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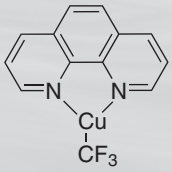

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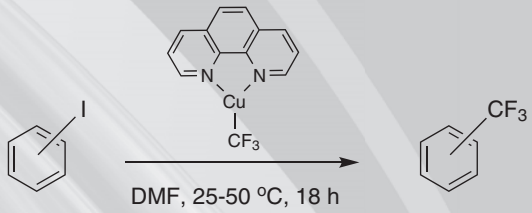
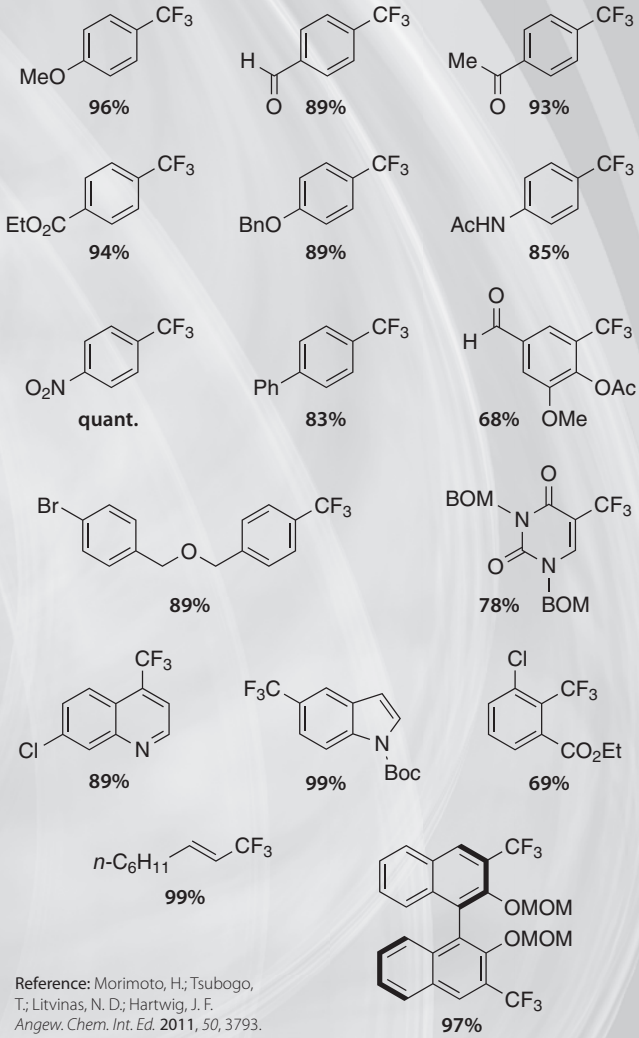


Representative Reaction Scope



Reference: Morimoto, H.; Tsubogo, T.; Litvinas, N. D.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 3793.

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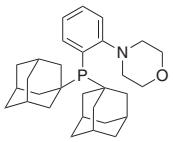
"PLEASE BOTHER US."

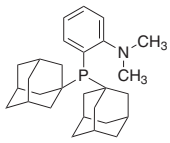
Dear Fellow Chemists,

We have had many suggestions for the DalPhos ligands shown below. These were recently developed by Professor Mark Stradiotto and his group at Dalhousie University. Both are air-stable, chelating N,P ligands that enable the Pd-catalyzed cross-coupling of ammonia. Mor-DalPhos is also effective in coupling hydrazine and acetone, and in the gold–catalyzed hydroamination. The catalysts are used with low loadings and exhibit excellent functional group tolerance and chemoselectivty.

(a) Lundgren, R. J.; Peters, B. D.; Alsabeh, P. G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4071. (b) Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8686.



751618



751413

751618	Di(1-adamantyl)-2-morpholinophenylphosphine (Mor-DalPhos)	250 mg 1 g
751413	Di(1-adamantyl)-2-dimethylaminophenylphosphine (Me-DalPhos)	250 mg 1 g

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John Radke
Director of Marketing, Chemistry

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Venice: The Dogana and San Giorgio Maggiore (oil on canvas, 91.5 × 122.0 cm) was completed in 1834 by Joseph Mallord William Turner (London, 1775–1851). A prolific British artist and an influential member of the Romantic Movement of the late eighteenth and first half of the nineteenth century, he elevated landscape painting to a level not achieved before and introduced several innovations to the genre. His talent manifested itself very early in life, and he was much admired as an artist in life and death, with institutions, works, and artistic prizes dedicated to preserving his legacy.

Detail from ***Venice: The Dogana and San Giorgio Maggiore***.
Photograph © Board of Trustees, National Gallery of Art, Washington.

This painting depicts a bustling maritime scene in the Grand Canal of Venice, which Turner had visited several times. (Another Venetian cityscape, painted seven years earlier by another British Romantic Movement artist, R. P. Bonington, has graced the cover of *Aldrichimica Acta*, Vol. 43, No. 1.) Turner intended this work as a celebration of commerce, as symbolized by the statue of Fortune atop the Dogana (Customs building) in the foreground. While Turner was not concerned with a faithful depiction of the scene, as evidenced by the apparent widening of the canal and placement of San Giorgio's church, his skill as a draftsman and his mastery of perspective drawing are evident in his precise, linear rendering of the buildings and sharp angles. His color combinations, freely handled layers of paint, and the sparkling water and light sky exemplify his lifelong preoccupation with the effects and significance of light in an awe-inspiring natural world.

This painting is part of the Widener Collection at the National Gallery of Art, Washington, DC.

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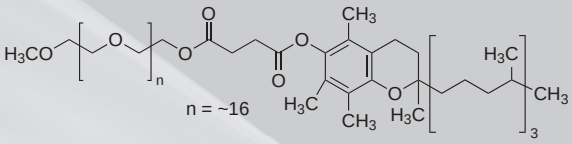

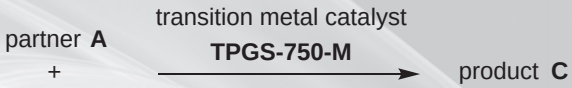

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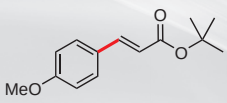

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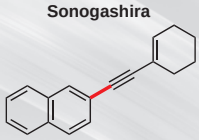

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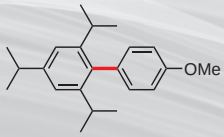

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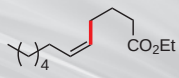

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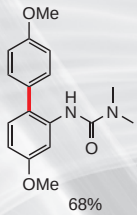

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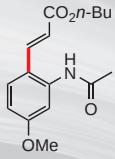
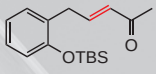


83%

ring-closing metathesis

88%

cross-metathesis



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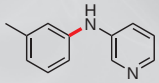

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Lipshutz, B. H. et al. *J. Org. Chem.* **2011**, *76*, 4379.

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"Designer"-Surfactant-Enabled Cross-Couplings in *Water* at Room Temperature

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Keywords. green chemistry; micellar catalysis; designer surfactants; cross-couplings; PTS; TPGS-750-M.

Abstract. New methodologies are discussed that allow for several commonly used transition-metal-catalyzed coupling reactions to be conducted within aqueous micellar nanoparticles at ambient temperatures.

Outline

1. Introduction

Green chemistry recently took a front row seat on the world stage. Unfortunately, it was not associated with any special technological advance; rather, the 200-million-plus gallons (ca. 5 million barrels) of oil that had leaked into the Gulf of Mexico focused attention on methods for dispersing such a huge quantity of localized hydrocarbons.[1] British Petroleum (BP) addressed this catastrophe by injecting dispersants at the site, the key ingredient being a mix of surfactants. While this tactic raised more than a few eyebrows with respect to additional pollutants having been introduced into the ecosphere, the presumption was that sodium dioctylsulfosuccinate (**1**), Span™ 80 (**3**), and a mixture of TWEEN® 80 (**4**) and 85 (**5**)—present in dispersants COREXIT® EC9500 and COREXIT® EC9527[2]—would help to "solubilize" the oil by forming micelles, thereby relocating over time the oil deposited within their lipophilic cores (**Figure 1**). While a disaster of this magnitude needs the tincture of time to assess its full impact on the environment, from a purely chemical perspective, tremendous hope has been placed on these surfactants in anticipation that they will prevent further damage to wildlife and shores.

This micellar chemistry undertaken on a grand scale by the petroleum industry highlights the potential for simple amphiphilic molecules to "solubilize" organic materials in a purely aqueous medium. Many other industries use surfactants routinely; examples include paint, cosmetics, cleaning, leather, carpet, asphalt, and pulp & paper companies.[3] Relatively small amounts have been used for decades in highly controlled environments, e.g., as "excipients" in the pharmaceutical arena, to help increase dissolution of otherwise water-insoluble drugs in aqueous media. But where are the studies on their usage in synthesis? Why not apply the same concepts of solubilization within micelles to reactants and catalysts that become, albeit transiently, the occupants? Of course, some synthetic chemistry can be, and has been, done in micelles.[4] Interestingly, this approach, oftentimes referred to as "micellar catalysis", is technically a misnomer since the micelle is not participating as a catalyst in the reaction itself. Nonetheless, why should these, or thousands of other surfactants created by industry and designed for a narrow range of specialized applications, be the most appropriate for use in state-of-the-art transition-metal-mediated cross-couplings? Since organic reactions are oftentimes very sensitive to solvent effects,[5] and since the lipophilic portions of micelles are functioning as the reaction medium, which surfactant should be used in this capacity to best assist metal-catalyzed reactions in water at room temperature? No one knows. *Perhaps it is time for synthetic chemists to start designing surfactants for synthetic chemistry.*

The situation just a few years ago was not encouraging in that there were virtually no *general* studies of the effect of varying micellar conditions on the most commonly used transition-metal-catalyzed couplings. As green chemistry continues to expand, critical reviews have appeared highlighting micellar media in which the "hydrophobic effect"—the tendency of nonpolar groups to cluster so as to shield themselves from contact with an aqueous environment[6]—assists with organometallic processes in water, such as in oxidation and reduction reactions,[7] as well as in selected C–C-bond forming reactions (e.g., hydroformylations). And so it was in recognition of the potential offered by micellar catalysis, performed in water as the gross reaction medium (and not the solvent), that we set out to develop "designer" surfactants for use in transition-metal-catalyzed cross-coupling reactions.

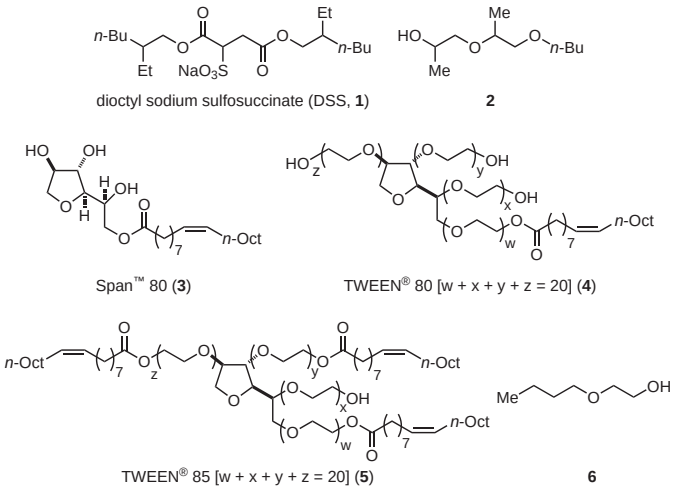


Figure 1. Ingredients of COREXIT® EC9500 (a Mixture of **1–5**) and COREXIT® EC9527 (Includes **1–6**). *(Ref. 2b)*

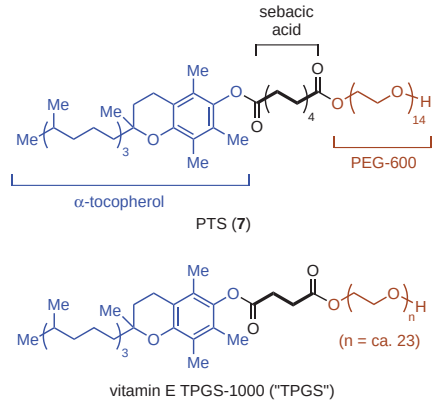


Figure 2. Polyoxyethanyl-α-tocopheryl Sebacate (PTS, **7**) and TPGS-1000. *(Ref. 8,13)*

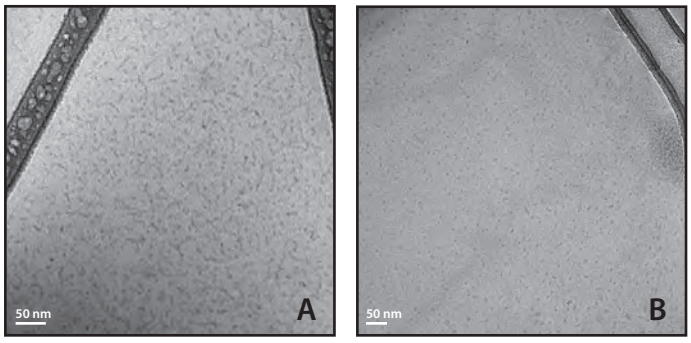


Figure 3. Cryo-TEM Data Comparing Nanoparticles of PTS (A) and TPGS-1000 (B). *(Ref. 8,14)*

2. Background

In our previous review in this journal,[8] we introduced PTS (**7**; **Figure 2**)[9] as a useful (nonionic) surfactant; a nanomicelle-forming species in which a variety of Pd- and Ru-catalyzed couplings took place in water at room temperature. The idea behind the choice of PTS was simple: in the Paul Anastas sense, it follows the "12 Principles of Green Chemistry",[10a] as explained in *Benign by Design*.[10b] That is—in being composed of racemic vitamin E, sebacic acid, and PEG-600—neither PTS nor any of its three components is environmentally of concern. Indeed, PTS is FDA GRAS affirmed for use in dietary supplements.[11] By itself, PTS is a provitamin; a modified version of "ester-E."

By comparison, readily available alternative amphiphiles, such as Triton® X-100 and those in the Brij® series,[12] only on occasion lead to comparable results in cross-coupling reactions. Even the closely structurally related TPGS (TPGS-1000, Figure 2)[13] affords quite different outcomes in cross-couplings under otherwise identical conditions. This seems particularly odd, since both PTS and TPGS-1000 share the same micellar lipophilic interior in the form of α-tocopherol. So what's responsible for the commonly observed greater rates of conversion in PTS? The answer seems to be that both the size and shape of their nanoparticles matter (**Figure 3**).[8,14] For PTS, both 8–10-nm spheres and larger worm- or rod-like particles are present (together averaging ca. 25 nm) according to cryo-TEM analysis (see Section 5). By contrast, TPGS in water forms very sharp 12–13-nm spherical micelles as indicated by microscopy and Dynamic Light Scattering (DLS) measurements.[14]

3. Chemistry in PTS–H_2O, an Update: a 1st-Generation Amphiphile for Transition-Metal-Catalyzed Cross-Couplings

It is not uncommon for synthetic chemistry to advance at a far greater pace than does our understanding of why the chemistry goes as observed. This is certainly true here as well, involving non-ionic surfactants that self-aggregate to form nanoreactors,[15] or what Fujita and co-workers refer to as "functional molecular flasks."[16] Early work focused mainly on a series of Pd-catalyzed "name" reactions (e.g., Heck,[17] Suzuki–Miyaura,[18] and copper-free Sonogashira[19] couplings), as well as olefin cross-[20] and ring-closing metathesis[21] reactions, all of which could be carried out in water at room temperature (**Figure 4**).

