Catalysis in the Service of Green Chemistry: Nobel Prize-Winning Palladium-Catalysed Cross-Couplings, Run in Water at Room Temperature

Heck, Suzuki-Miyaura and Negishi reactions carried out in the absence of organic solvents, enabled by micellar catalysis

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Palladium-catalysed cross-couplings, in particular Heck, Suzuki-Miyaura and Negishi reactions developed over three decades ago, are routinely carried out in organic solvents. However, alternative media are currently of considerable interest given an increasing emphasis on making organic processes 'greener'; for example, by minimising organic waste in the form of organic solvents. Water is the obvious leading candidate in this regard. Hence, this review focuses on the application of micellar catalysis, in which a 'designer' surfactant enables these award-winning coupling reactions to be run in water at room temperature.

1. Introduction

Decades ago, before palladium-catalysed cross-couplings arrived, copper was the transition metal of choice for mediating carbon–carbon bond formation, regardless of which organometallic complex was used as the precursor to arrive at various Cu(I) reagents. However, palladium eventually gained in popularity, and in 2010 with the recognition of Heck, Suzuki and Negishi as Nobel Prize recipients (1), the importance of Pd-catalysed carbon-carbon bond-forming reactions in organic synthesis was confirmed.

Each modern organic synthetic reaction was developed along traditional lines; that is, the chemistry was matched, not surprisingly, to an organic solvent in which the coupling best took place (**Scheme I**). And while the presence of varying percentages of water is not an issue for Heck reactions that lead (2–4) to products such as cinnamates, and Suzuki-Miyaura reactions that afford (5–7), for example, arylated aromatics, the far more basic nature of organozinc halides (RZnX; R = alkyl) (8–11) in Negishi couplings (12, 13) that give products such as alkylated aromatics
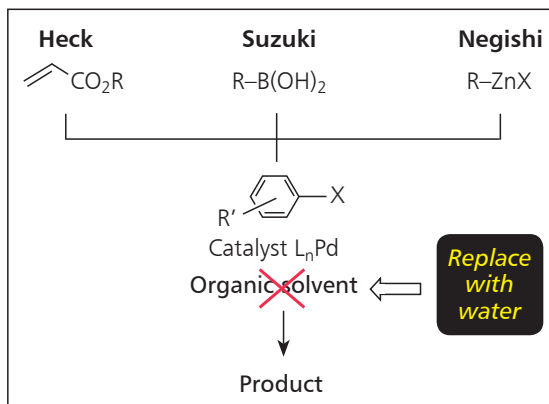
Scheme I. Traditional cross-coupling reactions going 'green'

precludes their use under aqueous conditions. None of these would typically be thought of as amenable to use in pure water especially at ambient temperatures, pK_a issues aside, if for no other reason than that organic substrates are not normally soluble in water.

The world is paying increased attention to organic waste produced by the chemical enterprise, and organic solvents play a considerable role in this regard (14). 'Sustainability' is becoming a guiding principle in many areas of science and engineering (15), and the concept of 'green chemistry' is gaining in importance (16–21). Much emphasis, therefore, is being directed towards 'alternative media' (22, 23) in which synthetic chemistry can be conducted. In this way, our dependence on organic solvents, whether derived from petroleum reserves or otherwise, is minimised.

It should be appreciated that green chemistry is an all-inclusive term, and an evaluation of the full cycle (a full life cycle assessment (LCA)) of all components associated with a given process should be considered in order to fully evaluate the 'greenness' of that process (24–26). Clearly, reductions in major factors such as the number of steps, the number of changes in solvent(s), and the number of product isolations can play a huge role in controlling the generation of organic waste. Notwithstanding the many virtues of water as a medium, its use could be costly in terms of its downstream handling and processing, and if heating is required either during a reaction or for its eventual evaporation. But it is also acknowledged that total LCAs can be both challenging to produce, and expensive, while on the other hand, solvents, whether organic or otherwise, are well known entities that can be readily assessed, quantified, and analysed in terms of their use in manufacturing and waste disposal.

Therefore this review considers solvents alone with regard to 'greener' processes.

The most likely alternative among the various choices available (for example, ionic liquids (27–30), supercritical carbon dioxide (31–37) etc.), in terms of potential generality, is water (38–41). To get around the substrate solubility issue, the leading candidate technology appears to be micellar catalysis, in which reactants can be 'solubilised' within the surrounding aqueous phase by the addition of surfactants (42, 43). Although this approach to mixing 'oil and water' is decades old, the nature of the surfactants available to the organic chemist through normal commercial channels is actually very modest; a handful of each type (ionic, nonionic and zwitterionic) is all that is normally seen in the literature. It seems odd, given the importance of solvent effects in organic chemistry (24–26), that the choice of amphiphile supplying the organic medium in which the chemistry is to take place would be so limited. Moreover, most common surfactants were created for use in the manufacture of paint, cosmetics, oil, cleaning fluids, leather, etc. rather than for their use in organic synthesis.

To be able to run Heck, Suzuki-Miyaura and Negishi cross-couplings in water at room temperature, thereby totally bypassing organic solvents as the reaction medium, as well as to derive energy savings by avoiding any need for either heating or cooling reaction mixtures, the requirements are: (a) identification of an existing, or possibly newly designed and synthesised surfactant that leads to results that are as good as or better than those in organic media; and (b) assurance that any amphiphile chosen is fully compliant with 'The 12 Principles of Green Chemistry' (44).

