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# Homogeneous catalysis for the production of fine chemicals. Palladium- and nickel-catalysed aromatic carbon–carbon bond formation

Charles E. Tucker<sup>a</sup> and Johannes G. de Vries<sup>b,\*</sup>

<sup>a</sup>DSM Catalytica Pharmaceuticals, 430 Ferguson Dr., Mountainview, CA 94043, USA

<sup>b</sup>DSM Fine Chemicals, Advanced Synthesis and Catalysis, PO box 18, 6160 MD Geleen, The Netherlands

E-mail: Hans-JG.Vries-de@dsm.com

In this article we describe our recent efforts in the area of palladium- and nickel-catalysed aromatic substitution reactions. Main focus is on low cost and low waste production methods. The use of aromatic carboxylic anhydrides in the Heck reaction leads to a waste-free protocol. In addition these reactions are easy to work up as no ligands or bases are used. For Heck reactions where substrates or products do not tolerate high temperatures we found that use of a bulky phosphoramidite (**13b**) as ligand for palladium leads to a very fast reaction at low temperatures. Recycle of palladium in ligand-free Heck and Suzuki reactions is easily accomplished by treating the palladium black that precipitates at the end of the reaction on a carrier material with a small excess of I<sub>2</sub> prior to its re-use in the next run. Use of aryl chlorides in the palladium- and nickel-catalysed formation of biaryls can be accomplished by using the nickel-catalysed coupling with arylzinc chlorides. Better still, it was possible to make use of the arylgrignard and use a catalytic amount of ZnCl<sub>2</sub>. Whereas the strength of these aromatic substitution reactions lies in their broad tolerance of functional groups, one exception was the Sonogashira reaction on 3-bromoaniline. The problem was solved by making use of *in situ* catalytic protection of the NH<sub>2</sub> group with benzaldehyde.

**KEY WORDS:** palladium catalyst; nickel catalyst; aromatic carbon bond formation

## 1. Introduction

Palladium-catalysed aromatic substitution goes back to discoveries largely made in the seventies and eighties of the previous century [1]. A great many publications in synthetic journals testify to the large popularity of this type of chemistry in organic synthesis on laboratory scale. Yet, it was only recently that the first Heck [2] and Suzuki [3] reactions were used on ton scale for the production of fine chemicals. Up to now Friedel–Crafts chemistry and other classical organic chemistry sufficed for the production of most aromatic compounds. This is slowly changing for a number of reasons. One of these is the desire to use synthetic routes with a high degree of atom economy that form the basis for environmentally friendly production processes [4]. Another reason stems from the area of pharmaceuticals. A better understanding of the biological processes underlying disease has led to a whole generation of new drugs targeted at key enzymes or receptors. As they often mimic the natural substrate, these drugs generally are of relatively high complexity. Economical production schemes often are based on the notion of convergent synthesis where several fragments are prepared in parallel paths and finally combined at the end of the synthesis, rather than a linear synthesis along a single path [5]. Methodology for the final coupling steps should be based on a technology that is highly compatible with a wide range of functional groups. This is exactly the reason why palladium-catalysed carbon–carbon bond formation has gained so much popularity for the production of pharmaceu-

tical intermediates over the past 5 years. Most of these coupling reactions can be performed without protection of functional groups.

Looking at this type of chemistry from an industrial perspective the cost aspect becomes very important too. The price of palladium, which has been high since the introduction of the automotive catalytic converter, has recently skyrocketed. This has led to approaches aimed at reducing the amount of palladium through the invention of more active catalysts or by recycling them. Replacement of palladium by the less expensive nickel constitutes another solution to this problem.

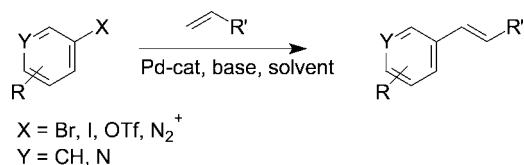
Availability of starting materials often is the main factor determining the synthetic pathway in fine chemical production. The ability to perform aromatic substitution reactions on readily available aryl chlorides is thus highly desirable. In this article we give an overview of some of our recent research efforts aimed at exactly these themes.

## 2. The Heck reaction

The Heck reaction has received increasing attention in the past five years, both from the academic community as well as from producers of fine chemicals (scheme 1) [6].

Recent applications in fine chemical production include Novartis' Prosulfuron<sup>TM</sup> (**1**), an agrochemical, the sun-screen agent octyl *p*-methoxy-cinnamate (**2**) (pilot production only), monomers for coatings (**3**) from Dow, Albenmarle's Naproxen (**4**) and the anti-asthma agent Singulair (**5**) from Merck (figure 1) [2]. A large effort was aimed

\* To whom correspondence should be addressed.



Scheme 1. The Heck reaction.