Since these initial reports, considerable progress has been made on many related Pd- or Ru-catalyzed couplings. In most cases, the species involved are tolerant of the presence of water as the gross reaction medium.[22] Although these couplings are likely occurring within the lipophilic portions of the micelles, some of a micelle's

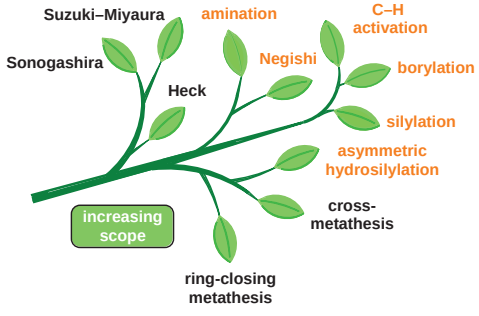


Figure 4. PTS-Enabled Reactions in Water at Room Temperature.

occupants may be exposed at any time to the surrounding water, given its dynamic character.[23] That is, there is constant exchange of monomeric units of surfactant between micellar arrays. This motion creates a mechanism by which educts, catalysts, and reaction product(s) can enter and exit a micelle. But the exchange phenomenon also leads to exposure to an aqueous environment through which they must traverse. This can have major (beneficial) consequences for the desired transformation; that is, the content of the water can be altered to great synthetic advantage. Foreshadowing associated with these effects was noted in the previous *Aldrichimica Acta* review,[8] where couplings run in seawater led, in some cases, to faster reactions than had been observed in pure (HPLC grade) water. Changes in the ionic strength[24] and pH of the aqueous medium have now been studied and, indeed, there are benefits to be had from such perturbations resulting from the simple addition of selected salts to water (vide infra).

3.1. Amination

The use of PTS is an effective enabling technology for two types of amination, both taking place in water at room temperature. Unsymmetrical di- and triarylamines can be constructed using aryl bromides and aniline derivatives. In the presence of $[PdCl(allyl)]_2$, Takasago's ligand, cBRIDP® (**14, Figure 5**), was the most effective among several catalysts (**8–16**) screened. Although these transformations appear to be general in that a variety of reaction partners can be used and yields tend to be good, perhaps the most intriguing aspect of this methodology is the influence of the base (**eq 1**).[25] Thus, while KOH (1.5 equiv) is oftentimes sufficient, reaction times can vary and may take up to a full day to reach completion. That KOH functions well in this capacity is rather interesting, since the coupling is occurring within the lipophilic core of the PTS micelle, where presumably polar species are not to be found. It is certainly possible that KOH remains in the aqueous phase, and that as species exchange between nanoreactors they are exposed to the surrounding water, and it is here when the proton may be abstracted from the participating nitrogen.[26] Likely to be more effective, rate-wise, at finding a protonated amine intermediate would be a more lipophilic base, capable of penetrating the micelle into the hydrophobic pocket (**eq 2**).[25] A switch, therefore, to KO*t*-Bu, made a favorable difference in this regard, notwithstanding the fact that this base in water is mainly KOH. Hence, the same outcome could be achieved by simply adding *tert*-butyl alcohol to the original mixture containing KOH. Even better, was addition of the commercially available potassium trimethylsilanolate ($KOSiMe_3$),[27] which reduced reaction times by almost an order of magnitude. Still more dramatic was inclusion of the far more lipophilic potassium triisopropylsilanolate [$(KOSi(i\text{-}Pr)_3$, or KO-TIPS], readily formed in situ from KOH and TIPS-OH.

Allylic aminations in water at room temperature can also be accomplished using allylic phenyl *ethers* as substrates.[28] These are unconventional partners in Pd-catalyzed couplings, where activation of the hydroxyl group in an allylic alcohol typically takes place in the form of an acetate, carbonate, sulfonate, or phosphate.[29] Nonetheless, under the influence of the hydrophobic effect, and in the presence of excess K_2CO_3 and methyl formate, couplings result in amination predominantly at the least hindered, terminal site and give high *E:Z* ratios (**eq 3**).[28] DPEPhos (**15**)[30] was found to be the ligand of choice, while the more rigid analogue XantPhos (**16**)[31] led to only traces of allylic amines.

Perhaps more intriguing is the same net amination, …but with allylic *alcohols* (**eq 4**).[32] While in situ activation has been achieved previously using a variety of protic or Lewis acids (e.g., $SnCl_2$,[33a] Et_3B,[33b] RCO_2H,[33a] and CO_2[33b]), efforts toward the exclusion of water are common. Those reactions run in pure water typically require harsh conditions.[33c–e] Under similar micellar conditions applied to allylic ethers (above), couplings give highly favored linear rather than

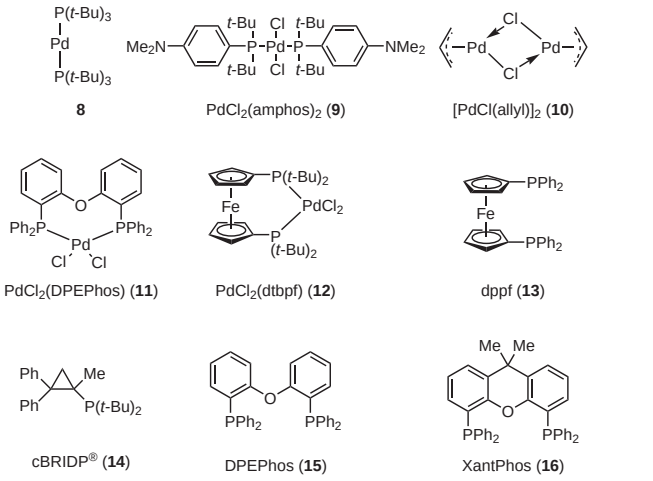
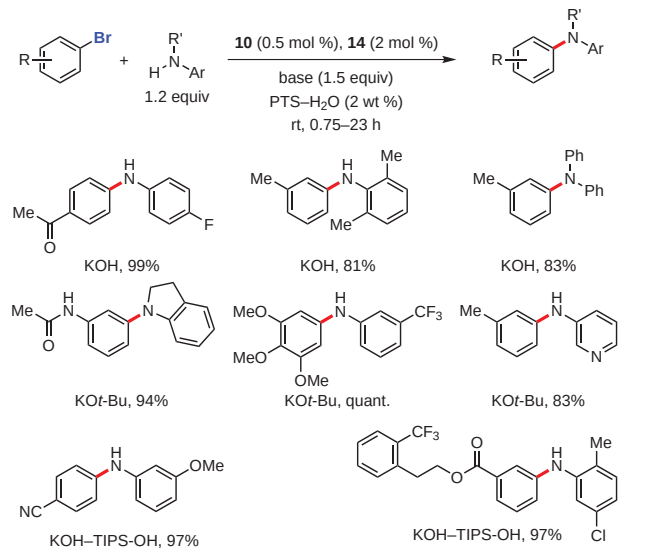
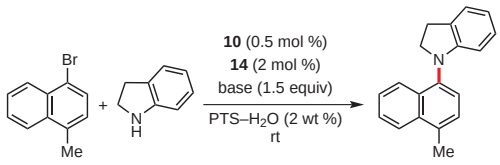


Figure 5. Ligands and/or Catalysts Used in Coupling Reactions. *(Ref. 25)*



Representative Amination in PTS–H_2O. 2′-(Trifluoromethyl)phenethyl 3-(5″-chloro-2″-methylphenyl)aminobenzoate {R = 3-[2-$F_3CC_6H_4(CH_2)_2OC(O)$], R′ = H, Ar = 5-Cl-2-MeC_6H_3}.[25] Inside a dry box, a 5-mL round-bottom flask equipped with a stir bar and fitted with a rubber septum under argon was sequentially charged with **10** (3.0 mg, 0.008 mmol), **14** (8.9 mg, 0.025 mmol), and KOH (89 mg, 1.58 mmol). Outside the dry box, under a positive flow of argon, were sequentially added via syringe to the mixture of **10** and **14**: *degassed* water (0.8 mL) and *degassed* 10 wt % PTS solution (0.2 mL) (to give a *degassed* 2 wt % PTS solution; 1.0 mL), then TIPS-OH (320 µL, 1.61 mmol), 5-chloro-*o*-toluidine (150 µL, 1.25 mmol), and, lastly, 2′-(trifluoromethyl)phenethyl 3-bromobenzoate (380 mg, 1.02 mmol). The milky reaction mixture was stirred under argon at rt for 45 min, after which complete consumption of the aryl bromide was observed by GC analysis. The reaction mixture was diluted with brine and extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation to give the crude residue. Purification by silica gel chromatography (gradient from hexanes to 2% EtOAc in hexanes) afforded the product (428 mg, 97%) as a viscous, beige-colored oil.

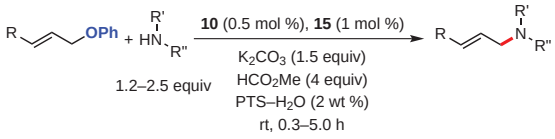
eq 1 *(Ref. 25)*



Base	Time	Conv.
Et_3N	42 h	79%
KOH	44 h	72%
KOH–*t*-BuOH	6 h	100%
$KOSiMe_3$	3 h	100%
KOH–TIPS-OH[a]	0.5 h	100%

[a] TIPS-OH = $(i\text{-Pr})_3SiOH$; in this case, a quantitative yield was obtained.

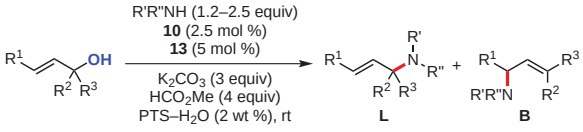
eq 2 *(Ref. 25)*

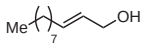
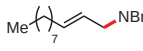
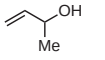
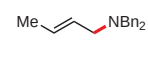
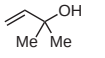
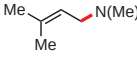
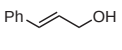
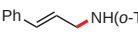
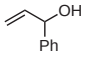
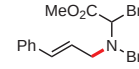


R	R'	R"	Yield
Ph	Me	1-NpCH_2	98%
n-Oct	Me	1-NpCH_2	90%
a	Me	1-NpCH_2	80%
Ph	Bn	4-Br$C_6H_4CH_2$	82%
Ph	H	2-MeC_6H_4	86%
H	EtO_2C(Bn)CH	*b*	85%

[a] RCH=$CHCH_2$ = cyclohexen-3-yl
[b] R" = (*E*)-4-(*t*-BuO_2CCH=CH)$C_6H_4CH_2$.

eq 3 *(Ref. 28)*



Alcohol	Product	Yield	L:B	*E*:*Z*
		84%	>25:1	16:1
		76%	24:1	11:1
		90%	63:1	----
		80%	100:0	all *E*
		80%	100:0	all *E*

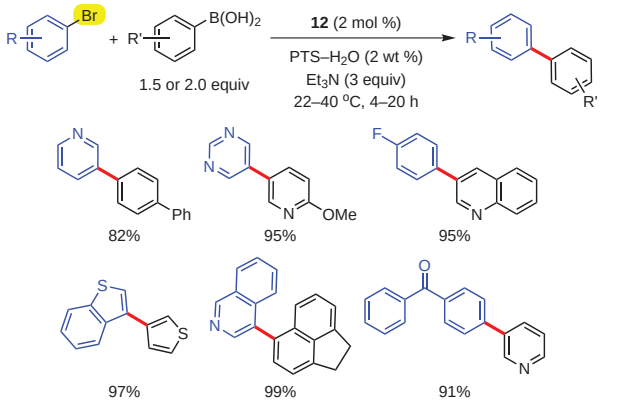
eq 4 *(Ref. 32)*

branched products, also strongly favoring *E* isomers. Here again, K_2CO_3 is the preferred base, while HCO_2Me in excess is required. Since none of the intermediate resulting from transesterification between the alcohol and methyl formate is observed at any point during the reaction, the proposed mechanism involves Pd(0), the educt, and the formate–reasonable given the presumed high concentration of species within the micelles.

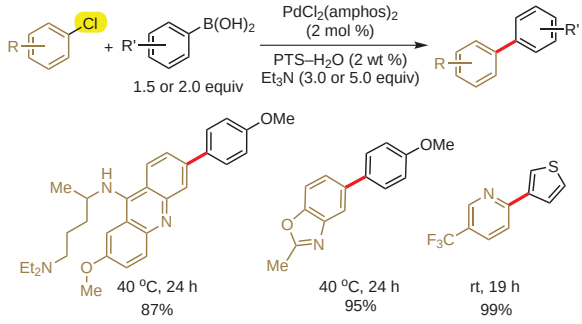
3.2. Suzuki–Miyaura Coupling

As previously described,[18] biaryls can be constructed from precursor aryl halides or pseudo-halides Ar–X (X = I, Br, Cl, OSO_2R) and boronic acids in 1% PTS in water mainly at ambient temperatures. Subsequent to this work, various heteroaromatic halides were also shown to be amenable.[34] Bromide was found to be the preferred leaving group (**eq 5**)[34] and, like chlorides, their reactions occasionally required mild heating to 40 °C (**eq 6**).[34] The choice of catalyst also varied by leaving group: bromides were best accommodated by $PdCl_2$(dtbpf), **12**, while chlorides seemed more responsive to $PdCl_2$(amphos)$_2$, **9**. A direct comparison with a literature case[35] showed the potential for this green chemistry to be highly competitive with traditional organic media (**eq 7**).[34] A review on the Suzuki–Miyaura cross-coupling as an entry to biaryls under green conditions has recently appeared, focusing on water as the reaction medium.[36]

Carbon–carbon bond formation between usually unreactive, acid- and base-stable allylic phenyl ethers and arylboronic acids is



eq 5 *(Ref. 34)*



eq 6 *(Ref. 34)*

also possible under micellar conditions.[37] As with allylic aminations (vide supra), there is a strong tendency to generate linear products where conjugation is maintained. Aliphatic ethers, on the other hand, favor branched products presumably due to the known faster rate of reductive elimination from a more hindered Pd(II) intermediate.[38] In addition to examples **17–19** (**eq 8**),[37] linchpin **20** bearing both acetate and phenyl ether moieties can be sequentially coupled, where, e.g., amination is followed by Suzuki–Miyaura coupling, all in one pot, all in water at room temperature (**eq 9**).[34]

3.3. Silylation

Palladium catalysis in PTS–water can also be extended to the formation of allylic silanes, likewise employing allylic phenyl ethers as substrates, in the presence of Et_3N (**eq 10**).[39] Such reactions do not occur in organic solvents (e.g., MeOH) at room temperature. Moreover, whereas silylations of the corresponding acetates require heating in organic solvents (e.g., DMF) for activation of a disilane ($R_3Si–SiR_3$),[40] cross-couplings in PTS nanoparticles take place at ambient temperatures in ≤20 hours at a global concentration of 0.16 M. The most effective catalyst source is $PdCl_2$(DPEPhos), **11**, as monodentate ligands on the metal (e.g., Ph_3P), or bidentate chelation of palladium by dtppf or dtbpf, afford only moderate levels of conversion (40–60%). Of the various products possible, linear over branched and *E* over *Z* isomers are both favored.[39]

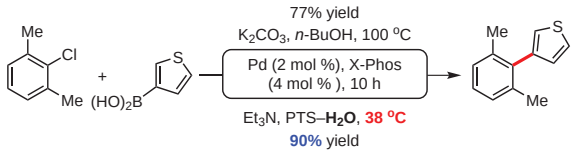
3.4. C–H Activation

With more than a handful of reviews on the topic of aromatic C–H activation reactions in just the past few years,[41] there is now a plethora of methods for introducing C–C bonds mainly ortho- to heteroatom-directing groups….but not in water at room temperature. This can be done, however, employing micellar catalysis.[42] Thus, aryl ureas, especially those bearing electron-donating groups, can be cross-coupled with aryl iodides in an aqueous medium containing any one of several surfactants; including PTS, TPGS, Triton® X-100, Solutol,[43] Brij® 30, and Brij® 35; where yields in optimization studies varied between 65 and 76%. The corresponding "on water" experiment led to only a 35% yield in the same time frame. Since the best results were obtained in nanomicelles containing Brij® 35, several additional examples were studied in this medium, along with ingredients $Pd(OAc)_2$, AgOAc, and HBF_4. Yields were in the 70–97% range (**eq 11**),[42] and products derived from double arylation were rarely observed, presumably reflecting the mild conditions involved.