2. The Amphiphile TPGS-750-M

Unlike many surfactants that contain lipophilic, usually hydrocarbon fragments that have been 'PEGylated' (PEG = polyethylene glycol), the newly designed amphiphile DL-α-tocopherol methoxypolyethylene glycol succinate (TPGS-750-M) (**1**, **Figure 1**) has three components (45): non-natural α-tocopherol (vitamin E), a succinic acid linker, and methoxy polyethylene glycol ('MPEG-750'). This latter, hydrophilic portion is monomethylated at one terminus and contains on average 17 oxyethanyl units (750 divided by 44). The 'TPGS' nomenclature derives originally from Kodak's 'TPGS', which by analogy is TPGS-1000, and contains the same α-tocopherol (albeit in its natural, nonracemic form) and succinic acid linker, while the PEG is PEG-1000 (which has *ca.* 23 oxyethanyl units
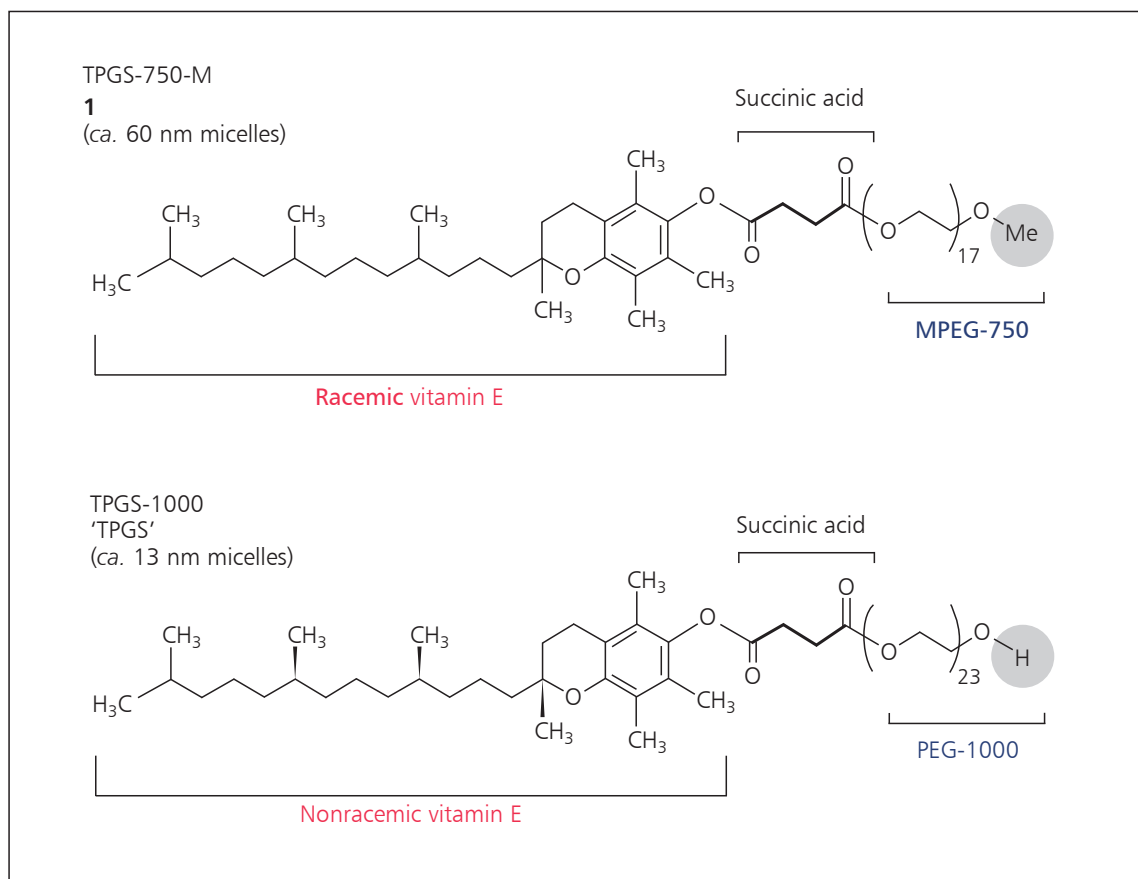
Fig. 1. Comparison of structures between 'TPGS' (TPGS-1000) and newly engineered TPGS-750-M

and a free hydroxyl residue at its terminus) (46). These look very similar on paper, but their chemistry is very different, allowing opportunities to fine-tune the nanoreactors formed during micellar catalysis that serve as an organic solvent-like medium for homogeneous cross-coupling reactions in water.

In designing TPGS-750-M (45), it was anticipated that the economics of its synthesis would be quite favourable, since it is based on racemic vitamin E, succinic anhydride, and a commercially available MPEG. It can be prepared in >90% overall yield using a simple two-step procedure (45). Couplings within its larger nanomicellar interior should be as fast or faster than those in other surfactants that form smaller particles in water, since both size and shape appear to be significant (for example, TPGS-1000 forms *ca.* 13 nm spherical micelles, while TPGS-750-M forms *ca.* 60 nm particles). An important implication was that a Pd catalyst would be found for each reaction type that would function well under the high concentrations

typically found in micelles. However, it was far from obvious whether the 'rules' of modern homogeneous catalysis, in which each process and catalyst is precisely matched with a particular organic solvent, would apply to homogeneous catalysis taking place at much higher concentrations within nanomicelles. Therefore, a wide range of Pd catalysts, obtained from Johnson Matthey, were screened for applicability to transition metal-catalysed couplings under the influence of the hydrophobic effect.

3. Heck Reactions

Cinnamate-forming reactions between aryl bromides and acrylates take place very smoothly at room temperature within the nanomicellar environment of TPGS-750-M (5 wt%) (45, 47), akin to those seen earlier in the first generation surfactant polyoxyethanyl α-tocopheryl sebacate PTS (PTS-600; **Figure 2**) (48, 49). The keys to success in this type of coupling are the use of 3 M sodium chloride solutions in
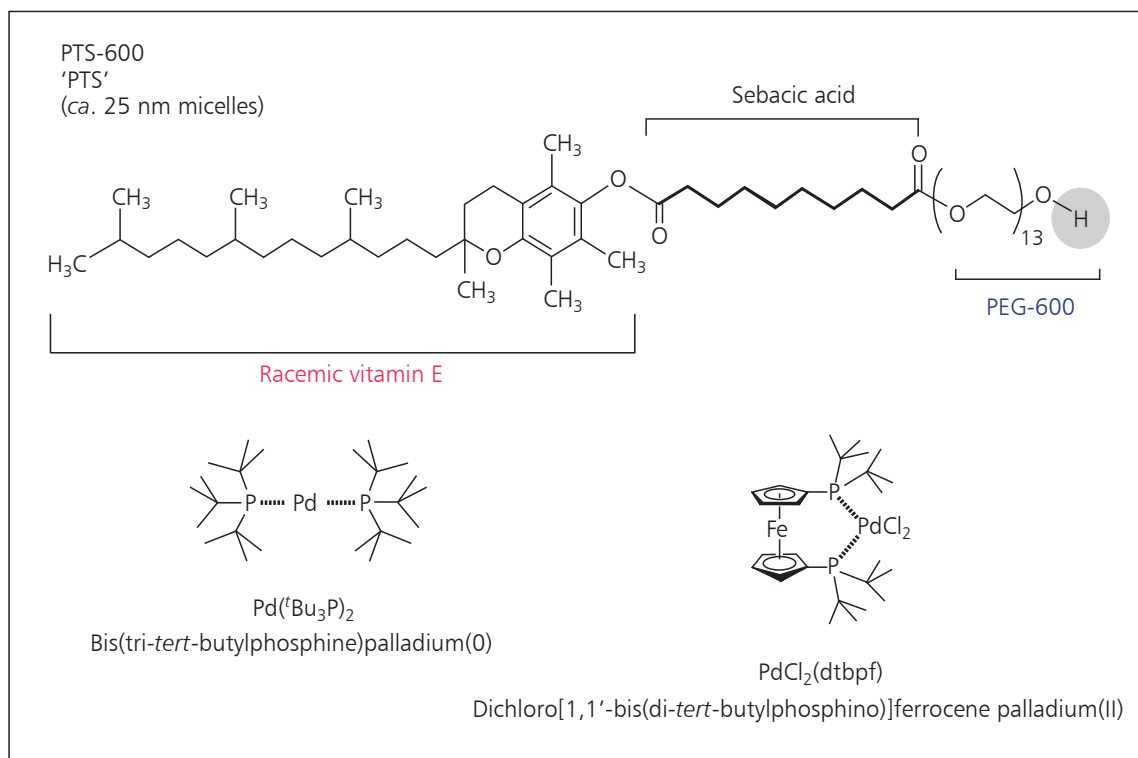
Fig. 2. Catalysts used in Heck reactions run in water at room temperature

