4, 34.0, 32.0, 29.9, 29.2, 27.4, 26.7, 25.1, 22.9, 14.5, 14.3; HRMS ($C_{14}H_{26}O_2$) calcd 226.1933, found 226.1934.

(*E*)-*n*-Butyl 3-(2-Acetamido-4-methoxyphenyl)acrylate. *N*-(3-Methoxyphenyl)acetamide (41 mg, 0.25 mmol), *n*-butyl acrylate (64 mg, 0.50 mmol), 1,4-benzoquinone (27 mg, 0.25 mmol), $AgNO_3$ (85 mg, 0.5 mmol), and $[Pd(MeCN)_4](BF_4)_2$ (11 mg, 0.025 mmol) were sequentially added under air to a reaction tube equipped with a stir bar and a septum. A degassed aqueous solution containing TPGS-750-M (1.0 mL, 2 wt %) was added by syringe, and the resulting mixture was vigorously stirred for 20 h. After this time, the contents of the flask were quenched with aqueous NaHCO$_3$ and extracted with EtOAc. The solution obtained was filtered through the plug of silica gel and anhydrous MgSO$_4$ and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with 50% EtOAc/hexanes to afford the product as an off-white solid (60 mg, 83%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, J = 15.6 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 1.7 Hz, 1H), 7.37 (br s, 1H), 6.74 (dd, J = 8.8, 1.7 Hz, 1H), 6.30 (d, J = 15.6 Hz, 1H), 4.19 (t, J = 6.7 Hz, 2H), 3.83 (s, 3H), 2.25 (s, 3H), 1.68 (quint, J = 6.7 Hz, 4H), 1.42 (sext, J = 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H).[31c]

3-(4,4′-Dimethoxybiphenyl-2-yl)-1,1-dimethylurea. 3-(3-Methoxyphenyl)-1,1-dimethylurea (49 mg, 0.25 mmol), 1-iodo-4-methoxybenzene (117 mg, 0.50 mmol), AgOAc (0.5 mmol, 83 mg), and Pd(OAc)$_2$ (0.025 mmol, 5.6 mg) were sequentially added under air to a reaction tube equipped with a stir bar and septum. An aliquot of TPGS-750-M/H$_2$O (1.0 mL; 2.0% TPGS-750-M by weight) solution and 48 wt % aqueous HBF$_4$ solution (1.25 mmol, 0.16 mL) were added by syringe and stirred vigorously for 24 h. After the reaction, the contents of the flask were quenched with NaHCO$_3$ and extracted with EtOAc. The solution obtained was dried over anhydrous MgSO$_4$ and concentrated by rotary evaporation. The residue was purified by flash chromatography eluting with 1:1 EtOAc/hexanes to afford the product (51 mg, 68%) as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (d, J = 2.6 Hz, 1H), 7.27 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 8.6 Hz, 2H), 6.61 (dd, J = 8.3, 2.6 Hz, 1H), 3.84 (s, 6H), 2.81 (s, 6H).[31b]

***N*-Cinnamyl-*N*-methylaniline (Table 7, entry 1).** Cinnamyl alcohol (100 mg, 0.75 mmol), *N*-methylaniline (53 mg, 0.50 mmol), dppf (14 mg, 0.025 mmol), K$_2$CO$_3$ (207 mg, 1.5 mmol), and [Pd(allyl)Cl]$_2$ (4.5 mg, 0.0125 mmol) were sequentially added under argon to a reaction tube equipped with a stir bar and a septum. Degassed TPGS-750-M solution (1.0 mL, 2 wt %) and HCO$_2$Me (0.12 mL, 2.0 mmol) were added by syringe and vigorously stirred for 20 h. After the reaction, the contents of the flask were diluted with brine and extracted with EtOAc. The solution obtained was dried over anhydrous MgSO$_4$, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography eluting with 10% EtOAc/hexanes to afford the product as a pale yellow liquid (102 mg, 92%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36−7.34 (m, 2H), 7.32−7.28 (m, 2H), 7.27−7.21 (m, 3H), 6.78 (dd, J = 8.8, 0.8 Hz, 2H), 6.72 (td, J = 7.3, 0.8 Hz, 1H), 6.51 (d, J = 15.9 Hz, 1H), 6.25 (dt, J = 15.9, 5.5 Hz, 1H), 4.08 (dd, J = 5.5, 1.6 Hz, 2H), 3.02 (s, 3H).[44]