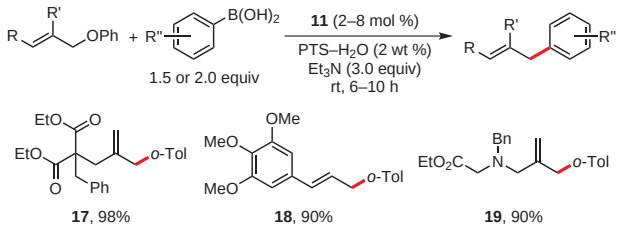
Arylations with $Pd(OAc)_2$ are typically run in highly acidic media; e.g., HBF_4, TFA, TsOH, or HOAc; which facilitate loss of HOAc from the catalyst and lead to electrophilic attack on an aromatic ring.[44] Alternatively, it has been shown that Fujiwara–Moritani coupling reactions with acrylates can be carried out in PTS–water (**eq 12**)[45] by using a *cationic* source of palladium, as in commercially available $[Pd(MeCN)_4](BF_4)_2$,[46] Both benzoquinone (1 equiv) and $AgNO_3$ (2 equiv) are required. Double functionalization ortho to the amide directing group is not observed here as well.

3.5. Negishi-like Couplings on the Fly…in Water

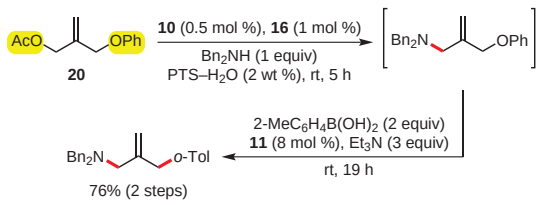
According to reference works on the topic, organozinc halides are not moisture-tolerant.[47] Indeed, Knochel and co-workers have spent, literally, decades elucidating the extent to which RZnX reagents can be used in the presence of protons of varying acidity.[48] Free alcohols, in general, require protection; the presence of even *tert*-butyl alcohol takes its toll on couplings run in the presence of this additive.[48a] Water is nowhere to be found among the various listings; hence, the message



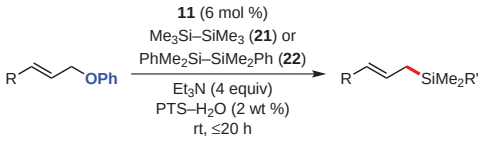
eq 7 *(Ref. 34)*



eq 8 *(Ref. 37)*



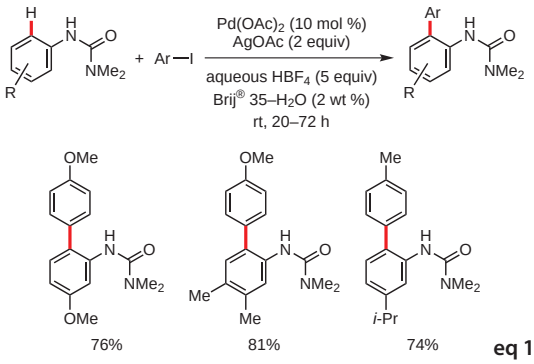
eq 9 *(Ref. 37)*



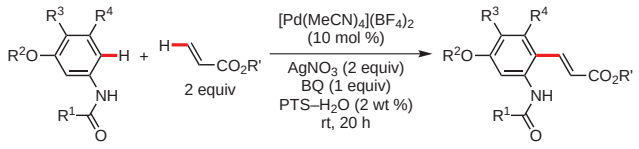
[a] In all cases, linear:branched = 25:1. [b] $PdCl_2(Ph_3P)_2$ (1.5 mol %) and $PdCl_2$(DPEPhos) (1.5 mol %) were used.

R^a	R'	Yield	*E:Z*
Ph	Me	91%	10:1
2-$MeOC_6H_4$	Me	86%	>25:1
3-$MeOC_6H_4$	Me	90%	9:1
n-C_8H_{17}[b]	Me	85%	3:1
Ph	Ph	91%	>25:1
2-$MeOC_6H_4$	Ph	87%	>25:1
3-$MeOC_6H_4$	Ph	91%	24:1
4-$MeOC_6H_4$	Ph	94%	>25:1
4-$EtO_2CC_6H_4$	Ph	95%	>25:1
2-Np	Ph	93%	>25:1

eq 10 *(Ref. 39)*



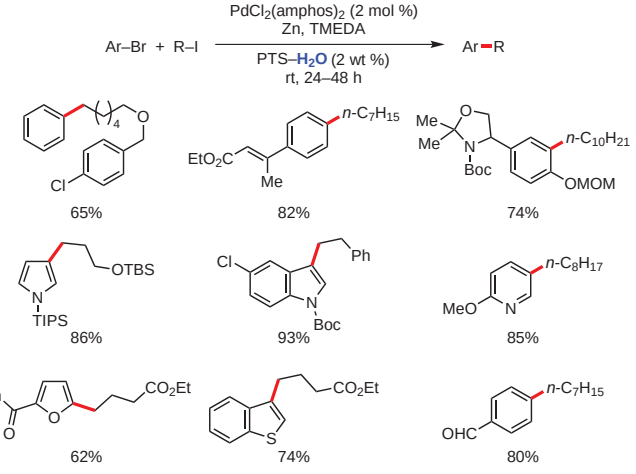
eq 11 *(Ref. 42)*



25	R^1	R^2	R^3	R^4	R'	Yield
a	*i*-Pr	Me	H	H	*n*-$C_{12}H_{25}$	80%
b	Me_2N	Me	H	H	$Me(CH_2)_5CHMe$	76%
c	*n*-Pr	Me	H	H	*n*-BuCH(Et)CH_2	80%
d	Me	*n*-Pr	H	H	*n*-BuCH(Et)CH_2	96%
e	*i*-Pr	Me	Me	H	3,7-$Me_2C_8H_{15}$	81%
f	*i*-Pr	Me	H	H	$Cy(CH_2)_2$	77%
g	*i*-Pr	Me	H	MeO	3,7-$Me_2C_8H_{15}$	80%

Representative Fujiwara–Moritani coupling of 23g and 24g to give cinnamate 25g.[45] Anilide **23g** (56 mg, 0.25 mmol), acrylate ester **24g** (106 mg, 0.5 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 in air to a reaction tube equipped with a stir bar and a septum. An aqueous solution containing PTS (1.0 mL, 2 wt %) was added by syringe and the resulting mixture vigorously stirred for 20 h. The contents of the flask were then quenched with aqueous $NaHCO_3$ and extracted with EtOAc. The ethyl acetate extracts were combined and filtered through a plug of silica gel and anhydrous $MgSO_4$, and then concentrated by rotary evaporation. The residue was purified by flash chromatography, eluting with hexane–EtOAc to afford analytically pure **25g** (86 mg, 80%). HRMS (ESI) m/z calcd for $C_{25}H_{39}NO_5Na$ (M + Na^+) 456.2726, found 456.2721 (Δ = 1.1 ppm).

eq 12 *(Ref. 45)*



eq 13 *(Ref. 50a)*

is clear: whether it's "on water", "in water", or "with water",[49] the only conditions applicable to zinc reagents involve "no water".[47]

Could the textbooks be "wrong"? Not likely. But in this obvious acid–base chemistry between RZnX and H_2O two assumptions are implied: (i) that RZnX and H_2O find each other, and (ii) that a stoichiometric amount (or more) of RZnX is used; otherwise, with lesser amounts, the anticipated yield must suffer. If both of these conditions are removed; that is, if RZnX could be "insulated" from any water present, and if the amount of RZnX at any given time is minimized and yet, over time, a stoichiometric level of RZnX is formed in the pot, then the desired Pd-catalyzed cross-couplings of organzinc reagents, in water, might be possible. Well, they are, thanks to micellar catalysis.

For both aryl bromides[50] and alkenyl halides,[51] couplings with primary and secondary alkyl halides can now be accomplished in a remarkably straightforward fashion. The recipe calls for the two precursor halides, a specific (commercially available) palladium catalyst, and importantly, TMEDA. These are combined in water (ca. 0.3 M) containing 2 wt % PTS to which is added inexpensive zinc metal in the form of powder or dust; and the whole mixture is then stirred. After a reasonable period of time, which is substrate-dependent, the cross-coupled product is obtained in good yield. Representative examples involving aromatic and heteroaromatic bromides are illustrated in **eq 13**.[50a]

This remarkable process can be envisioned as depending entirely on the precise timing of the various events that need to take place, just like the gears of a fine-tuned pocket watch (**Figure 6**). Within the nanoparticles of PTS are housed the various reaction components, densely packed due to the hydrophobic effect; no organometallic (RZnX) is present. As nanoparticles collide with zinc metal on its surface, preferential insertion of Zn into the sp^3 halide (R–X) takes place in a likely successive one-electron-transfer sequence. The resulting water-sensitive RZnX is insulated from the surrounding water. RZnX is also stabilized by the TMEDA present, which may assist in shuttling it into the micelle where both the Pd catalyst and sp^2 halide await, in relatively high concentrations. If the rate of formation of RZnX is too fast for subsequent passage into the hydrophobic micellar core, the reagent escapes and is rapidly quenched by water, as expected. Thus, while electron transfer en route to RZnX can be controlled for both 1° and 2° alkyl halides, reactions involving 3° precursors are far too rapid; thus, only quenched material (R–H) results.[50]

The corresponding couplings with alkenyl iodides and bromides, rather than aryl bromides, also give the anticipated products with retention of stereochemical integrity (**eq 14**).[51] With both types of educts (aryl and alkenyl), the choice of catalyst is absolutely crucial: $PdCl_2(amphos)_2$ (**9**)[52] is the only species screened to date that affords high levels of conversion and, thus, good isolated yields. Even the parent species; i.e., the bis(des-dimethylamino) analogue, was not nearly as effective. (*Note that the nomenclature for "amphos" as used for this ligand*[52] *is seemingly inconsistent with prior literature.*[53])

4. New Insights into Micellar Catalysis for Organic Synthesis

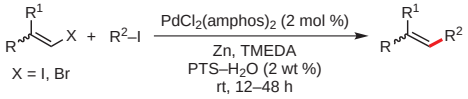
The observation that several of these Pd-catalyzed couplings not only can be run in seawater,[54] but actually take place in this medium at a greater rate than in HPLC grade water, has led to some very exciting developments of potential practical value. The presence of salts in the water can influence the chemistry in two significant ways:[55] (1) the size and shape of the nanoparticles in which these couplings take

place are altered, and (2) the pH of the aqueous medium which can impact the nature of the catalysts involved. With NaCl, a "salting out" effect exists,[56] which removes water from the PEGylated portions of the particles, tending to increase micellar size and/or modify particle shape as the PEG expands into the water. This effect is due to the anion, and several salts examined lead to similar particle changes, although the corresponding coupling chemistry in the presence of each salt has yet to be examined. Particle shape can also be dramatically altered. These effects can be shown by cryo-TEM analysis, e.g., on PTS with and without NaCl (**Figure 7**).[54] The "salting in" effect, which tends to decrease micellar size, is observed, e.g., with iodides NaI and KI.[57]

Changes in pH resulting from addition of small amounts of a salt such as $KHSO_4$ can impact couplings due to the dynamic nature of micelles; i.e., they are constantly in flux.[23] Their amphiphiles traverse a sea of surrounding water for the exchange phenomenon to occur. For catalysts that contain phosphines, e.g., ruthenium carbenes, as used routinely in olefin metathesis,[58] their phosphine ligands can be protonated upon exposure to aqueous acid,[59] and hence, may arrive at the micelle as a coordinatively unsaturated species (and thus, quite "hot"). These phenomena are illustrated below by Heck couplings and olefin metathesis reactions.

4.1. Heck Coupling in PTS–3 M NaCl (aq)

Heck reactions in micellar PTS–H_2O are especially responsive to changes in the ionic strength of the medium.[54] This effect is not to be expected in related reactions that, albeit conducted in water, rely on alternative phenomena. For example, supported catalysts such as



Entry	SM	R	R^1	R^2	X	Yield	*E*:*Z*
1	*Z*	*n*-Hex	H	$TMSCH_2$	I	95%	1:99
2	*Z*	$Cl(CH_2)_4$	H	$BnCH_2$	I	85%	3:97
3	*E*	TMS	H	$EtO_2C(CH_2)_3$	Br	83%	96:4
4		Ph	Me	Cy	Br	66%	----
5	*E*	$BnO(CH_2)_3$	H	*n*-Hex	I	85%	>99:1
6	*E*	Ph	H	*n*-Hex	Br	92%	91:9
7	*Z*	*n*-Hex	H	$EtO_2C(CH_2)_3$[a]	Br	74%	4:96

[a] $EtO_2C(CH_2)_3Br$ used.

Representative Pd-catalyzed, Zn-mediated coupling in PTS–H_2O. Preparation of Ethyl (Z)-5-dodecenoate (entry 7).[51] In a 5-mL, round-bottom flask under argon containing zinc powder (260 mg, 4 mmol) and $PdCl_2(amphos)_2$ (**9**; 7 mg, 0.01 mmol) was added a solution of 2 wt % of PTS (2 mL). *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) (232 mg, 2 mmol), was added at rt followed by addition of (*Z*)-1-bromooctene (181 mg, 1 mmol; *Z*:*E* = 99:1) and ethyl 4-bromobutanoate (390 mg, 2 mmol). The flask was stirred vigorously at rt for 48 h. The product was extracted with EtOAc. Silica gel (1 g) was added to the combined organic phase and the solvents were removed under reduced pressure. The resulting dry, crude product mixed with SiO_2 was introduced on top of a silica gel chromatography column which was eluted with 5% EtOAc–petroleum ether, affording the analytically pure product (167 mg, 74%; *Z*:*E* = 96:4); HRMS (ESI) *m*/*z* calcd for $C_{14}H_{26}O_2$ (M^+) 226.1933, found 226.1934 (Δ = 0.4 ppm).

eq 14 *(Ref. 51)*

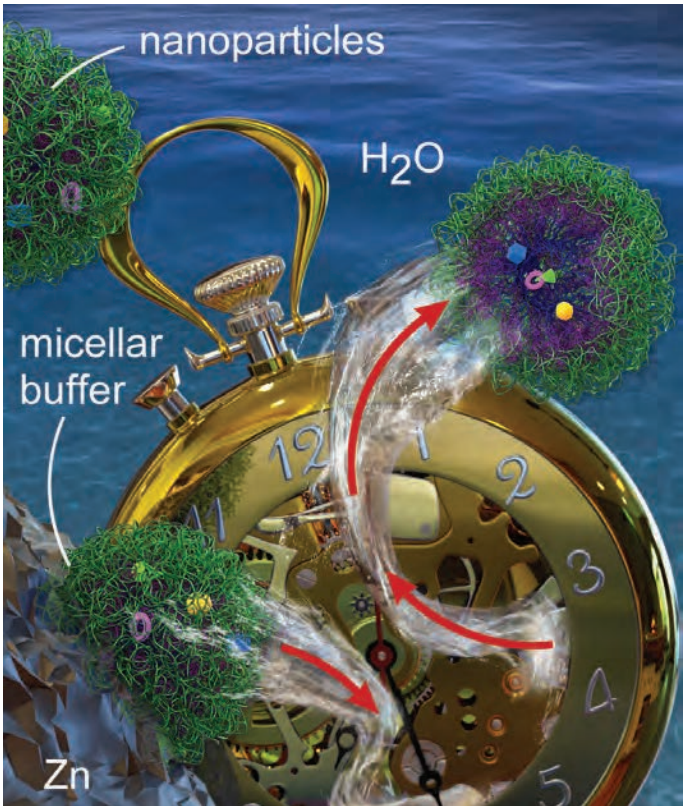


Figure 6. Pictorial Account of Couplings of RZnX in Water: Timing Is Key.