place of water alone, and either of the electron-rich Johnson Matthey catalysts bis(tri-*tert*-butylphosphine)-palladium(0) (Pd(^{t}Bu$_3$P)$_2$) or dichloro[1,1'-bis(di-*tert*-butylphosphino)]ferrocene palladium(II) (PdCl$_2$(dtbpf)) (**Figure 2**). Other catalysts, such as those derived from various Pd(II) salts (for example palladium(II) acetate (Pd(OAc)$_2$), palladium(II) chloride (PdCl$_2$), or tris(dibenzylideneacetone)dipalladium(0) (Pd$_2$(dba)$_3$)) as Pd(0) precursors in the presence of various bidentate phosphine ligands were all less effective. The 'salting out' effect (50) of the NaCl leads to a complete alteration from spherical to worm-like micellar arrays (as seen by cryogenic transmission electron microscopy (cryo-TEM) analysis) (49) with presumably greater binding constants of substrates within the particles and hence, faster rates of reactions. Triethylamine appears to be the common base for these Heck couplings. Representative examples, in general, of (*E*)-favoured arylated products are shown in **Scheme II**.

Likewise, (*E*)-stilbenes constructed from aryl halides and styrene derivatives can be readily fashioned under similar micellar conditions (**Scheme III**) (45, 47). Reactions with aryl iodides and styrene derivatives

can be performed at room temperature in aqueous micellar solutions using either deionised water or 3 M NaCl and typically are complete in less than four hours (global concentration = 0.50 M). The product stilbenes are obtained in excellent yields with >8:1 *E:Z* selectivity, and often precipitate directly from the reaction mixture. As with the case of acrylates (**Scheme II**), 3 M NaCl can be used to enhance the rates of otherwise sluggish reactions.

4. Suzuki-Miyaura Cross-Couplings

Biaryl-forming reactions of arylboronic acids and aryl or heteroaryl bromides can be efficiently catalysed by PdCl$_2$(dtbpf) at room temperature in aqueous solutions of either PTS or TPGS-750-M. Three representative cases are illustrated in **Scheme IV**, including the cross-coupling of a relatively hindered 2,4,6-triisopropyl-substituted bromide.

The air stable complex, PdCl$_2$(dtbpf), has seen less extensive use in organic solvents for Suzuki-Miyaura chemistry than its diphenyl analogue, dichloro-[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (PdCl$_2$(dppf)). Nonetheless, early reports from Johnson Matthey suggested far greater activity
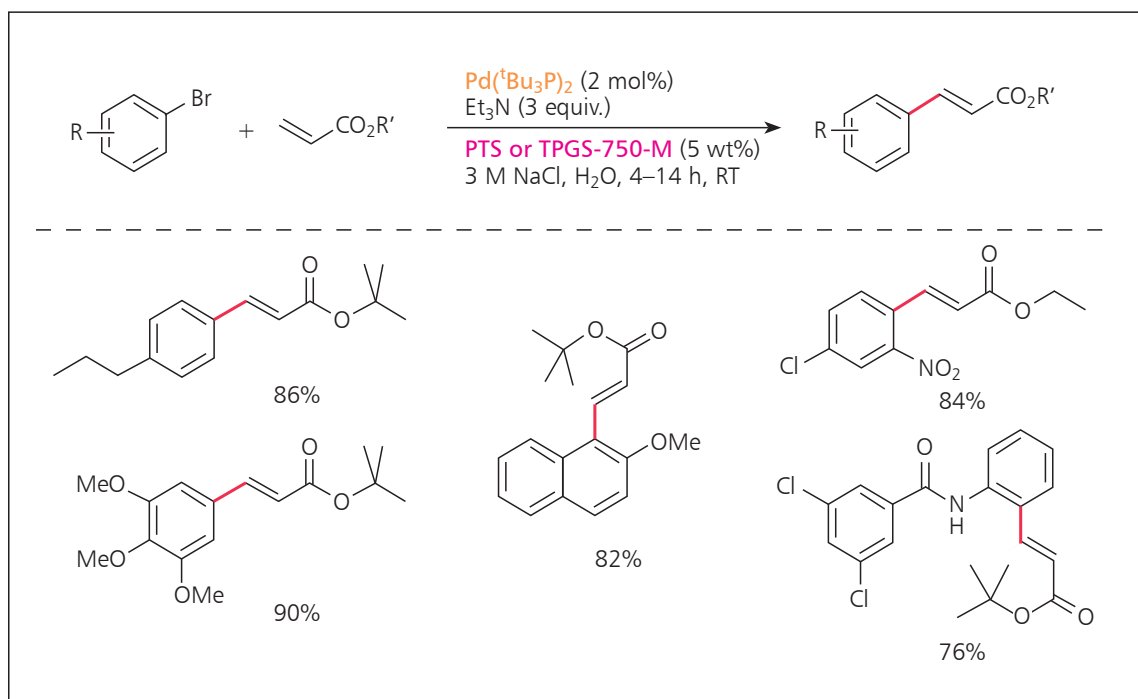
Scheme II. Representative Heck couplings in water at room temperature using [Pd(^{t}Bu$_3$P)]$_2$

of PdCl$_2$(dtbpf) in promoting cross-couplings of aryl chlorides over its more established relative (51). However, under micellar conditions, with challenging aryl chlorides, PdCl$_2$(dtbpf) appears not to be the catalyst of choice (**Scheme V**). The Pd(0) catalyst Pd(^{t}Bu$_3$P)$_2$ showed little improvement, despite the ^{t}Bu$_3$P ligand's effectiveness at promoting Suzuki-Miyaura couplings at room temperature in tetrahydrofuran (THF) (52). And while dichlorobis(*p*-methylaminophenyl-di-*tert*-butylphosphine)palladium(II) (PdCl$_2$(Amphos)$_2$) showed a marked improvement, the *N*-heterocyclic carbene (NHC) bound catalyst phenylallylchloro[1,3-bis(diisopropylphenyl)imidazole-2-ylidene]palladium(II) ([(IPr)Pd(cinnamyl)Cl] or Neolyst CX31), which has been shown to be highly efficient in an organic solvent (53), was the most effective for these reactions being carried out in nanomicelles.