General Procedure for Aminations with Allylic Ethers (Table 7). An allylic phenyl ether (0.5 mmol), amine (0.75 mmol), DPEphos (0.005 mmol, 2.7 mg), K$_2$CO$_3$ (0.75 mmol, 103 mg), and [Pd(allyl)Cl]$_2$ (0.0025 mmol, 0.9 mg) were sequentially added under air to a reaction tube equipped with a stir bar and a septum. Degassed TPGS-750-M solution (1.0 mL, 2 wt %), and HCO$_2$Me (2.0 mmol, 0.12 mL) were added by syringe and vigorously stirred for 0.5 − 2.5 h. Upon completion of the reaction, the contents of the flask were diluted with brine and extracted with EtOAc. The solution obtained was dried over anhydrous MgSO$_4$, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product.

(*E*)-*N*-Benzyl-*N*-(3-phenyl-2-propenyl)-3-phenylalanine Ethyl Ester (Table 7, entry 2). Following the general procedure using cinnamyloxybenzene (105 mg, 0.50 mmol) and ethyl 2-(benzylamino)-3-phenylpropanoate (212 mg, 0.75 mmol), the reaction was stirred for 2.5 h at rt. Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product as a pale yellow liquid (190 mg, 95%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33−7.11 (m, 15H), 6.47 (d, J = 16.2 Hz, 1H), 6.04 (ddd, J = 16.2, 7.8, 5.0 Hz, 1H), 4.24−4.10 (m, 2H), 4.03 (d, J = 14.2 Hz, 1H), 3.75 (dd, J = 8.2, 7.2 Hz, 1H), 3.62 (d, J = 14.2 Hz, 1H), 3.52 (ddd, J = 14.5, 4.9, 1.8 Hz, 1H), 3.28 (ddd, J = 14.5, 7.8, 0.6 Hz, 1H), 3.11 (dd, J = 13.7, 7.2 Hz, 1H), 2.98 (dd, J = 13.7, 8.2 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H).[32]

***N*-Methyl-*N*-(2-methallyl)-1-naphthylmethylamine (Table 7, entry 3).** Following the general procedure using (2-methylallyloxy)-benzene (74 mg, 0.50 mmol) and *N*-methyl-*N*-naphthylmethylamine (128 mg, 0.75 mmol), the reaction was stirred for 1 h at rt. Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product as a colorless liquid (88 mg, 80%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.32 (d, J = 8.8 Hz, 1H), 7.83 (dd, J = 7.1, 2.3 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.51−7.37 (m, 4H), 4.92 (s, 1H), 4.85 (s, 1H), 3.87 (s, 2H), 2.96 (s, 2H), 2.14 (s, 3H), 1.73 (s, 3H).[32]

(*E*)-*N*,*N*-Dibenzyl-3-phenylprop-2-en-1-amine (Table 7, entry 4). Following the general procedure using cinnamyloxybenzene (105 mg, 0.50 mmol) and dibenzylamine (148 mg, 0.75 mmol), the reaction was stirred for 0.5 h at rt. Column chromatography on silica gel (eluting with 8% EtOAc/hexanes) afforded the product as a pale yellow liquid (145 mg, 93%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41−7.15 (m, 15H), 6.52 (d, J = 15.9 Hz, 1H), 6.29 (dt, J = 15.9, 11.4 Hz, 1H), 3.63 (s, 4H), 3.22 (d, J = 11.4 Hz, 2H).[45]