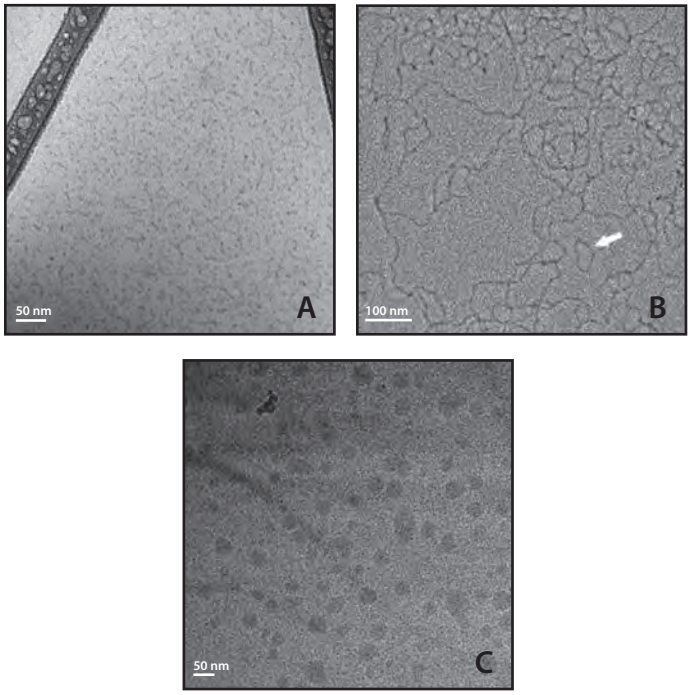
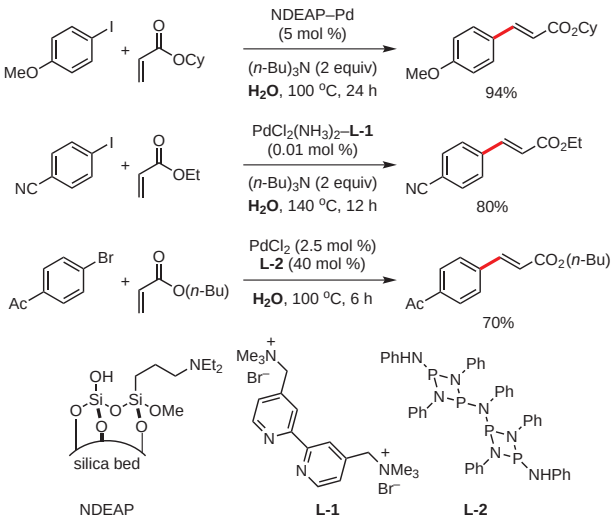
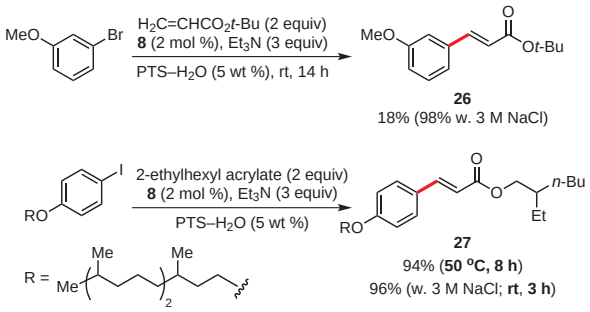


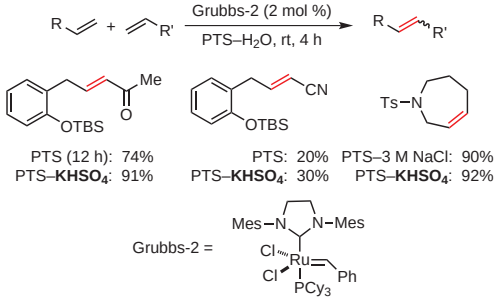
Figure 7. Cryo-TEM Image of (A) Aqueous PTS (50-nm Scale), (B) Aqueous PTS in the Presence of 3 M NaCl (100-nm Scale), and (C) TPGS-750-M. *(Ref. 54)*



Scheme 1. Recent Examples of the Heck Coupling in Water. *(Ref. 60–62)*



Scheme 2. Two Examples of the Influence of Added Salt on the Outcome of the Heck Coupling in PTS–H_2O. *(Ref. 54)*



eq 15 *(Ref. 54)*

$Pd(OAc)_2$ mounted on a reverse-phase *N,N*-diethylaminopropylated (NDEAP) silica gel impregnated with ionic liquid [bmim]PF_6 have been used (**Scheme 1**).[60] Other advances include applications of new Pd-complexed cationic bipyridyl ligands (**L-1**),[61] and new P–N ligands in the form of diazadiphosphetidines (**L-2**).[62] In each case involving an acrylate partner, while water is the reaction solvent, heating is needed to improve conversion.

Two examples of reactions subject to the influence of salts under micellar conditions are worth noting. In the first, cinnamate **26** is formed in PTS–water to a limited extent after 14 hours (**Scheme 2**, top reaction).[54] However, in the presence of NaCl (3 M) and at an identical global concentration (0.50 M), the reaction reaches full conversion in the same time period, with an associated high yield. In the second example, the formation of **27** requires mild heating to 50 °C to reach completion after 8 hours; in PTS–3 M aqueous NaCl, however, the reaction was complete at room temperature in 3 hours (**Scheme 2**, bottom).[54]

4.2. Olefin Metathesis at pH 2–3

In 2006, Hong and Grubbs reported on ring-opening polymerization (ROMP) reactions in aqueous acid, and showed that the 2nd-generation Grubbs catalyst has its phosphine sequestered via protonation.[59] The same protonation is presumably responsible for accelerating cross-metathesis under micellar conditions in water, most visibly in reactions involving tough type-2 olefins such as methyl vinyl ketone (MVK) and acrylonitrile (**eq 15**).[54] For related ring-closing reactions, e.g., forming a 7-membered ring, the net effect of added $KHSO_4$ was equivalent to that seen using 3 M NaCl.

5. Designing a Better Micelle: TPGS-750-M, a 2nd-Generation Amphiphile

Notwithstanding the progress made utilizing the first-generation designer surfactant PTS, the many lessons learned insofar as altering the nature of the surfactant to maximize reaction rates and reagent or catalyst stability encouraged the design of a second-generation amphiphile, TPGS-750-M.[63] Experience had shown that micelle size and shape matter; that improvements in rate in going from TPGS-1000 to PTS, where particle size increases from 13 to (on average) 25 nm,[54] seems to be an important clue. Since differences between the two were best visualized by cryo-TEM (see Figure 3), showing the longer rods or worms present only with PTS, TPGS-750-M (Figure 7C) was engineered to have a higher percentage of larger particles, preferably in the 50–100-nm range. A shorter PEG chain requiring less volume in its coiled state, and hence micelles able to accommodate more molecules per particle, should expand the particle's radius. A structural comparison between TPGS, PTS, and TPGS-750-M is illustrated in **Figure 8**.

From the standpoint of synthesis, a switch to four-carbon succinic acid as found in TPGS-1000,[13] rather than the ten-carbon sebacic acid as in PTS, makes a huge difference in overall efficiency of the two-step sequence (**Scheme 3**). That is, opening of succinic anhydride by vitamin E allows for a virtually quantitative esterification involving the most expensive component in the process. By contrast, PTS relies on sebacoyl chloride, a diacid chloride that reacts at both termini with α-tocopherol, thereby affording mixtures of the mono- and the diester.[8] Conversion of monoester **28** to TPGS-750-M via traditional esterification can be smoothly done in toluene in the presence of catalytic acid (TsOH), another close to quantitative event.[63] Here, use of a mono-methylated polyethylene glycol, or MPEG, rather than PEG (a diol) is the key to avoiding reactions at both ends. This is

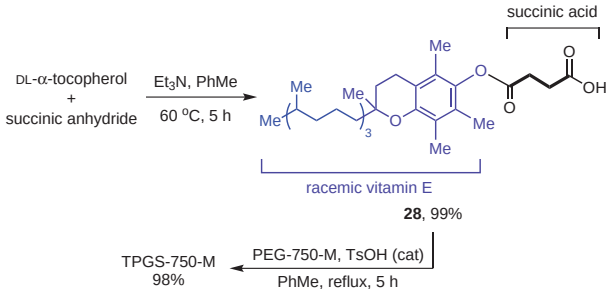
yet another problem in the route to PTS, which uses PEG-600 (and not an MPEG analogue). The 'net-net' of these changes is that the targeted amphiphile can be prepared in an overall yield that exceeds 95%, while the efficiency of making PTS is ca. 45%.

The greatly improved cost implies that couplings enabled by TPGS-750-M–H_2O need only be as good as those done in PTS. Of course, faster reactions might also be anticipated due to larger particle sizes. By virtue of increases in binding constants of the substrates and catalysts within the micellar environment (i.e., longer time spent within a micelle), reactions should reach higher states of conversion more rapidly.[64] What has been found in this regard is that most types of cross-couplings in TPGS-750-M do, in fact, lead to isolated yields that are equal to, or better than, those seen in aqueous PTS. Some direct comparisons are illustrated in **Scheme 4**, with each pair of reactions being run at the identical concentration and time frame.

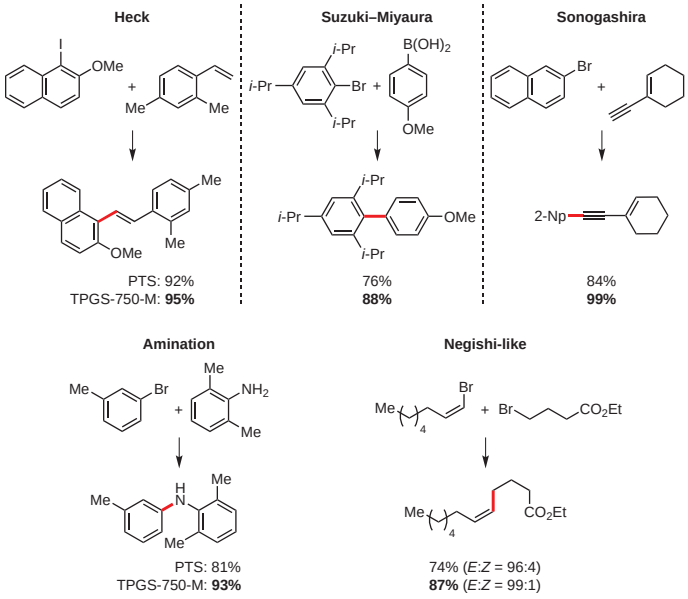
Likewise gold-catalyzed cycloisomerizations of allenols take place readily in both aqueous PTS and TPGS-750-M, where the presence of NaCl was found to shorten reaction times (**eq 16**).[65] In a number of cases, yields were better with the second-generation surfactant, although some substrate dependence was noted.

5.1. CuH-Catalyzed Asymmetric Hydrosilylation

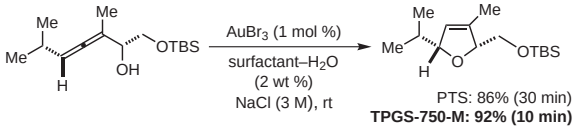
The in situ generation and use of copper hydride, derived from precursors such as CuCl–NaO*t*-Bu, CuF_2, or $Cu(OAc)_2$, routinely takes place in organic media: toluene, THF, etc.[66] Although the reagent is stable to water and, in fact, was used long ago by Stryker to enhance the rate of quenching of copper(I) intermediates (e.g., enolates resulting from 1,4 addition of hydride from $(Ph_3P)CuH$,[67] its use in a strictly aqueous medium is not among the available protocols. It might even be argued that water as "solvent" presents a likely major



Scheme 3. Straightforward, High-Yield Synthesis of TPGS-750-M. *(Ref. 63)*



Scheme 4. Cross-Couplings in PTS–H_2O and in TPGS-750-M–H_2O. *(Ref. 63)*



eq 16 *(Ref. 65)*

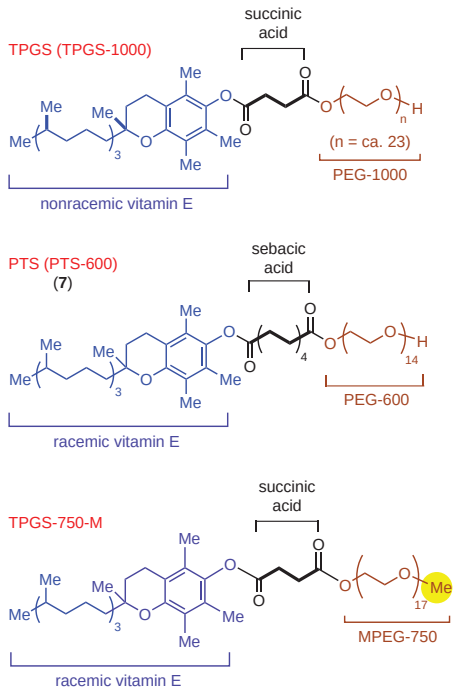


Figure 8. Structures of TPGS, PTS, and the Newly Engineered TPGS-750-M. *(Ref. 63)*

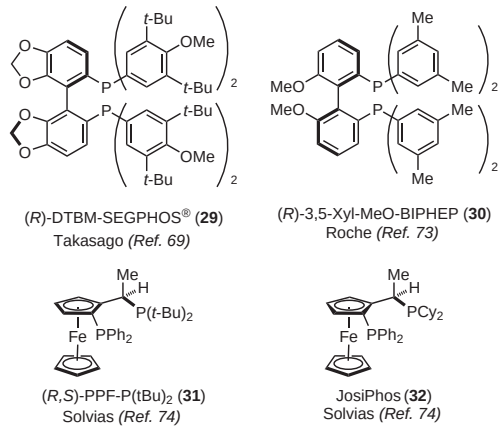
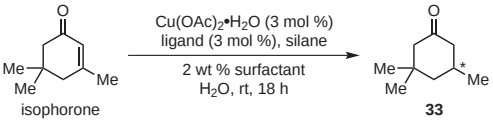
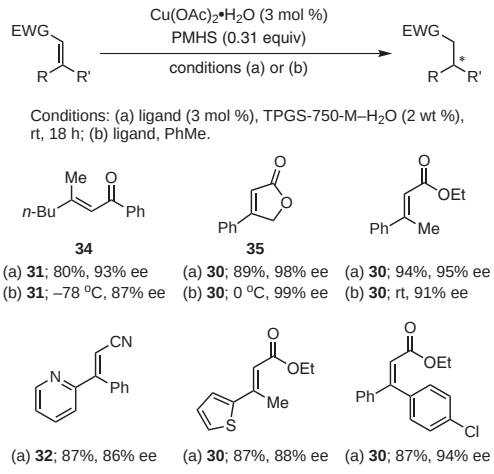


Figure 9. Nonracemic Ligands Used in CuH-Catalyzed Asymmetric Hydrosilylation.



Ligand	Silane	Hydride	Surfactant	Conv. (Yield)	ee
29	$PhSiH_3$	36 equiv	PTS	100% (89%)	99%
30	PMHS	9 equiv	TPGS-750-M	100% (88%)	94%
30	PMHS	9 equiv	none	18%	nd

eq 17 *(Ref. 70)*



eq 18 *(Ref. 70a)*

limitation, since the literature on these conjugate reductions clearly suggests that lower reaction temperatures tend to maximize ee's.[68] Thus, while eliminating organic solvents from these reactions would impart an element of "greenness", the tradeoff in substrate insolubility and potentially lower ee's might not favor a "green" approach. On the other hand, such reactions being run at high concentrations within micelles at room temperature may not follow the same rules, in which case the use of organic solvent and consumption of energy for cooling would both be averted.