Interestingly, the scope of Suzuki-Miyaura couplings in surfactant-water catalysed by this NHC-ligated catalyst proved to be rather narrow, as PdCl$_2$(Amphos)$_2$ generally provided superior results with heteroaryl chlorides (**Scheme VI**). More surprisingly, a large number of aryl bromide combinations for which PdCl$_2$(dtbpf) had previously proven effective (**Scheme VII**) failed to reach completion under

catalysis with the NHC complex, despite this catalyst's demonstrated competence with these substrate types in organic solvents (53). The effectiveness of PdCl$_2$(Amphos)$_2$ with heteroaryl coupling partners was not unexpected given early reports by Amgen researchers of its high efficiency with educts of this type in Suzuki-Miyaura reactions (54, 55). *trans*-Dichlorobis(tricyclohexylphosphine)palladium(II) (PdCl$_2$(Cy$_3$P)$_2$) notably led to very low conversions with heteroaromatic chlorides under PTS-water conditions, in spite of previous reports of the Cy$_3$P ligand's effectiveness in this role for reactions in dioxane/water (albeit at elevated temperatures) (56). While an extensive study comparing specific catalysts' efficacy in water *vs.* organic solvent has not been undertaken, and notwithstanding the corresponding change of other parameters (most notably the choice of base), catalysts PdCl$_2$(dtbpf) and PdCl$_2$(Amphos)$_2$ clearly do seem especially well-suited to use in water relative to organic solvents.

5. Negishi-Like Couplings in Water
Negishi couplings today have come to imply a Group 10 metal-catalysed cross-coupling between an organozinc reagent and an sp^2-hybridised electrophilic partner (12, 13). In fact, there were several other organometallics
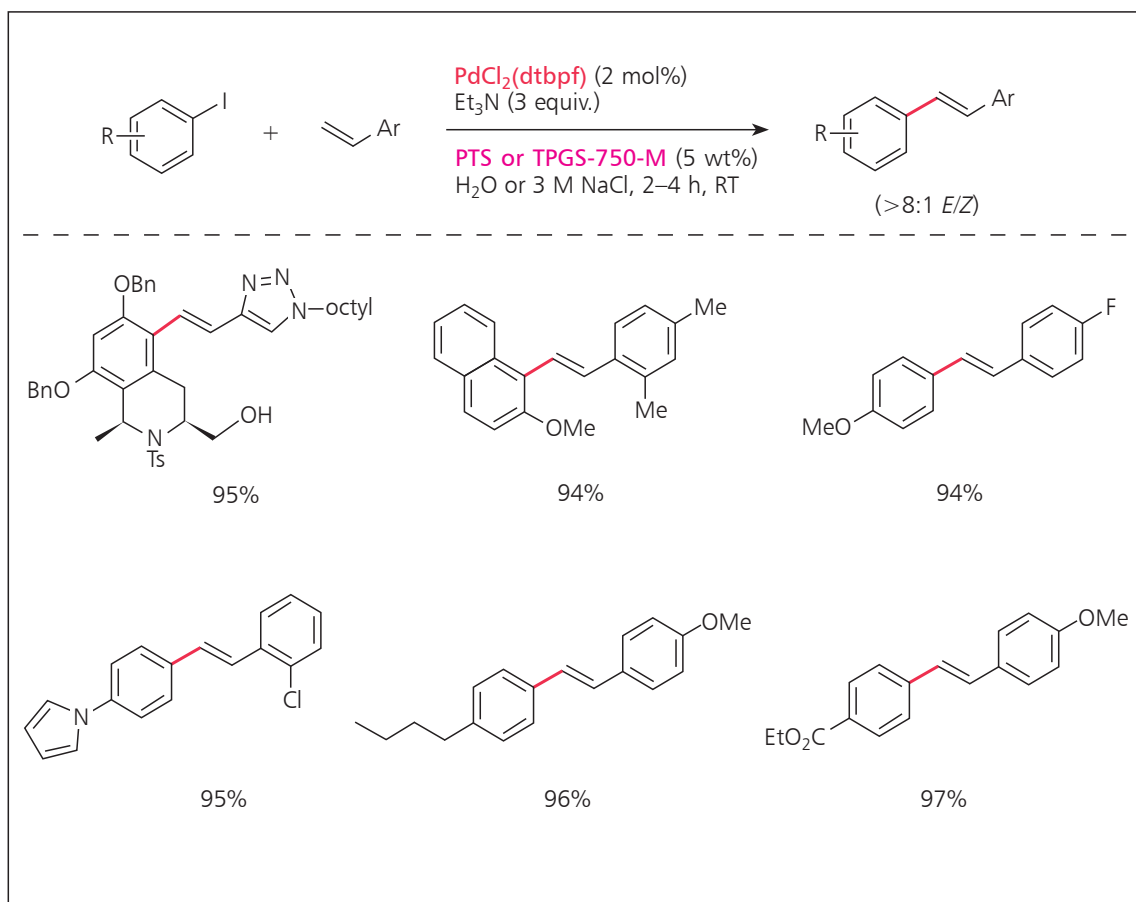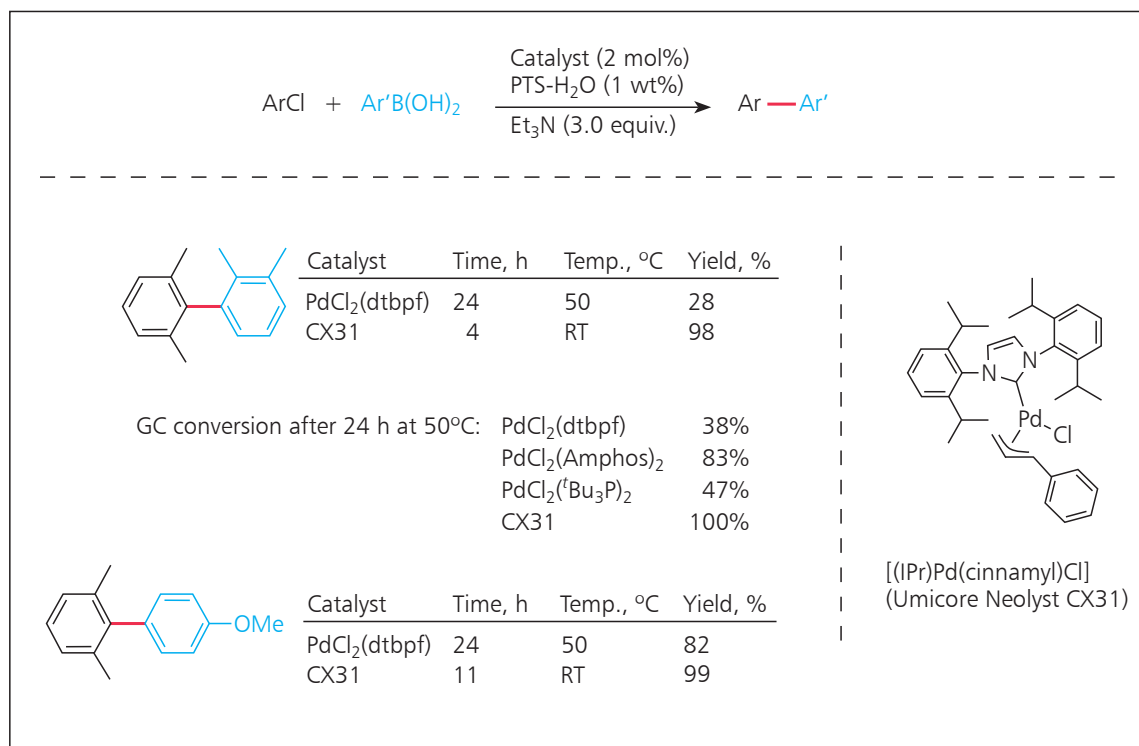
Scheme III. Representative Heck couplings to form stilbenes using PdCl$_2$(dtbpf) in water at room temperature
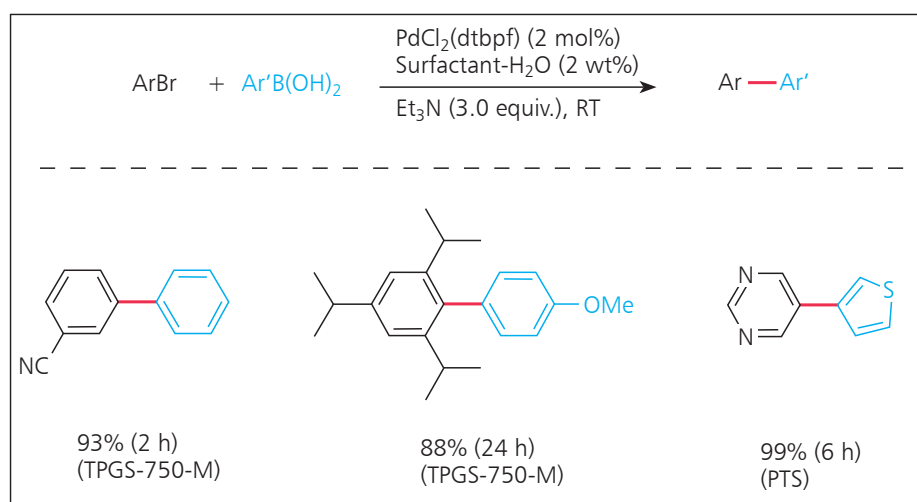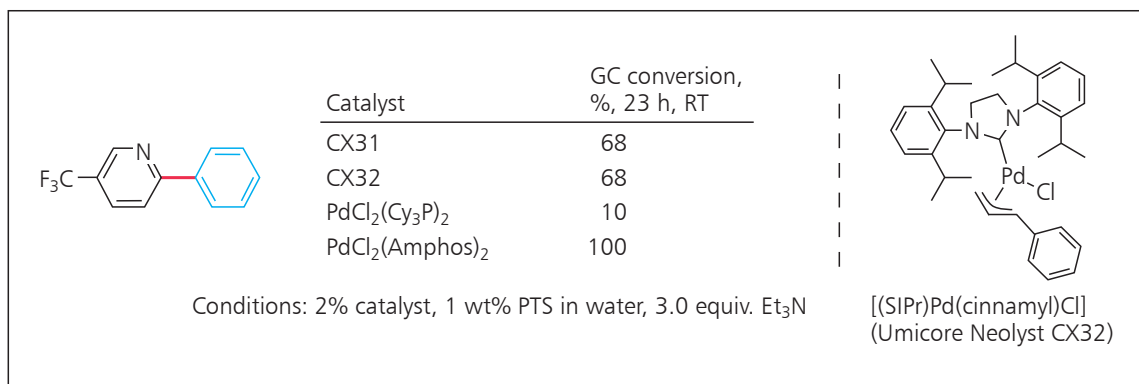