General Procedure for Suzuki−Miyaura Coupling with Allylic Ethers (Table 8). An allylic phenyl ether (0.25 mmol), arylboronic acid (0.38 mmol), and PdCl$_2$(DPEphos) (0.005 mmol, 3.6 mg) (or PdCl$_2$(dtbpf) were sequentially added under air to a reaction tube equipped with a stir bar and a septum. Degassed TPGS-750-M solution (0.8 mL, 2 wt %), and Et$_3$N (0.75 mmol, 0.1 mL) were added by syringe and vigorously stirred for 5−20 h. After the reaction, the contents of the flask were diluted with brine and extracted with EtOAc. The solution obtained was dried over anhydrous MgSO$_4$, filtered, and concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane/EtOAc to afford the product.

1-Cinnamyl-2-methylbenzene (Table 8, entry 1). Following the general procedure using cinnamyloxybenzene (53 mg, 0.25 mmol), *o*-tolylboronic acid (51 mg, 0.38 mmol), and PdCl$_2$(DPEphos) (0.005 mmol, 3.6 mg), the reaction was stirred for 5 h at rt. Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless liquid (51 mg, 99%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34−7.25 (m, 4H), 7.19−7.14 (m, 5H), 6.39−6.32 (m, 2H), 3.51 (d, J = 4.8 Hz, 2H), 2.32 (s, 3H).[33]

(*E*)-1-(3-(4-Methoxyphenyl)allyl)-2-methylbenzene (Table 8, entry 2). Following the general procedure using (*E*)-1-methoxy-4-(3-phenoxyprop-1-enyl)benzene (60 mg, 0.25 mmol), *o*-tolylboronic acid (51 mg, 0.38 mmol), and PdCl$_2$(DPEphos) (0.015 mmol, 11 mg), the reaction was stirred for 6 h at rt. Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless liquid (51 mg, 84%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29 (d, J = 8.7 Hz, 2H), 7.22−7.14 (m, 4H), 6.84 (d, J = 8.8 Hz, 2H), 6.33 (d, J = 15.8 Hz, 1H), 6.20 (dt, J = 15.8, 6.5 Hz, 1H), 3.80 (s, 3H), 3.52 (dd, J = 6.4, 1.1 Hz, 2H), 2.34 (s, 3H).[33]

1-Chloro-4-cinnamylbenzene (Table 8, entry 3). Following the general procedure using cinnamyl-oxybenzene (53 mg, 0.25 mmol), 4-chlorophenylboronic acid (58 mg, 0.38 mmol), and PdCl$_2$(D*t*-BPF) (0.015 mmol, 9.8 mg), the reaction was stirred for 20 h at rt. Column chromatography on silica gel (eluting with 3% EtOAc/hexanes) afforded the product as a colorless liquid (43 mg, 75%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 (d, J = 7.9 Hz, 2H), 7.32 (t, J = 7.3 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 7.9 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.42 (d, J = 15.8 Hz, 1H), 6.29 (dt, J = 15.8, 6.8 Hz, 1H), 3.49 (d, J = 6.7 Hz, 2H).[33]

General Procedure for Silylation with Allylic Ethers (Table 8). A 1 dram vial containing a strong magnetic stir bar was loaded with PdCl$_2$(DPEphos) (6 mol %, 10.8 mg, 15 μmol) and an allylic phenyl ether (0.25 mmol) and brought into a glovebag. After an atmosphere of argon was applied, hexamethyldisilane (77 μL, 0.38 mmol)/1,2-diphenyltetramethyldisilane (101.4 mg, 0.38 mmol), NEt_3 (139 μL, 1.0 mmol), and 2% TPGS-750-M/H_2O (1.5 mL) were added. The vial was *immediately* closed with a Teflon-coated cap and vigorously stirred for 20 h at rt. The reaction mixture was poured into brine (2 mL) and extracted with EtOAc (3 × 2 mL). All organic phases were collected, dried over anhydrous Na_2SO_4 and filtered through a short plug of silica gel, and the solvent was removed by a constant stream of argon. The residue was loaded on silica gel and purified by flash chromatography eluting with hexanes/EtOAc to afford the product.