It came with some surprise, therefore, that treatment of isophorone with CuH ligated by Takasago's (*R*)-DTBM-SEGPHOS® (**29**)[69] (**Figure 9**) in 2 wt % PTS–H_2O at room temperature afforded the product of 1,4 addition in high yield and in 99% ee (**eq 17**).[70] This result is comparable to the best that has been seen to date, albeit done in toluene at low temperatures.[71] Unfortunately, this conversion required far too much $PhSiH_3$ (12 equiv, or 36 equiv of hydride), as this reagent is competitively decomposed in aqueous solution. Eventually, the best conditions identified focused on the use of polymethylhydrosiloxane (PMHS)[72] as hydride donor (⅓ equiv, 9 equiv of hydride) in 2 wt % TPGS-750-M, giving the same product in 94% ee. By way of comparison, the identical reaction run in water only gave 18% conversion after the same 18-h reaction time.

Other ligands, including Roche's 3,5-Xyl-MeO-BIPHEP (**30**)[73] and Solvias's JosiPhos ligands (**31** and **32**)[74] are also effective, depending upon the nature of the substrate.[70] Particularly interesting is enone **34**, where in combination with ligand **31** and at –78 °C in toluene, an 87% ee was reported.[71] The identical reaction run in water at room temperature gave a comparable yield; however, the ee was *higher*: 93% (**eq 18**).[70a] Likewise, butyrolactone **35** reacted at room temperature and led to a similar yield and ee relative to that seen earlier, where the reaction was run at 0 °C. That ee's can be obtained that are on par with, or even exceed, those normally realized at low temperatures may be a consequence of restricted reagent and/or substrate movement within tightly packed micellar arrays, where energetic differences between diastereomeric transition states are accentuated, and less favorable orientations are minimized. The nature of the micelle interior also plays a crucial role, as documented by these asymmetric hydrosilylations run under otherwise identical conditions using alternative amphiphiles (Brij® 30, Cremophor®, SDS, and Solutol®)–water solutions (**eq 19**).[70] Clearly, the newly designed TPGS-750-M affords the most effective medium for this type of transformation. That high ee's can be realized at room temperature within a micellar array without normal recourse to low temperatures is particularly striking.

5.2. Borylation of Aryl Halides

Aryl boronates, in particular those derived from pinacol using bis(pinacolato)diboron (B_2pin_2), figure prominently as coupling partners in Suzuki–Miyaura reactions.[75] Aryl bromides are common educts, although borylations in organic media (e.g., dioxane, DMSO, or THF) at room temperature are very rare.[76] Couplings "on water" do lead to product, but to a limited and unpredictable extent. However, in water containing 2–3 wt % TPGS-750-M, aryl pinacolatoboranes (**36**) could be smoothly prepared usually within three hours at a global concentration of 0.25 M (**eq 20**).[77] A Pd(0) catalyst, Pd(P*t*-Bu_3)$_2$ (8, 3 mol %), afforded the highest yields over several alternatives examined (e.g., $Pd(OAc)_2$–XPhos, $PdCl_2$(dppf), $Pd_2(dba)_3$–$2PCy_3$, etc.). Given that palladium is already present in the form of Pd(P*t*-Bu_3)$_2$, as well as its known use in Suzuki–Miyaura couplings,[78] introduction of a second aryl bromide into the reaction mixture ultimately leads to biaryl **37**

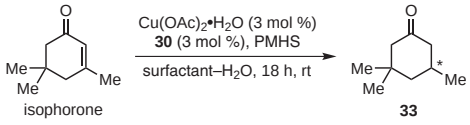
(**eq 21**). Compound **37** is formally the net cross-coupling product of two aryl bromides, achieved in one pot in water at room temperature.[79]

6. Summary and Outlook

Surfactants have an especially rich history of service to many areas of organic chemistry.[3] But most amphiphiles listed in catalogs perused by organic chemists today are from decades ago; they are rarely "green", nor are they matched in any way to the nanoscale environments that maximize the quality of transition-metal-catalyzed reactions. However, starting to appear are newly engineered "designer" surfactants that better accommodate reaction partners, additives, and catalysts characteristic of modern organic synthesis. In the interest of sustainability, the goal in designing new surfactants for synthesis is to develop reproducible and scalable processes that minimize involvement of organic solvents, at least from the standpoint of the reaction medium. Historically, however, "surfactant science & technology as pursued in academia has not overlapped well with the mindset of industrial chemists in this area".[80] That is, while academicians tend to strive for purified, homogeneous materials that are readily subject to analytical techniques (e.g., surfactants such as Triton® X-100 and SDS), industrial researchers oftentimes are faced with a "Make it work and don't worry about why!" approach. As author Drew Meyers unabashedly continues in his monograph,[80] "The sad fact of life is that real surfactant systems are almost always composed of mixed chemical isomers, contaminants, and added materials that can alter the effects of a given surfactant on a system…" This is precisely the current state of affairs surrounding PTS, since, in fact, it is a mix of many components: PEG-600 contains a broad range of polyethylene units, and the many byproducts from its preparation, as discussed earlier, are likely to be present in varying amounts. Its chromatographic purification using peak-shaving techniques led to the unexpected observation that, remarkably, PTS of >95% purity is actually *insoluble* in water![81]

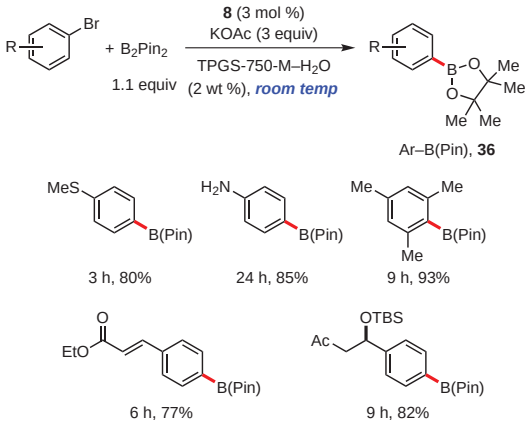
The switch to TPGS-750-M, therefore, provides an amphiphile that avoids many of these contaminants by virtue of its design. While remaining benign, it offers the community a better economic profile, along with enhanced reaction rates for the cross-couplings taking place within its nanomicelles. As with PTS, it also usually leads to a very attractive impurity profile, given the room temperature conditions for the vast majority of reactions in this aqueous medium. For the intended industrial uses, time in the kettle (i.e., throughput) is another virtue, since there is no time (or energy) investment due to heating and/or cooling of these coupling reactions. While this second-generation surfactant has yet to be fully evaluated, it would be naïve to assume that future generations of designed nanomicelles that offer even better matches between reaction ingredients and micellar interiors will not be forthcoming.

Part of the insight yet to be gained will come from just hard work; making and testing surfactants that address variables that may provide additional clues as to how to improve metal-catalyzed couplings. For example, the surfactant "Nok" (**Figure 10**) is currently being studied as an analogue of TPGS-750-M; it relies on a "healthy" phytosterol, β-sitosterol, in keeping with the theme that any newly created surfactant should pose no potential environmental insult regardless of scale of usage. The point to be tested, however, is whether in providing a hydrophobic interior as solvent composed of a cyclic hydrocarbon, as opposed to the linear hydrocarbon found in the vitamin E portion of TPGS-750-M, along with the anticipated control of size in the 50–100-nm range, there are further improvements in any or all of the cross-coupling chemistry of interest. Moreover, let's

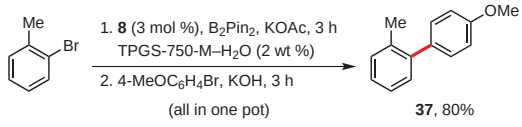


Surfactant	Conv.	ee
Brij® 35	20%	92%
Brij® 30	50%	81%
Cremophor® EL	100%	86%
SDS	6%	95%
Solutol® HS15	21%	92%
TPGS-750-M	**100%**	**94%**

eq 19 *(Ref. 70)*



eq 20 *(Ref. 77)*



eq 21 *(Ref. 77)*

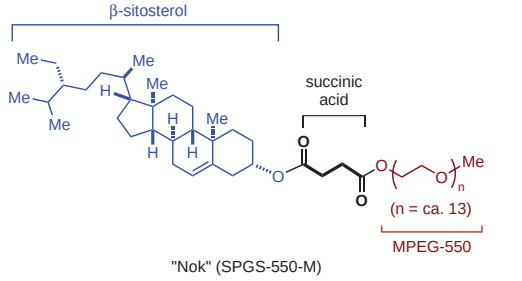


Figure 10. Structure of "Nok" (SPGS-550-M) Currently under Study.

appreciate that micellar catalysis, by virtue of synthetic design and manipulation, de facto offers a virtually unlimited array of potential reaction media tailored to best match a given transformation, each to be used catalytically as a nanoreactor.[82] By contrast, consider just how few the choices of traditional organic solvents there really are.

New discoveries of potential major consequence in synthesis that take advantage of the hydrophobic effect await us; two of these have been discussed herein: organozinc-mediated cross-couplings in water (see Section 3.5),[50,51] and unexpectedly high ee's from asymmetric hydrosilylations with CuH at room temperature (see Section 5.1).[70] More are on the way; e.g., homogeneous catalytic organocopper chemistry that forms *C–C bonds in water* at room temperature.[83] This latter discovery is seemingly difficult to accept, given the many reviews on copper chemistry written by one of the authors. This is especially true in the Schlosser *Manuals*,[84] advising readers to be extremely cautious about the sensitivity of carbon-based copper reagents to moisture! One interpretation of these data could be that the "rules" for doing chemistry at high concentrations in nanoparticles may well be different from those accumulated over the past 40–50 years of modern organic synthesis. This notion was foreshadowed by Lindström and Andersson in their *Angewandte Chemie* article "Hydrophobicity Directed Organic Synthesis",[85] in which these authors suggest that, "The design of stereoselective reactions based on hydrophobic interactions is an area of great potential that is still largely unexplored." After all, Nature does not do chemistry by matching substrates and catalysts to organic solvents as we know them. Nature's macroscopic medium is water, which is used either as a legitimate solvent, or to force molecular organization to create hydrophobic pockets. Isn't that precisely what we call "micellar catalysis"?

7. Acknowledgements

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About the Authors

Bruce Lipshutz has been on the faculty at UC Santa Barbara for the past 33 years. His training initially as an undergraduate with Howard Alper (SUNY at Binghamton), then Harry Wasserman (Yale), and finally as a postdoctoral student with E. J. Corey (Harvard) set the stage for his interest in organic synthesis and, in particular, organometallics. From his early contributions in the form of reagents such as SEM-Cl and higher order cyanocuprates to heterogeneous catalysts in the form of nickel- and copper-in-charcoal, the focus has been on providing technologies that are broadly applicable to synthetic problems. More recently, he and his co-workers have turned their attention in large measure to "green" chemistry, in appreciation of the major problems now facing society from the standpoint of sustainability, and, more specifically, issues associated with the reduction of organic waste, much of which is solvent-related. Hence, the Lipshutz group has introduced the concept of "designer" surfactants, utilizing micellar catalysis as an environmentally innocuous means of carrying out important transition-metal-catalyzed cross-coupling reactions, as well as several other reaction types (e.g., organocatalysis), in water at room temperature.

Subir Ghorai was born in 1977 in Panskura, West Bengal, India. After receiving his B.S. and M.S. degrees in chemistry from Jadavpur University, India, he joined the Indian Institute of Chemical Biology (IICB), Jadavpur, in 2000 as a CSIR research fellow. He received his Ph.D. degree in 2005 from IICB, working under the supervision of Dr. Anup Bhattacharjya on the synthesis of chiral dendrimers and heterocycles from carbohydrate precursors. From 2005 to 2006, he worked on isonitrile chemistry as a postdoctoral fellow with Professor Michael C. Pirrung at the University of California, Riverside. He then moved to UC Santa Barbara as a postdoctoral fellow working with Professor Bruce H. Lipshutz, where he helped initiate "green" chemistry involving transition-metal-catalyzed reactions in aqueous media. Recently, he has taken a position at Sigma-Aldrich in Sheboygan, Wisconsin, as an R&D scientist in the Catalysis and Organometallics group.

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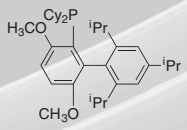
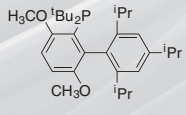


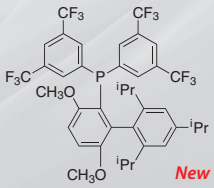
New

BrettPhos
718742



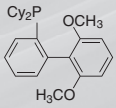
New

t-BuBrettPhos
730998



New

JackiePhos
731013



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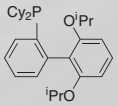

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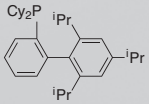

XPhos
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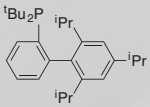

t-BuXPhos
638080

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Common Applications:

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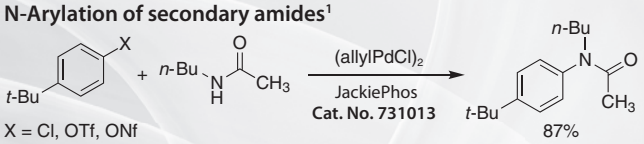
- Suzuki, Negishi, Stille, Hiyama, Sonogashira cross-couplings
- α-Arylation reaction

New Applications for Buchwald Ligands

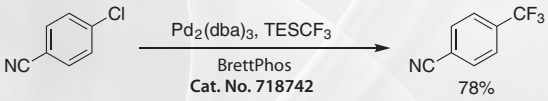
N-Arylation of secondary amides[1]



X = Cl, OTf, ONf

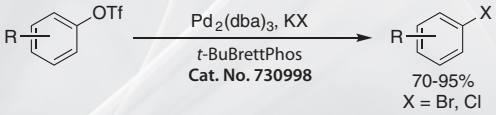
87%

Trifluoromethylation of aryl chlorides[2]



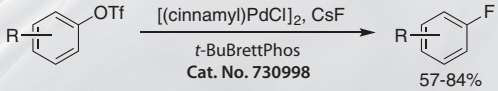
78%

Conversion of aryl and vinyl triflates to bromides and chlorides[3]



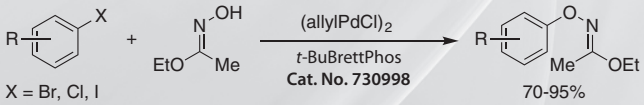
70-95%
X = Br, Cl

Conversion of aryl triflates to aryl fluorides[4]



57-84%

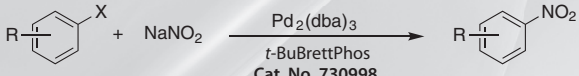
O-Arylation of ethyl acetohydroximate[5]



X = Br, Cl, I

70-95%

Conversion of aryl chlorides and sulfonates to nitroaromatics[6]



X = Cl, OTf, ONf

74-98%

References:
(1) Hicks, J. D. et al. *J. Am. Chem. Soc.* **2009**, *131*, 16720. **(2)** Cho, E. J. et al. *Science* **2010**, *328*, 1679. **(3)** Shen, X. et al. *J. Am. Chem. Soc.* **2010**, *132*, 14076. **(4)** Watson, D. A. et al. *Science* **2009**, *325*, 1661. **(5)** Maimone, T. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 9990. **(6)** Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898.