Scheme IV. Representative Suzuki-Miyaura couplings in water at room temperature

that were utilised by the Negishi school before zinc (for example, aluminium, zirconium and boron) (57–61). The synthetic potential of zinc reagents, RZnX,

however, is undeniable, as they possess a suitable level of nucleophilicity to participate in a transmetalation step to a Pd(II) intermediate, while being especially

$$ArCl \; + \; Ar'B(OH)_2 \xrightarrow[\text{Et}_3\text{N (3.0 equiv.)}]{\begin{array}{c}\text{Catalyst (2 mol\%)}\\\text{PTS-H}_2\text{O (1 wt\%)}\end{array}} Ar - Ar'$$

Catalyst	Time, h	Temp., °C	Yield, %
PdCl$_2$(dtbpf)	24	50	28
CX31	4	RT	98

GC conversion after 24 h at 50°C:

PdCl$_2$(dtbpf)	38%
PdCl$_2$(Amphos)$_2$	83%
PdCl$_2$(^{t}Bu$_3$P)$_2$	47%
CX31	100%

Catalyst	Time, h	Temp., °C	Yield, %
PdCl$_2$(dtbpf)	24	50	82
CX31	11	RT	99

[(IPr)Pd(cinnamyl)Cl]
(Umicore Neolyst CX31)

Scheme V. Comparison of catalysts for Suzuki-Miyaura couplings of aryl chlorides in water at room temperature

Catalyst	GC conversion, %, 23 h, RT
CX31	68
CX32	68
PdCl$_2$(Cy$_3$P)$_2$	10
PdCl$_2$(Amphos)$_2$	100

Conditions: 2% catalyst, 1 wt% PTS in water, 3.0 equiv. Et$_3$N

[(SIPr)Pd(cinnamyl)Cl]
(Umicore Neolyst CX32)