Cinnamyldimethyl(phenyl)silane (Table 8, entry 4). Following the general procedure, using (*E*)-cinnamyl phenyl ether (52.6 mg, 0.25 mmol) and 1,2-diphenyltetramethyldisilane (101.4 mg, 0.38 mmol), silica gel chromatography (hexanes) yielded the product as a colorless oil (57.4 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.13 (m, 10H), 6.27−6.17 (m, 2H), 1.90 (dd, *J* = 4.8, 2.0 Hz, 2H), 0.32 (s, 6H).[13]

(*E*)-(3-(2-Methoxyphenyl)allyl)dimethyl(phenyl)silane (Table 8, entry 5). Following the general procedure, using (*E*)-1-methoxy-2-(3-phenoxyprop-1-enyl)benzene (60.1 mg, 0.25 mmol) and 1,2-diphenyltetramethyldisilane (101.4 mg, 0.38 mmol), silica gel chromatography (0−10% EtOAc/hexanes) yielded the product as a colorless oil (62.8 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59−7.34 (m, 6H), 7.19−7.16 (m, 1H), 6.92−6.85 (m, 2H), 6.59 (d, *J* = 15.5 Hz, 1H), 6.22 (dt, *J* = 15.5, 8.5 Hz, 1H), 3.84 (s, 3H), 1.96 (dd, *J* = 8.5, 1.5 Hz, 2H), 0.35 (s, 6H).[13]

(*E*)-(3-(3-Methoxyphenyl)allyl)trimethylsilane (Table 8, entry 6). Following the general procedure, using (*E*)-1-methoxy-3-(3-phenoxyprop-1-enyl)benzene (60.1 mg, 0.25 mmol) and hexamethyldisilane (77 μL, 0.38 mmol), silica gel chromatography (0−10% EtOAc/hexanes) yielded the product as a colorless liquid (48.5 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.20 (m, 1H), 6.94−6.73 (m, 3H), 6.28 (dt, *J* = 16.0, 7.5 Hz, 1H), 6.22 (d, *J* = 16.0 Hz, 1H), 3.83 (s, 3H), 1.69 (d, *J* = 7.0 Hz, 2H), 0.07 (s, 9H).[13]

Recycling of TPGS-750-M (Table 9). *N*-Allyl-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (26.5 mg, 0.10 mmol) and Grubbs-2 catalyst (1.7 mg, 0.002 mmol) were both added into a Teflon-coated stir-bar-containing Biotage 5 mL microwave reactor vial at rt, and the vial was sealed with a septum. An aliquot of TPGS/H_2O (1.0 mL; 2.5% TPGS by weight) was added via syringe, and the resulting solution was allowed to stir at rt for 2 h. Et_2O (3 mL) was then added to the reaction mixture and stirred for 10 s. The reaction mixture was then allowed to separate, and the upper (Et_2O) layer was removed by pipet. The aqueous layer was successively washed with Et_2O (3 × 3 mL). The combined Et_2O extracts layers were evaporated to afford the crude product, which was examined by 400 MHz ^{1}H NMR spectroscopy to reveal complete conversion of diene and clean formation of the corresponding cyclized product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 5.25−5.24 (m, 1H), 4.07−4.05 (m, 2H), 3.97−3.95 (m, 2H), 2.42 (s, 3H), 1.65 (s, 3H).[46] For the second run, the diene (26.5 mg, 0.10 mmol) and Grubbs-2 catalyst (1.7 mg, 0.002 mmol) were both added again to the same reaction vessel and stirred at rt for another 2 h. The workup was conducted in exactly the same way as described for the first cycle. This reaction was repeated six more times, each using the above diene (26.5 mg, 0.10 mmol) and Grubbs-2 catalyst (1.7 mg, 0.002 mmol).

ASSOCIATED CONTENT

S Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra of all new compounds and copies of ^{1}H NMR spectra of all known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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