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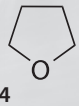
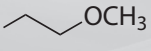
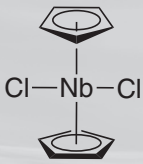
$NbCl_5$	$Nb(OCH_2CH_3)_5$	Nb_2O_5
215791	339202	203920
NbO_2	$LiNbO_3$	$NbCl_4 \cdot 2$ 
383163	254290	326364
$NbCl_3 \cdot H_3CO$ 		$NaNbO_3$
326356		400653



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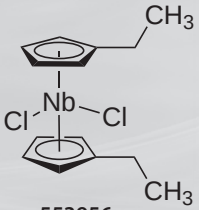
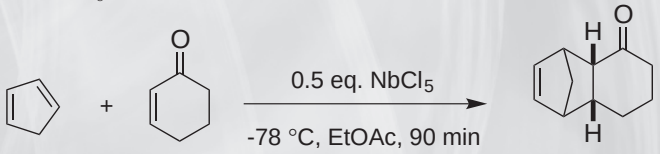


553956

Professor Lacerda's review focuses on applications of niobium compounds in catalysis of:

- Aldol Reactions
- Diels–Alder Reactions
- Friedel–Crafts Reactions
- Epoxide Ring-Openings
- Multicomponent Reactions
- Protection and Deprotection Reactions
- Demethylation Reactions

A representative example employing $NbCl_5$ as a Lewis acid in a Diels–Alder reaction is shown below. The use of $NbCl_5$ ensures formation of the endo stereoisomer. In contrast, the reaction does not take place in the absence of Lewis acids, and gives mixtures of endo and exo products, when the more commonly used $AlCl_3$ is utilized.



74% (endo)

Constantino, M. G.; Lacerda, V., Jr.; da Silva, G. V. J. *Molecules* **2002**, *7*, 456.

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The Growing Impact of Niobium in Organic Synthesis and Catalysis

Prof. Dr. Valdemar Lacerda, Jr.

Ms. Deborah Araujo dos Santos

Prof. Luiz Carlos da Silva-Filho

Prof. Sandro José Greco

Prof. Reginaldo Bezerra dos Santos

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Keywords. catalysis; organic synthesis; niobium chlorides; niobium oxides; selectivity; versatility; efficiency.

Abstract. The growing interest in, and applications of, niobium compounds in organic synthesis and catalysis are surveyed, with a focus on their efficiency and versatility in several classical and broad organic reaction types. It is our hope that this review will spur further investigations of this lesser studied, but equally important, member of group 5 transition metals.

Outline

1. Introduction

Being in the same periodic table group as tantalum and vanadium (which is known for its many applications in organic synthesis), niobium is highly oxophilic.[1,2] Niobium can easily accommodate a number of ligands presenting different coordination numbers.[3,4] For this reason, its organometallic chemistry is very rich,[5] and a large number of niobium complexes have been reported.[5,6] Niobium possesses different oxidation states, which range from +5 to –3. Its chemistry, however, is dominated by the higher oxidation states, especially the +5 one.[4] Niobium was originally called columbium (Cb) by Hatchett in 1802,[7] was renamed niobium by Rose in 1844,[8] and then niobe. Finally, over a century later, IUPAC officially adopted the name niobium in 1949–1950.[9] Niobium does not occur in nature in its free metal form,[1c] but as a mixture of metal oxides such as columbites $[(Fe,Mn)(Nb,Ta)_2O_6]$ and pyrochlore $[(Na,Ca)_2Nb_2O_6(OH,F)]$. The most commercially important ore deposits are in Brazil, Canada, Nigeria, and Zaire. About 86% of world reserves are in Brazil, which accounts for roughly 60% of total niobium production.[1b,1c]

Many researchers have focused on the solid-state chemistry of niobium and its compounds, in order to produce catalysts and other materials for industrial applications.[1b,10] Because of its high resistance to corrosion and high electrical conductivity, niobium is ideal for chemical and metallurgical applications such as: (i) heterogeneous catalysis (catalyst components and co-catalysts), (ii) space and aeronautical industries (Nb–Al–Ti alloys), (iii) superconductivity (magnets based on Nb–Sn alloys), and (iv) electronics industry (capacitors, ceramics, bone implants, and internal suturing—since it is completely inert to bodily fluids). Nevertheless, around 85 to 90% of the niobium produced worldwide is used in the steel industry as iron–niobium alloys (ferroniobium), which can contain from 40 to 70% niobium.[11]

The most commonly used niobium compound is undoubtedly commercially available niobium pentachloride ($NbCl_5$), which is highly Lewis acidic and, for this reason, has received increasing attention in recent years. $NbCl_5$ can be prepared in several ways,

but the easiest one is the direct chlorination of metallic niobium at 300–350 °C.[1c] Niobium pentachloride is a yellow solid that is quickly hydrolyzed and transformed into HCl and $NbOCl_3$ or Nb_2O_5•nH_2O (niobic acid). It dissolves into nonaqueous solvents such as alcohols and acetonitrile, and forms stable 1:1 complexes with a number of donor ligands, including ethers, thioethers, tertiary amines, nitriles, etc.[12] $NbCl_5$ exists as dimeric units in the solid state, in which the metal is surrounded by a distorted octahedron of chlorine atoms.[4] This dimer can be seen as two octahedra sharing one edge (**Figure 1**).[4] It is strongly electrophilic and hence is able to catalyze a variety of organic reactions, which is the subject of this review.

The applications of $NbCl_5$ in organic synthesis and the prospects for this promising reagent have been reviewed.[13,14] Interestingly, several reactions mediated by $NbCl_5$ had a different outcome as compared to the same reactions employing other Lewis acids. The main purpose of this article is to highlight the most recent (over the last five years) applications of niobium pentachloride and other niobium compounds in organic synthesis and catalysis, including our own recent results. In this context, $NbCl_5$ offers several benefits such as ease of handling and, generally, low catalyst loadings.

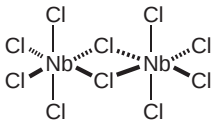
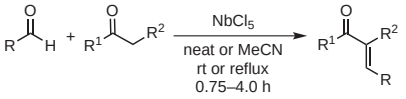
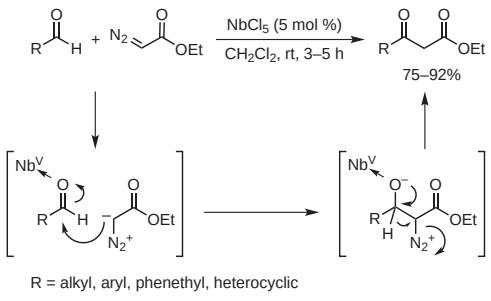


Figure 1. Dimeric Structure of Niobium Pentachloride in the Solid State. *(Ref. 4)*



$NbCl_5$ (mol %)	R	R^1	R^2	Yield
10	Ph	EtO	CN	90%
10	3-Py	EtO	CN	84%
10	2-Fur	EtO	CN	92%
10	*n*-C_7H_{15}	EtO	CN	88%
20	Ph	EtO	CO_2Et	86%
20	2-$O_2NC_6H_4$	Me	Ac	90%
20	*n*-C_7H_{15}	Me	Ac	70%
20	4-ClC_6H_4	Me	CO_2Me	80%

eq 1 *(Ref. 15)*



eq 2 *(Ref. 16)*

2. Catalysis by Niobium Pentachloride ($NbCl_5$)

2.1. Aldol and Related Reactions

Niobium pentachloride effectively catalyzes the Knoevenagel condensation of aromatic and aliphatic aldehydes with active methylene compounds (**eq 1**).[15] This has proven to be an efficient method for preparing α,β-unsaturated carbonyl compounds in good yields, high selectivity, shorter reaction times, and under mild reaction conditions in the presence or absence of solvent. The reaction proceeds presumably through activation of the aldehyde by complexation with Nb(V), followed by nucleophilic addition of the active methylene compound.

Another type of Aldol reaction, described by Yadav et al. involves the $NbCl_5$-catalyzed preparation of β-keto esters through insertion of ethyl diazoacetate (EDA) into the C–H bond of various aldehydes (**eq 2**).[16] These reactions readily occur at room temperature in good yields and high selectivity (no glycidic esters, diethyl maleate, or diethyl fumarate side products are observed), and are believed to take place as shown in equation 2. Of a number of Lewis acid catalysts ($InCl_3$, $CeCl_3$•$7H_2O$, $TaCl_5$, and $GdCl_3$) also tested in this reaction, $NbCl_5$ was found to be the most effective. No reaction was observed between the aldehyde and EDA in the absence of the Lewis acid.

2.2. Diels–Alder Reactions

In the Diels–Alder reaction between dienes and dienophiles, some of the usually sluggish dienophiles (e.g., 2-cycloenones **1–4**) can undergo the cycloaddition at 3 different temperatures (–78 °C, rt, or reflux) with unusually high stereoselectivity in the presence of $NbCl_5$ as a Lewis acid (**eq 3**).[17] $NbCl_5$ induces a decrease in the energy of the LUMO of the carbonyl substrate through complexation with the carbonyl oxygen, thus reducing the electron density of the double bond.

A related study has described the efficient synthesis of biologically important, fused pyrano[3,2-*c*]quinoline derivatives by the aza-Diels–Alder reaction of Schiff bases (**5**) and 3,4-dihydro-2*H*-pyran (**6**) facilitated by niobium(V) chloride (**eq 4**).[18] In this context, $NbCl_5$ is effective, promoting short reaction times and generally improved yields and diastereoselectivities, especially when lower molar concentrations of $NbCl_5$ are employed.

A versatile intermediate in the synthesis of eremophilanes and bakkanes has been prepared by a highly regioselective and stereoselective one-step synthesis that relies on an $NbCl_5$-catalyzed Diels–Alder reaction (**Scheme 1**).[19] The cycloaddition does not take place in the absence of Lewis acids. $NbCl_5$ plays a critical role, since it increases the reactivity to the point that the reaction is carried out at ≤ –50 °C, thus reducing diene polymerization and improving selectivity. The importance of this intermediate was demonstrated in the total synthesis of (±)-bakkenolide A.

2.3. Friedel–Crafts Reactions

Inter- and intramolecular Friedel–Crafts acylations are also highly efficiently catalyzed by $NbCl_5$.[20] In the intermolecular variant, the introduction of additives, such as $AgClO_4$, significantly enhances the catalytic action of the niobium complex. Arai et al. have reported that

$NbCl_5$ smoothly catalyzes the acylation of aromatic compounds with Ac_2O and Bz_2O to form the corresponding ketones in excellent yields (**eq 5**).[20a]

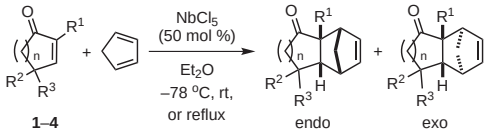
An intramolecular variant was described by Constantino and co-workers, who converted 3-arylpropanoic acids (**11**) into 1-indanones **12** in good yields and under mild conditions in the presence of 1.5–2.5 equivalents of $NbCl_5$ (**eq 6**).[20b] The authors demonstrated through NMR experiments that $NbCl_5$ initially performs the conversion of the 3-arylpropionic acids into acyl chloride and anhydride derivatives. These intermediates are then converted into 1-indanones through a Friedel–Crafts acylation reaction.

2.4. Epoxide Ring-Opening Reactions

The opening of epoxide rings is one of the most studied applications of $NbCl_5$ as catalyst. What this growing number of studies has shown is that small changes in reaction conditions can result in significantly different products being formed. One study reported that a number of cyclohexene oxide derivatives reacted rapidly with 0.13–0.5 equivalents of $NbCl_5$, resulting in good conversions, but led to mixtures of chlorohydrins (products containing solvent residues) and rearrangement products.[21]

In contrast, Oh and Knabe reported that addition of metallic zinc to the epoxide and $NbCl_5$ promoted deoxygenation to the corresponding *E* alkenes under mild conditions and in good yields and relatively short reaction times (**eq 7**).[22]

β-Amino alcohols are versatile intermediates in the synthesis of, among others, a wide variety of biologically active compounds, synthetic amino acids, β-blockers, oxazolines, and chiral auxiliaries. The $NbCl_5$-catalyzed ring-opening of epoxides with aromatic amines leads to the formation of β-amino alcohols in excellent yields and regioselectivity under mild reaction conditions (**eq 8**).[23] The reaction is noteworthy since it does not require anhydrous solvents or stringent reaction conditions and does not proceed in the absence of $NbCl_5$.



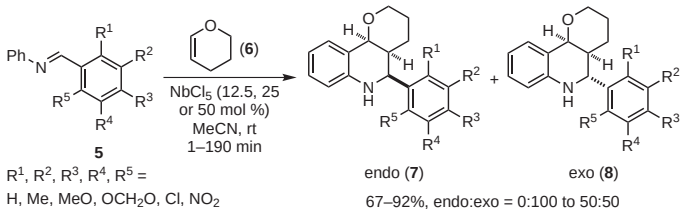
1–4

1; $R^1 = R^2 = R^3$ = H, n = 1; **2**; $R^1 = R^2 = R^3$ = H, n = 2
3; R^1 = Me, $R^2 = R^3$ = H, n = 2; **4**; R^1 = H, $R^2 = R^3$ = Me, n = 2

No.	Temp	Time	Yield	Endo:Exo
1	–78 °C	3 h	61%	89:11
1	rt	0.42 h	58%	78:22
1	reflux	0.08 h	65%	74:24
2	–78 °C[a]	3 h	72%	100:0
2	rt	0.75 h	58%	80:20
2	reflux	0.25 h	62%	78:22
3	–78 °C	8 h	32%	48:52
3	rt	24 h	43%	42:58
3	reflux	12 h	65%	30:70
4	–78 °C	8 h	40%	100:0
4	rt	24 h	34%	100:0
4	reflux	24 h	48%	100:0

[a] With $AlCl_3$ (25 mol %) and 6 equiv of cyclopentadiene at 40 °C, 7 h in PhMe: 80%, endo:exo = 89:11. With $SnCl_4$ (1.0 equiv) and 50 equiv of cyclopentadiene at –20 °C, 14 h: 93%, endo:exo = 92:8.