Scheme VI. Comparison of NHC-containing catalysts with phosphine-ligand containing catalysts

tolerant of most functionality (62). Unfortunately, however, they are definitely not tolerant of water (12, 13). Nonetheless, Negishi couplings can be, and have been, conducted in pure water (63–65). The secret to success in this unlikely methodology is avoidance of the traditional up-front use of stoichiometric Zn reagents; this is achieved by generating a zinc reagent over time on the surface of the metal, surrounded by the hydrophobic pocket of a nanomicelle. The

catalyst must: (a) be readily available while tolerating exposure to water; and (b) respond favourably to the hydrophobic effect associated with micellar catalysis. One species has been identified to date that meets these criteria: PdCl$_2$(Amphos)$_2$ (54, 55) (**2**, **Figure 3**). Other species, including the parent bis-desamino system PdCl$_2$(^{t}Bu$_2$PhP)$_2$ (**Figure 3**), were screened, but the rates of conversion were too low to make the reaction synthetically viable. Interestingly, among the
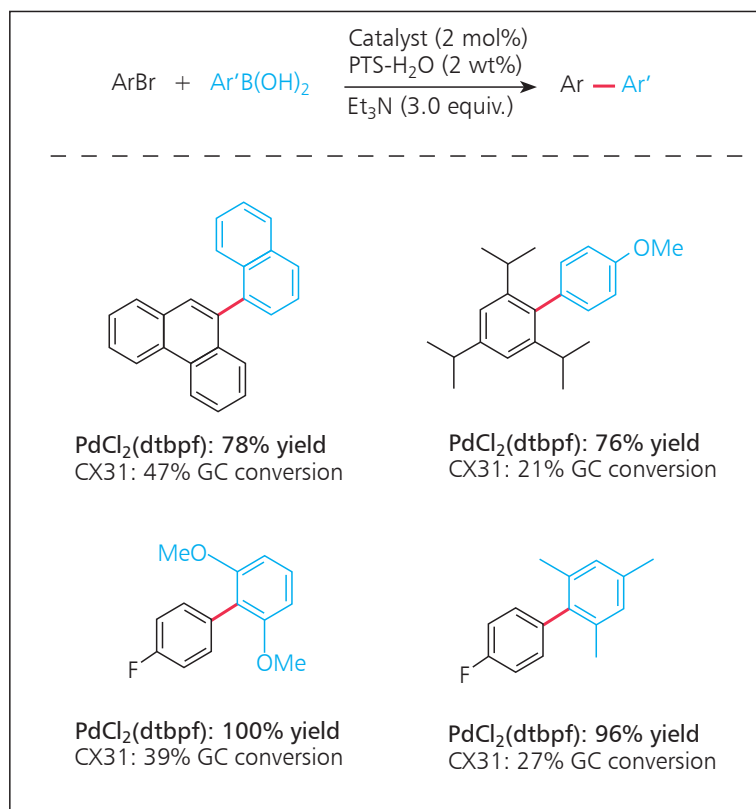
Scheme VII. Comparison of catalysts for Suzuki-Miyaura couplings of aryl bromides

catalysts shown in **Figure 3** are selected cases that are well known to mediate Negishi couplings in THF (66, 67). Clearly, in a nanomicelle, they are not the preferred species.

There is a third essential component: the 'gatekeeper', without which there is no coupling whatsoever: tetramethylethylenediamine (TMEDA). TMEDA likely plays several important roles in these couplings: (i) to clean the metal surface for subsequent electron transfer; (ii) to chelate and thereby stabilise the newly formed RZnX; and (iii) to enhance the transfer of RZnX into the nanomicellar interior.

When an alkyl halide (iodide or bromide), an aryl bromide, excess TMEDA, and PdCl$_2$(Amphos)$_2$ are mixed together in water containing 2 wt% TPGS-750-M (or PTS), nanomicelles are formed containing high concentrations of these species. Upon addition of either Zn powder or dust, chemistry takes place in water at room temperature. The selective insertion of Zn into the sp^3-carbon-halogen bond *via* successive electron transfer steps is presumed to form RZnX on the metal surface, protected momentarily by the surrounding micelle. The newly formed organozinc halide, thought to be chelated by TMEDA, then enters

the hydrophobic interior where a coupling partner and associated reagents are located.

As illustrated in **Scheme VIII**, C–C bond formation takes place smoothly with aryl bromides, including coupling with a secondary alkylzinc reagent to give product **3** in good yield (45, 63). It is especially worthy of note that traditional Negishi couplings with aryl bromides in THF do not typically occur at room temperature (**Scheme IX**; **C**) (12, 13); heating at reflux is common, especially for non-activated substrates. A control experiment using RZnX (prepared in THF) in an aqueous surfactant environment gave the expected low level of conversion due to quenching of the organozinc halide (**A** in **Scheme IX**). Thus, the hydrophobic effect adds yet another benefit to these reactions (**B** in **Scheme IX**).

Several heteroaromatic halides have also been studied under micellar catalysis conditions (**Scheme X**) (64). Here again, PdCl$_2$(Amphos)$_2$, used in catalytic amounts (2 mol%), is crucial for success. Bromides located on each position on a *substituted* pyridyl ring lead to good yields of alkylated products, although the parent 2-, 3- or 4-bromopyridines gave
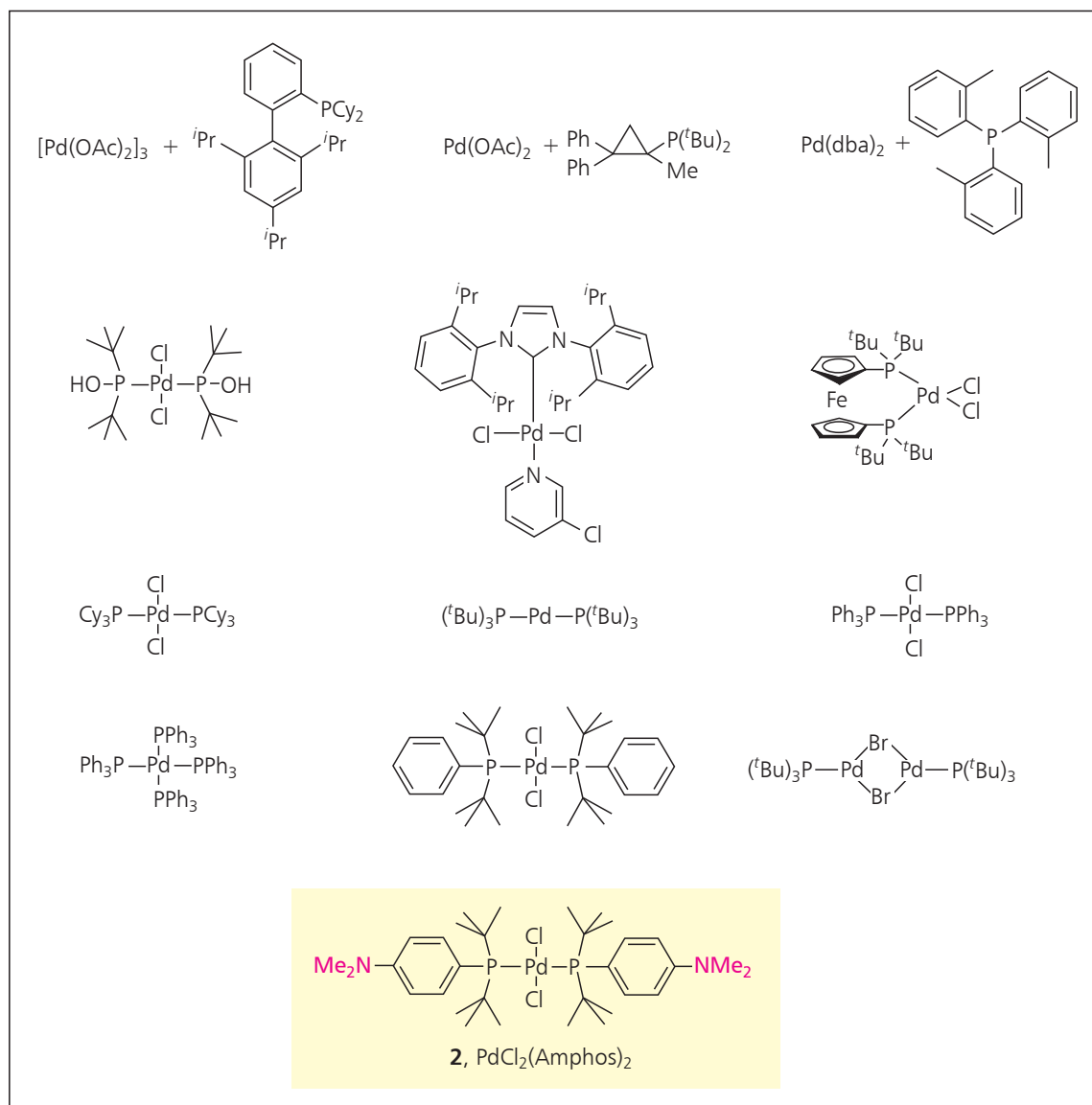
Fig. 3. Ligands/catalysts screened for Zn-mediated, Pd-catalysed cross-couplings in water at room temperature

only traces of substitution. Heteroaromatics including thiophenes, benzothiophenes, indoles and quinolines appear to be amenable. As expected for organozinc reagents, excellent tolerance to functionality in either partner is observed. Noteworthy is the case of indole derivative **4**, where a secondary centre can be directly inserted onto the ring in high yield.