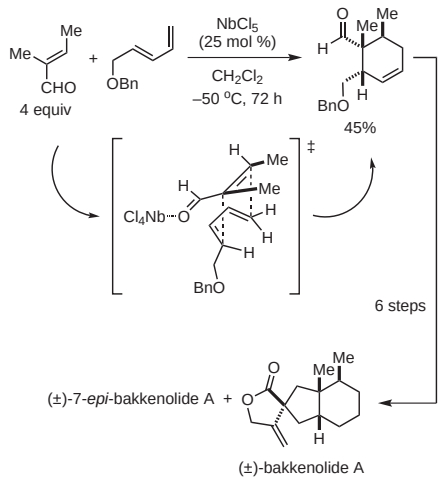
eq 3 *(Ref. 17)*



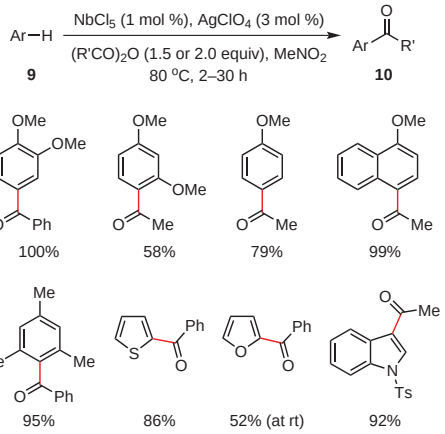
R^1, R^2, R^3, R^4, R^5 =
H, Me, MeO, OCH_2O, Cl, NO_2

67–92%, endo:exo = 0:100 to 50:50

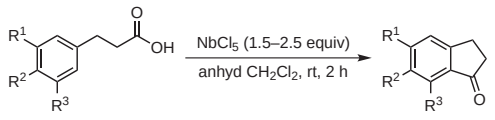
eq 4 *(Ref. 18)*



Scheme 1. The Key, $NbCl_5$-Catalyzed Step in the Synthesis of Eremophilane and Bakkane Systems. *(Ref. 19)*



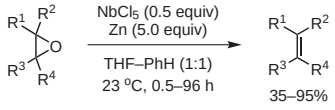
eq 5 *(Ref. 20a)*



11 → 12

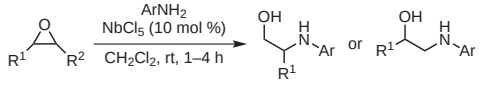
R^1	R^2	R^3	Yield
H	H	H	82%
H	MeO	H	31%
MeO	MeO	H	83%
MeO	MeO	MeO	95%

eq 6 *(Ref. 20b)*



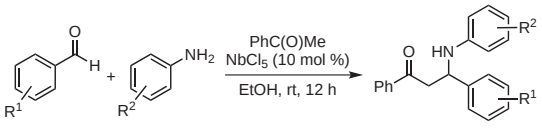
R^x = alkyl, aryl, CO

eq 7 *(Ref. 22)*



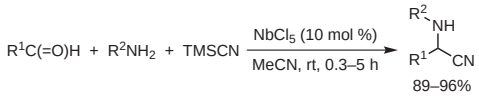
R^1 = Ph, $PhOCH_2$, $ClCH_2$; R^2 = H
R^1,R^2 = $(CH_2)_4$
Ar = mono- or disubstituted benzene

eq 8 *(Ref. 23)*



R^1 = H, 4-Me, 4-NO_2
R^2 = H, 4-Me, 3,4-Me_2, 4-MeO, 3-Cl, 4-Cl, 4-NO_2, 3-CO_2H, 4-CO_2H

eq 9 *(Ref. 24)*



R^1 = alkyl, vinyl, aryl, heteroaryl, and others groups
R^2 = Ph, Bn, 4-$MeC_6H_4CH_2$, 4-$MeOC_6H_4$

eq 10 *(Ref. 25)*

2.5. Multicomponent Reactions

A multicomponent reaction (MCR) is defined as a process in which three or more reactants are combined in one pot to form a structurally complex product that incorporates structural elements from each reactant. Lu and co-workers have described such an MCR in which β-amino carbonyl compounds were synthesized in high yields by an $NbCl_5$-catalyzed Mannich-type reaction between acetophenone, benzaldehydes, and anilines (**eq 9**).[24] Similarly, Kim's group reported a simple and efficient one-pot, $NbCl_5$-catalyzed synthesis of α-aminonitriles through an MCR involving aldehydes, amines, and trimethylsilyl cyanide (**eq 10**).[25]

2.6. Protection and Deprotection Reactions

One of the major challenges in total synthesis is effecting the protection and deprotection of a variety of functional groups. Low concentrations of $NbCl_5$ catalyze the acetylation of alcohols, phenols, amines, and thiols under mild reaction conditions (**eq 11**).[26] These reactions are characterized by short reaction times, cleaner products, and high yields. Based on these conditions and results, the following order of ease of acetylation of OH groups was established: phenolic > benzylic > primary aliphatic > secondary aliphatic > tertiary.

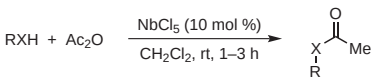
As a homogeneous catalyst, $NbCl_5$ is even more effective in catalyzing the acetylation of the carbonyl group of aldehydes to form acetals. The transformation takes place with acetic anhydride in the absence of solvent, and leads to excellent yields in short reaction times (**eq 12**).[27] The acetals thus formed tend to be stable in neutral, basic, and acidic media and have been employed in synthesis as starting materials, intermediates, and cross-linking reagents for cellulose.

Tetrahydropyrans (THPs) are attractive alcohol protecting groups because they are stable under a variety of reaction conditions, yet can be easily cleaved in dilute acid when needed. Niobium pentachloride catalyzes the smooth tetrahydropyranylation of alcohols and phenols at room temperature, leading to the protected counterparts in high-to-excellent yields (**eq 13**).[28] Some of the advantages of this method, when compared to previously reported hydroxyl-protection methods, are: (i) mild reaction temperature, (ii) shorter reaction times, (iii) lower catalyst loadings, (iv) better yields, (v) greater tolerance of other functional groups, and (vi) easier workup.

It is important to note that, not only does $NbCl_5$ readily promote functional-group-protection reactions, it can also effect the smooth deprotection of functional groups such as methoxy methyl ethers (MOMs) of alkyl, allyl, propargyl, and benzyl alcohols; MOMs of phenols; and the cleavage of MOM esters (**Scheme 2**).[29]

2.7. Demethylation Reactions

Hashimoto and co-workers showed that niobium pentachloride can effect the regioselective demethylation of **13**, a key step in the catalytic asymmetric synthesis of descurainin (**15**), which is widely used as a Chinese traditional medicine to relieve coughing, prevent



X = O, S, NH
R = alkyl, allyl, cycloalkyl, aryl

eq 11 *(Ref. 26)*

asthma, reduce edema, and as a diuretic. Employing the Arai–Nishida protocol, they treated **13** with $NbCl_5$ in 1,2-dichloroethane at 70 °C to effect the regioselective demethylation of the 4-MeO group, affording phenol **14** as the sole product in 79% yield (**Scheme 3**).[30]

3. Other Niobium-Based Catalysts

3.1. Solid-Phase Niobium(V)

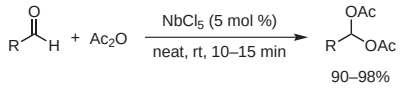
Barbosa's group has demonstrated a clean, efficient, and rapid method for esterifying sterically (biodiesels) or other inactive (aromatic) carboxylic acids by using Lewis acids on solid supports. In all cases investigated, the yields obtained with the mixed catalysts were similar to, or higher than, those reported in the literature. Results for the Nb_2O_5–Zn and Nb_2O_5–Fe are presented in **eq 14**.[31] Trial experiments without the solid-phase Lewis acid did not produce any ester product.

Another study by the same group showed that alcohols and acids can be switched to produce ethers or esters by varying the alcohol-to-catalyst molar ratio in the case of $NbCl_5$–Al_2O_3 under "solvent free" conditions and microwave irradiation. A "two sites" mechanism was proposed for the reaction to explain the tendency of the catalyst effectiveness to be dependent on the steric and electronic characteristics of the alcohol alone during the esterification process.[32]

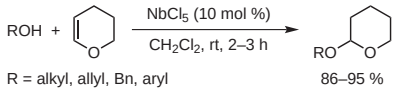
10 wt % Nb_2O_5 supported on silica–alumina catalyzes the liquid-phase esterification of acetic acid with a variety of alcohols at 85–128 °C. After 8 h, and using an acid:alcohol molar ratio of 2:1, 100% selectivity in all cases and good conversions were observed for ethyl (83%), *n*-butyl (87%), and isopentyl (91%) acetates.[33] Following a series of tests, conversions with the supported catalyst were better than those obtained with the isolated oxides, and better yet than those obtained in the absence of catalyst.

Nb_2O_5–SiO_2 mixed-oxide nanocomposites containing 7–37 wt % Nb were synthesized by a new sol–gel route, and their textural and surface acid properties investigated. Their activity as heterogeneous catalysts was tested in the epoxidation of cyclooctene with H_2O_2. The materials containing up to 23.0 wt % Nb were stable and active catalysts for the epoxidation of cyclooctene. The highest activity and selectivity for H_2O_2 was exhibited by the catalyst with the lowest Nb content, which also showed high stability in reuse. The catalytic properties were shown to be related to new acid sites that are different from those that exist in pure Nb and Si oxides, and to the presence of NbO_x species.[34] Niobium(V) oxide efficiently catalyzes the transesterification of β-keto esters with a variety of alcohols. Good conversions and moderate-to-good isolated yields have been obtained at faster rates than those recently reported for various other catalysts (**eq 15**).[35] Gonçalves and co-workers have reported that biodiesel can be obtained from fatty acid raw materials through esterification, and investigated, empirically and theoretically, the reactivity of lauric, palmitic, stearic, oleic, and linoleic fatty acids towards methanol by using powdered niobic acid (niobium oxide solid) as a heterogeneous catalyst.[36]

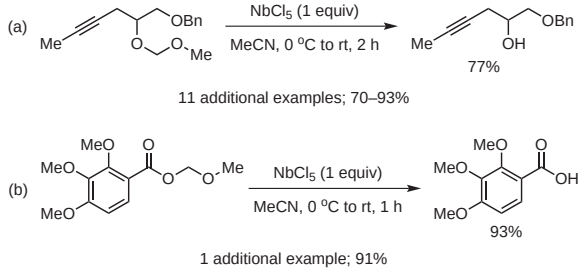
Somma et al. have described the preparation of a series of niobium-based aerogel samples (Nb_2O_5–SiO_2, Nb_2O_5–Al_2O_3, Nb_2O_5–ZrO_2) under acidic and basic conditions, and investigated the effect of the matrix (SiO_2, Al_2O_3, ZrO_2) and of the gelation conditions (acidic or basic) on the surface area, the porosity, and the catalytic activity of the solids in the oxidation of different substrates with hydrogen peroxide. The amount of niobium was constant in all samples tested in the oxidation of unsubstituted (cyclooctene) and substituted (geraniol, nerol, and *trans*-2-pentene-1-ol) olefins. It was found that, even though the catalysts were moderately active, they still produced the epoxides in good yields, and that yields are influenced by the matrix properties



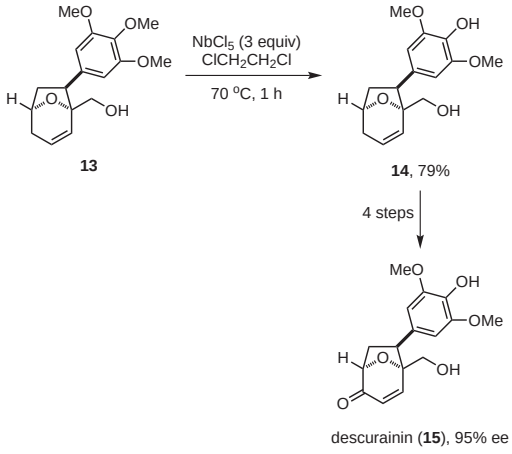
eq 12 *(Ref. 27)*



eq 13 *(Ref. 28)*



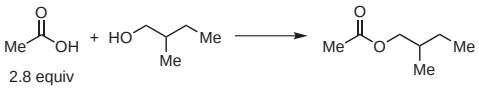
Scheme 2. Deprotection of MOM Ethers and Esters with $NbCl_5$. *(Ref. 29)*



Scheme 3. Regioselective Demethylation with $NbCl_5$. *(Ref. 30a)*

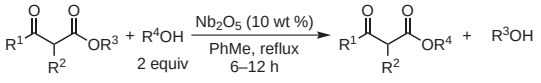
(surface acidity and surface area). The merits of this approach is that it permits the preparation of catalysts that are resistant to leaching and can be recycled several times without appreciable loss of catalytic activity.[37]

A new approach for functionalizing activated and deactivated arenes with iodine, promoted by heterogeneous catalysts, has been reported by Carniti et al. The overarching goal of this study was the development of "greener" iodination processes. Thus, the activity of several different types of solid acid catalysts (acid resins, zeolites, mixed oxides, niobium oxide, and niobium phosphate) was examined in the direct iodination reaction of phenol as a model arene. The mild, eco-friendly conditions (50 °C in methanol in the presence of H_2O_2 as oxidant) led to the efficient introduction of one, two, or three iodines in the arene. Different selectivity distributions of the iodo compounds formed were obtained with the different catalysts, and the latter could be grouped into distinct families on the basis of their ortho or para directing tendencies.[38]



Cat (80 wt %)	360 W μw 70 °C, 1 min	360 W μw 60 °C, 1 h
Nb_2O_5 on $ZnCl_2$	87%	84%
Nb_2O_5 on $FeSO_4$	87%	82%

eq 14 *(Ref. 31)*

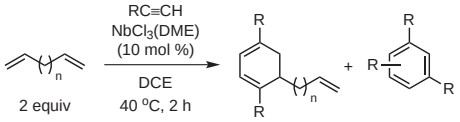


R^1 = Me, MeO_2CCH_2; R^2 = H
R^1,R^2 = $(CH_2)_4$
R^3 = Me, Et
R^4 = *i*-Pr, *n*-Bu, *t*-Bu, Bn, allyl, glycidyl, (–)-menthyl

50–100% conv
33–98% yield

removed by distillation

eq 15 *(Ref. 35)*



16 **17**

n	R	Yield 16	Yield 17
2	*t*-Bu	78%	6%
4	*t*-Bu	84%	trace
6	*t*-Bu	97%	trace
6	TMS	65%	18%
8	*t*-Bu	73%	trace
10	*t*-Bu	56%	nd

eq 16 *(Ref. 40)*

3.2. $NbCl_3$ and Niobium(III) Complexes

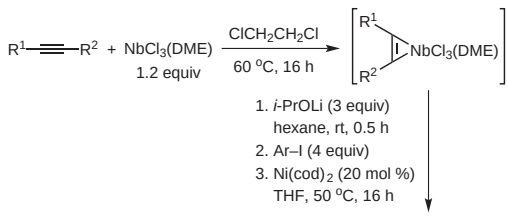
Obora and co-workers have demonstrated that $NbCl_3$(DME) successfully catalyzes the intermolecular [2 + 2 + 2] cycloaddition of alkynes and alkenes, giving 1,4,5-trisubstituted 1,3-cyclohexadiene derivatives in good yields.[39] A year later, the same group reported excellent yields and high chemo- and regioselectivities in the $NbCl_3$(DME)-catalyzed intermolecular [2 + 2 + 2] cycloaddition of *tert*-butylacetylene with α,ω-dienes, affording 5-ω-alkenyl-1,4-disubstituted-1,3-cyclohexadienes (**eq 16**).[40]

Interestingly, Ni(0) catalyzes the cross-coupling of Nb(III)–alkyne complexes with aryl iodides. An excess of lithium alkoxide, as additive, is indispensable for the success of this reaction, which leads to good yields of the corresponding 1,2-diarylalkene products (**Scheme 4**).[41]

$NbCl_3$(DME) mediates the reaction of aliphatic ketones with aryl-substituted alkynes to form a variety of 1,1,2-trisubstituted-1*H*-indenes in good yields (**Scheme 5**).[42] This remarkable transformation is believed to be the first example of a preparative route to the relatively rare 1,1-disubstituted indenes from aliphatic ketones, and is thought to proceed as depicted in Scheme 5.