In addition to aryl bromides, cross-couplings involving alkenyl halides are also amenable using catalyst PdCl₂(Amphos)₂, although in these cases the added feature of olefin geometry is present (**Scheme XI**) (65). As anticipated, (*E*)-alkenyl halides, whether iodides or bromides, retain their original geometry in the coupled products. Likewise, (*Z*)-alkenyl halides maintain their stereochemical integrity (45) which was unexpectedly found not to be the case for the corresponding reactions under traditional Negishi coupling conditions in THF (66, 67). The positive stereochemical outcome for these reactions in water is a fortunate occurrence, since the choice of ligands that help mediate these couplings (as noted above), at least to date, is not broad.
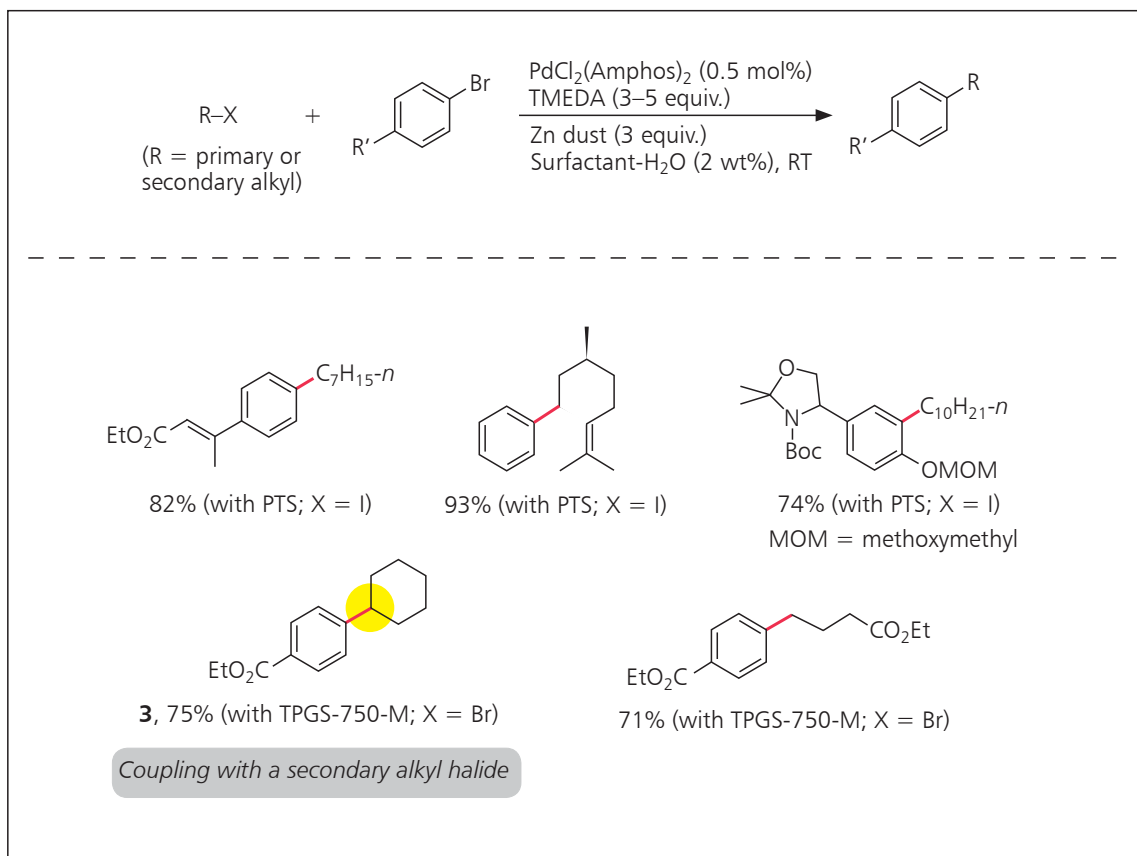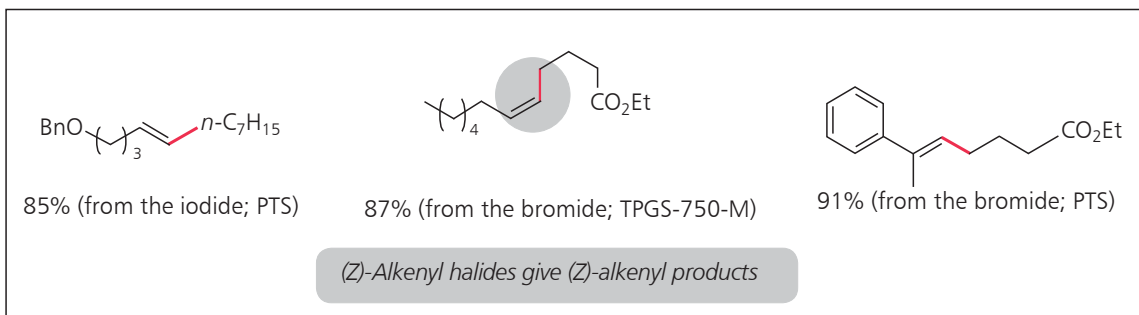
Scheme VIII. Representative Negishi-like couplings between two halides, in water at room temperature
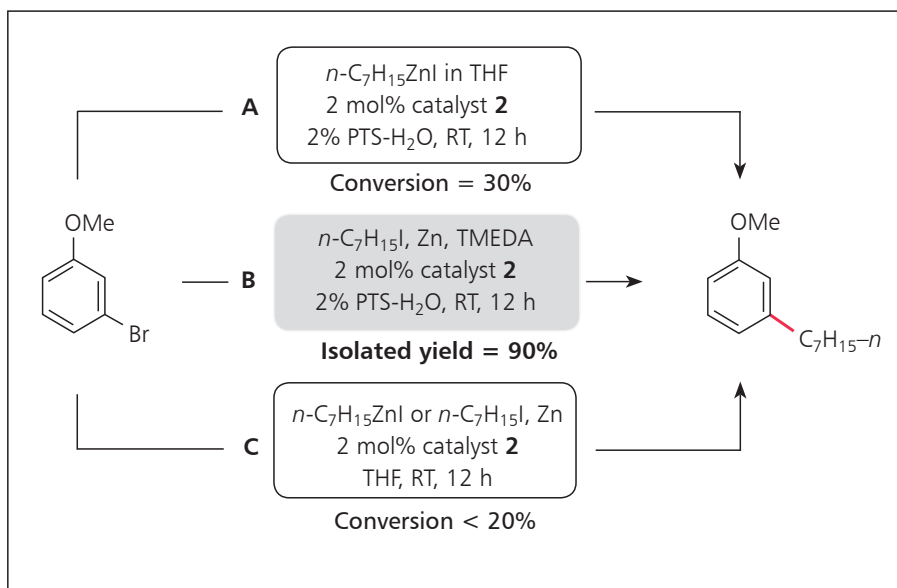
Scheme IX. Comparison reactions: traditional Negishi coupling conditions vs. micellar conditions
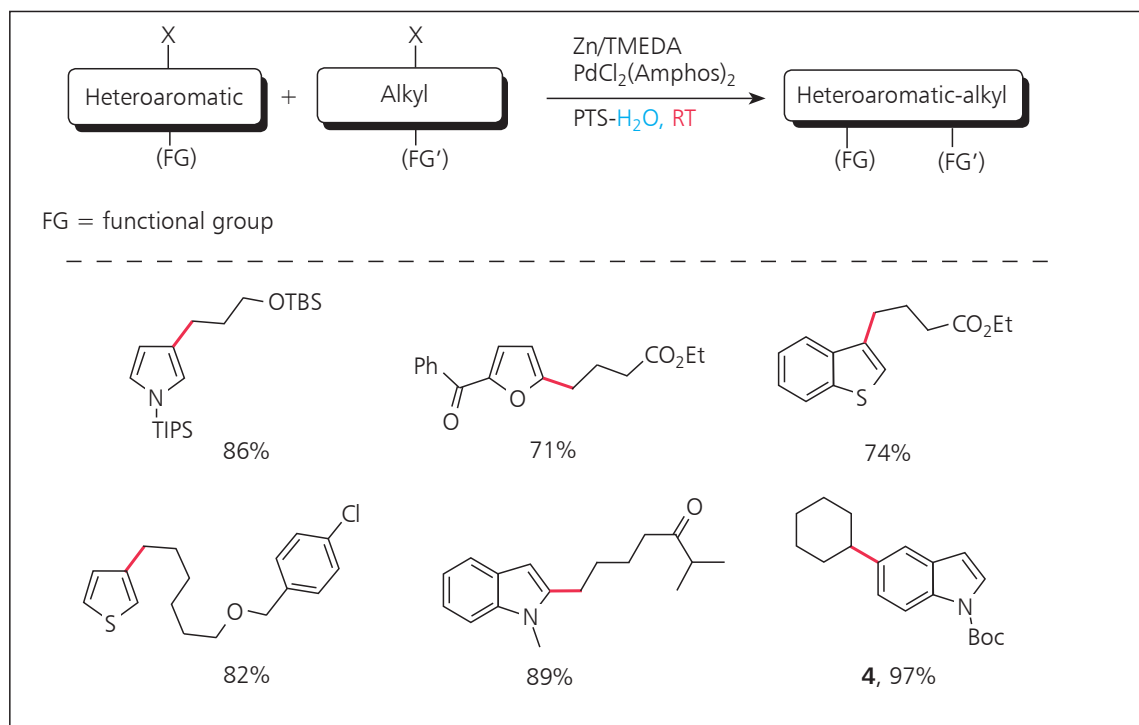
Scheme X. Cross-couplings of heteroaromatic and alkyl halides using catalyst PdCl$_2$(Amphos)$_2$ in water at room temperature

Scheme XI. Representative cross-couplings of alkenyl and alkyl halides, in water at room temperature

6. Conclusions

The Nobel Prize awarded for the Heck, Negishi and Suzuki cross-coupling reactions is further recognition of the importance of the role that catalysis, in particular by Pd, plays in society. But catalysis is also a key component of green chemistry, and this requires ligands on the metal that adjust catalyst reactivity and selectivity. Catalysts that work well in traditional organic solvents at modest concentrations (usually 0.1 to 1 M in substrate) may not be the species of choice under far higher concentrations in an alternative medium such as nanomicelles in water. A completely new set of factors that control catalyst motion in and out of micelles and result in greater time spent within nanoreactors (greater binding constants) may require alternative or even newly devised ligands for Pd-catalysed cross-couplings. Thus, as an outgrowth of the hydrophobic effect, some rules for catalysis may change, giving rise to both new discoveries and opportunities for new catalysts.

Acknowledgements

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