3.3. $HNbMoO_6$•nH_2O

$HNbMoO_6$ functions as a strong solid-acid catalyst in a number of commonly used reactions. It exhibits high catalytic activity in acetalization, esterification, and hydration reactions, and its activity exceeds those of zeolites and ion-exchange resins in the Friedel–Crafts alkylation. In the first report of successful acid catalysis using a layered transition-metal oxide, the catalytic activity of $HNbMoO_6$ is attributed to the intercalation of reactants into the interlayer and the development of strong acidity. Layered $HNbMoO_6$•nH_2O consists of layers formed of randomly sited MO_6 (M = Nb and Mo) octahedra with H_2O in the interlayer. In one example, the performance of $HNbMoO_6$ was compared with those of niobic acid (Nb_2O_5•nH_2O), zeolites,



R^1	R^2	Ar	Isolated Yield	Isomer Ratio
Ph	Me	Ph	65%	----
Ph	Me	3-MeC_6H_4	63%	59:41
Ph	Me	4-MeC_6H_4	62%	59:41
Ph	Me	4-FC_6H_4	58%	nd
Ph	Me	4-$MeOC_6H_4$	46%	55:45
Ph	Me	4-ClC_6H_4	35%	53:47
Ph	Me	4-$MeO_2CC_6H_4$	53%	55:45
Ph	Ph	Ph	66%	----
3-$F_3CC_6H_4$	Me	Ph	72%	51:49
4-MeC_6H_4	Me	Ph	61%	54:46
n-Pr	Me	Ph	55%	64:36
n-Pr	*n*-Pr	Ph	51%	65:35

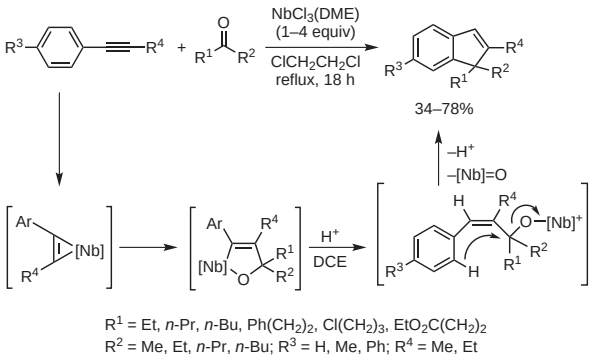
Scheme 4. Ni(0)-Catalyzed Cross-Coupling of Nb(III)–Alkyne Complexes with Aryl Iodides. *(Ref. 41)*

and ion-exchange resins in the Friedel–Crafts alkylation of anisole, toluene, and benzene with benzyl alcohol in the liquid phase over the layered oxide (**eq 17**).[43] The yield of benzyl anisole reached 99% after 30 min, whereas those obtained with the ion-exchange resins reached only ca. 42% even after 1 h. The turnover rate of $HNbMoO_6$ in the alkylation of anisole was more than three times higher than that of Nafion® NR50. It is worth noting that other layered transition-metal oxides such as HNb_3O_8 and $HTiNbO_5$ did not exhibit the activity.

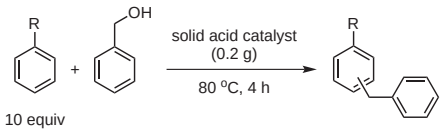
3.4. Niobium Alkoxides

Kobayashi and co-workers have reported the first example of the complementary stereoselective and catalytic desymmetrization of meso epoxides and meso aziridines with anilines as nucleophiles. This approach utilizes an extremely unusual and highly selective niobium catalytic system that promotes closely related reactions with opposite stereochemical outcomes. This Lewis acid system is based on the complex formed from niobium alkoxides and a tetradentate BINOL derivative. The resulting (*R*,*R*)-1,2-amino alcohols and (*S*,*S*)-1,2-diamines are obtained in good-to-excellent yields and very high-to-excellent enantioselectivities (**Scheme 6**).[44] Because of its sensitivity to steric bulk at the β carbon of epoxides, the catalyst displays a remarkable ability to distinguish between different meso epoxides by selectively facilitating the ring-opening of less sterically hindered epoxides in the presence of more sterically hindered ones. In the ring-opening reactions of both epoxides and aziridines, formation of the catalyst in the presence of molecular sieves—which were then filtered off before addition of reactants—was found to be important for the realization of high yields and stereoselectivities.[44]

Katsuki's group discovered a unique asymmetric catalysis by niobium–salan complexes of the epoxidation of allylic alcohols with hydrogen peroxide. It was first shown that a μ-oxo $[Nb(salan)]_2$ complex catalyzes the asymmetric epoxidation of allylic alcohols with the adduct of urea and hydrogen peroxide. Following analysis of the time course of the epoxidation, it was also discovered that in situ prepared Nb(salan) complexes catalyze the epoxidation of allylic alcohols with hydrogen peroxide in aqueous media (**eq 18**).[45] This latter method does not require the troublesome purification of the catalyst, and allows easy tuning of the ligand. It is the first example of a highly enantioselective epoxidation of allylic alcohols with aqueous



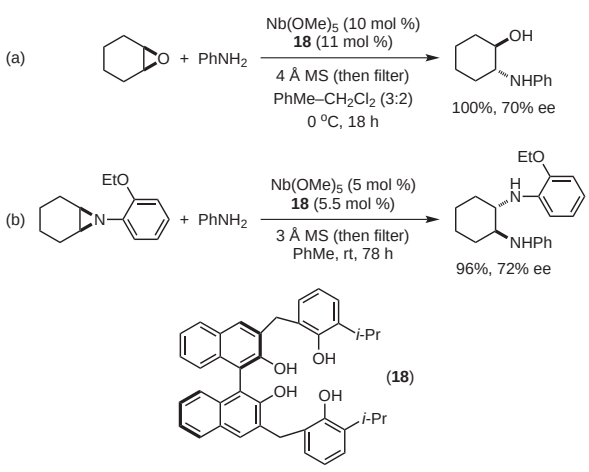
Scheme 5. First Example of a Preparative Route to 1,1-Disubstituted Indenes. *(Ref. 42)*



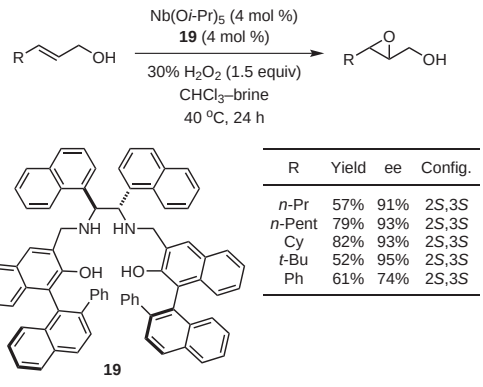
Solid Acid	Amount (mmol•g^{-1})	Yield for R = MeO[a]	Me	H
$HNbMo_6$[b]	1.9	99%	74%	22%
$HNbMo_6$[c]	1.9	94%	22%	8%
Nb_2O_5•nH_2O	0.3	1%	nd	nd
Nafion® NR50	0.9	42%	19%	10%
Amberlyst® 15	4.8	42%	14%	7%
H-ZSM-5 zeolite[d]	0.2	9%	1%	nd
H-Beta zeolite[e]	1.0	31%	1%	nd

[a] At 100 °C for 1 h. [b] Protonated with H_3PO_4. [c] Protonated with HNO_3; reaction time = 0.5 h. [d] SiO_2:Al_2O_3 = 90 (JRC-Z-5-90H). [e] SiO_2:Al_2O_3 = 25 (JRC-Z-HB25).

eq 17 *(Ref. 43)*

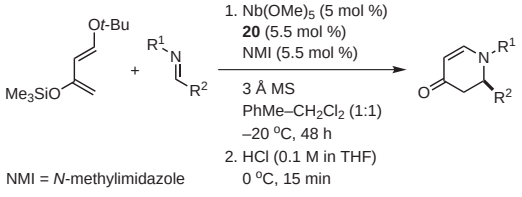


Scheme 6. Nb(V) Catalytic System Promotes the Desymmetrization of Closely Related Systems with Opposite Stereochemical Outcomes. *(Ref. 44)*

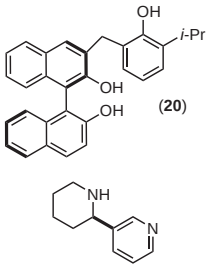


R	Yield	ee	Config.
n-Pr	57%	91%	2*S*,3*S*
n-Pent	79%	93%	2*S*,3*S*
Cy	82%	93%	2*S*,3*S*
t-Bu	52%	95%	2*S*,3*S*
Ph	61%	74%	2*S*,3*S*

eq 18 *(Ref. 45)*



NMI = *N*-methylimidazole

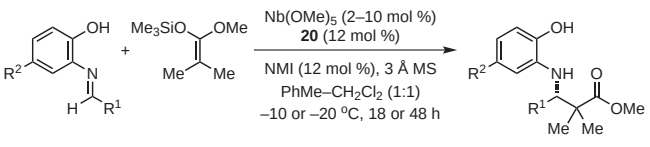


(+)-anabasine

R^1	R^2	Yield	ee
2-HOC$_6$H$_4$	Ph	81%	96%
2-HOC$_6$H$_4$	1-Np	89%	92%
2-HOC$_6$H$_4$	4-MeC$_6$H$_4$	90%	94%
2-HOC$_6$H$_4$	2-F$_3$CC$_6$H$_4$	94%	99%
2-HOC$_6$H$_4$	2-ClC$_6$H$_4$	89%	91%
2-HOC$_6$H$_4$	3-Py	74%	92%
2-HO-5-MeC$_6$H$_3$[a]	Cy	67%	90%
2-HO-5-MeC$_6$H$_3$[b]	*i*-Pr	63%	92%
2-HO-5-MeC$_6$H$_3$[b]	*i*-Bu	47%	90%

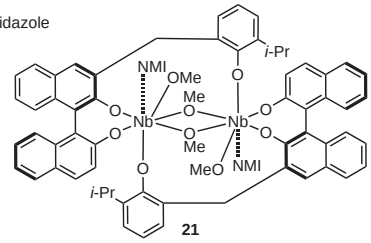
[a] In dichloromethane. [b] In toluene.

eq 19 *(Ref. 46)*



R^1 = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 1-Np, 2-Np, thien-3-yl, 2-Fur
R^2 = H, CF$_3$
NMI = *N*-methylimidazole

40–86%, 91–99% ee



21

eq 20 *(Ref. 47)*

H_2O_2 and of asymmetric catalysis by a niobium complex in aqueous medium.

A chiral, Nb(V)-based Lewis acid effectively catalyzes the aza-Diels–Alder reaction of imines with Danishefsky's diene. The reaction proceeds in high yield and high enantioselectivity for aromatic and aliphatic imines, and has been applied to the total synthesis of (+)-anabasine (**eq 19**).[46]

In an earlier study, Kobayashi's group had identified a novel dinuclear chiral niobium catalyst, **21**, formed from Nb(OMe)$_5$ and **20**. In the presence of a catalytic amount of this complex, asymmetric Mannich-type reactions proceed smoothly to afford the desired adducts in high yields and with high enantioselectivities (**eq 20**).[47]

4. Conclusion

The recently disclosed reactions presented in this review have highlighted the efficiency and versatility of niobium compounds as catalysts and reagents in organic synthesis. Interest in niobium compounds and their applications in chiral catalysis and total synthesis of natural products is growing steadily as evidenced by the increasing number of research groups around the world, who are studying these compounds and developing new applications for them.

5. Acknowledgments

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About the Authors

Valdemar Lacerda, Jr. was born in 1975 in Goiânia, GO, Brazil. He received a B.Sc. degree in chemistry in 1997 from the Federal University of Goiás, where he worked in the laboratory of Professor Pedro Henrique Ferri. He received his M.Sc. degree in 2000 and his Ph.D. degree in 2004 from São Paulo University, Ribeirão Preto, working with Professor Mauricio Gomes Constantino in organic synthesis and NMR studies. In 2004, he began working as a postdoctoral researcher at the NMR laboratory coordinated by Professor Gil Valdo José da Silva. In 2006, he joined the department of chemistry of the Federal University of Espirito Santo (ES State, Brazil) as an associate professor. His current research interests focus on organic synthesis, NMR studies, theoretical calculations, and petroleum studies. He has been Head of the Department of Chemistry since 2007, and is presently also a CNPq level 2 researcher.

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Sandro J. Greco was born in Rio de Janeiro, RJ, Brazil. He received his B.Sc. degree in chemistry in 1997 and his M.Sc. and Ph.D. degrees in 2001 and 2005 from the Fluminense Federal University (Rio de Janeiro, Brazil), working under the guidance of Professor Sergio Pinheiro on studies of the use of terpenes and terpenoids in the enantioselective synthesis of potential anticholinergic agents, and on the synthesis of amino alcohol based, new chiral phase-transfer catalysts. In 2006, he joined Professor Maria D. Vargas's group at the Fluminense Federal University as a postdoctoral researcher to work on the synthesis and pharmacological evaluation of new anticancer drugs containing the ferrocenyl group. He is currently an associate professor of organic chemistry at the Federal University of Espírito Santo, with research interests in the design and synthesis of potential bioactive compounds and the development of new organocatalysts and chiral phase-transfer catalysts for asymmetric synthesis.

Reginaldo B. dos Santos was born in Matão, Brazil, and obtained his B.Sc. degree in chemistry in 1986 from the Federal University of São Carlos (SP State, Brazil). He then received his M.Sc. and Ph.D. degrees at the same University in 1990 and 1995, working under the supervision of Professor U. Brocksom in the field of organic synthesis. In 1991, he was appointed Assistant Professor in the Department of Chemistry at the Federal University of Espirito Santo (ES State, Brazil), and was promoted to Associate Professor in 1995.

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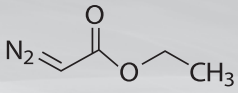

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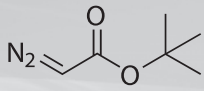

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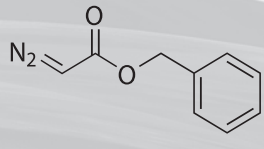

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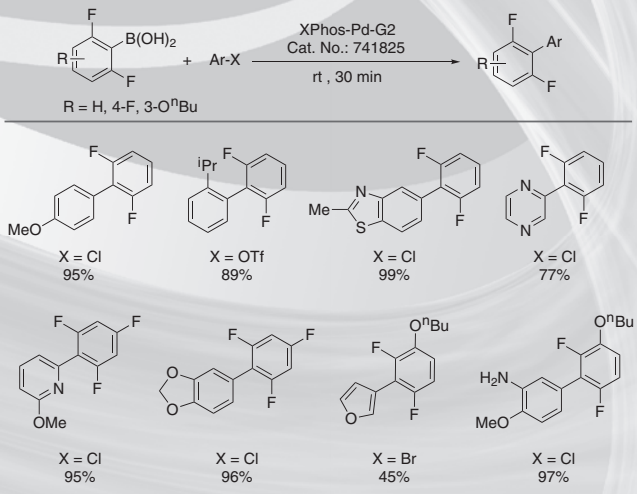

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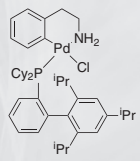
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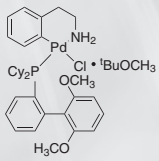
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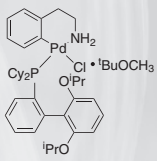
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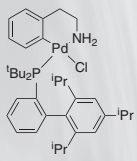
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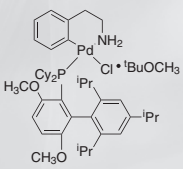
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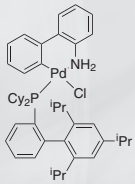
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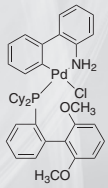
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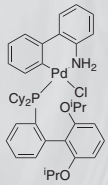
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Bruce Lipshutz has been on the faculty at UC Santa Barbara for the past 33 years. From his early contributions in the form of reagents such as SEM-Cl and higher order cyanocuprates to heterogeneous catalysts in the form of nickel- and copper-in-charcoal, his research focus has been on providing technologies that are broadly applicable to synthetic problems. More recently, he has turned his attention to "green" chemistry, with the goal of developing micellar catalysis as an environmentally benign way of carrying out transition-metal-catalyzed cross-coupling reactions in water at room temperature.

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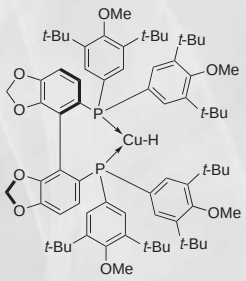

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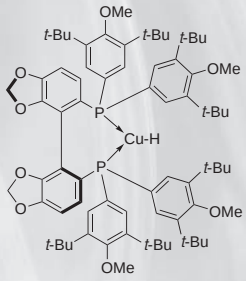

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