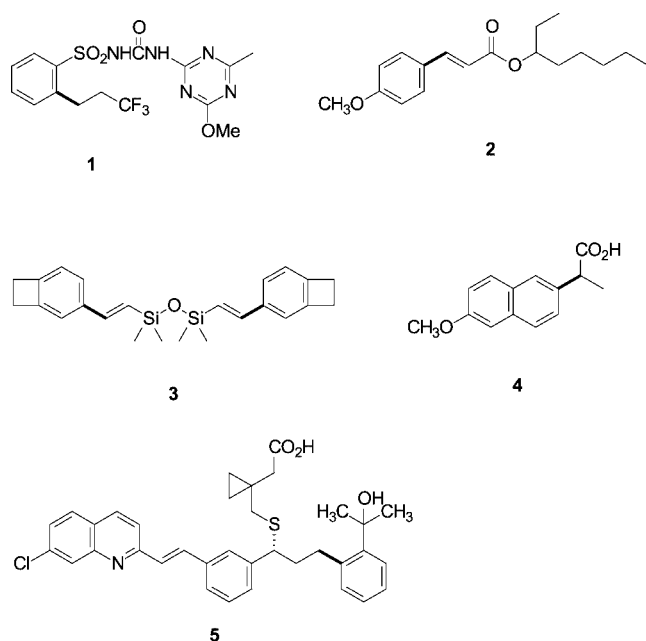
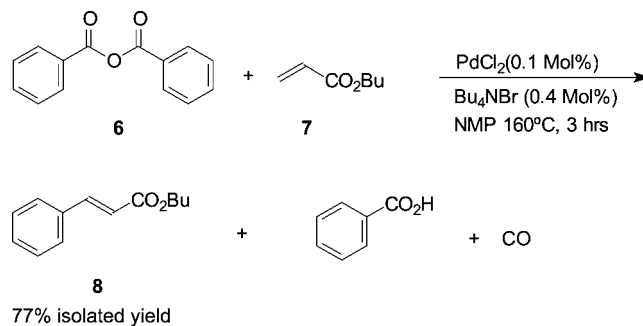


Figure 1. Fine chemicals produced with the Heck reaction (bold bond is the newly created bond).

at finding catalysts that are more stable than the classical palladium(0) phosphine complexes. Typical examples are palladacycles, which remain active at higher temperatures leading to higher reaction rates and thus allow lower catalyst loadings [6,7]. Recent findings indicate that these might just act as a reservoir of ligand free Pd(0) [8]. Another goal that has been achieved recently was to find highly active catalysts which can be used for the Heck reaction on aryl chlorides [7a,i,9]. Efforts to immobilise palladium catalysts are often hampered by leaching [10]. In fact, it might well be the leached palladium that is the active catalyst in some cases [11].

### 2.1. The DSM Heck reaction; a waste-free solution

In spite of the fact that the Heck reaction is much cleaner than the commonly used Friedel-Crafts chemistry, it still produces an equivalent of halide waste. We felt that it should be possible to eliminate the salt waste by introducing a halide-free arylating agent. Our initial search centred on oxygen based leaving groups. Esters of phenol, such as phenol carbonate, phenol phosphate and phenol sulphate were not active in the Heck reaction with *n*-butyl acrylate (7) using a variety of different palladium catalysts. However, very good results were obtained with aromatic anhydrides. Thus, benzoic anhydride (6) was reacted with 6 using 0.1 mol% of



Scheme 2. The DSM Heck reaction.

PdCl<sub>2</sub> activated with 0.4 mol% of bromide or chloride salts (Na, Li or tetra-alkylammonium salts) at 160 °C in NMP as solvent (scheme 2) [12]. Under these conditions the Heck reaction proceeds at relatively high speed and in good selectivity to give *n*-butyl cinnamate (8) in 77% isolated yield.

Other aromatic anhydrides also react, but with aliphatic carboxylic anhydrides no Heck reaction occurred. The reaction works particularly well with olefins substituted by an electron-withdrawing group. Simple aliphatic olefins, both linear and cyclic, also react cleanly, though extensive double bond isomerisation occurs leading to random arylation. Olefins substituted with oxygen or nitrogen functionalities gave mixtures of  $\alpha$ - and  $\beta$ -arylated Heck products in poor to moderate yields (table 1).

For industrial application the higher reaction temperature might be limiting the scope of the reaction to thermally stable starting materials and products. With respect to the availability of the starting anhydrides: they can easily be prepared from the carboxylic acids by reaction with Ac<sub>2</sub>O [13]. Careful removal of the formed acetic acid is essential as it may retard the reaction considerably. The real strength of the method lies in the greatly simplified work-up. As neither base nor ligands are needed, product isolation is greatly simplified. After distilling off the solvent NMP, the residue can be further distilled to give the product directly. In case the product boiling point is close to that of the aromatic carboxylic acid the residue can be extracted first with aqueous NaHCO<sub>3</sub> or even with hot water to remove the acid, after which the product can be distilled or crystallised.

We have performed extensive mechanistic research, which will be published elsewhere, which gives evidence for a catalytic cycle involving anionic monomeric Pd(0)/Pd(II) but where most of the palladium remains stored in the form of nanoclusters [14]. As far as we know, this is the only Heck reaction where use of a base is not required. Possible explanations are the high reaction temperature and the ability of benzoic acid to act as a base.

### 2.2. Very fast Heck reaction of aryl iodides using a bulky phosphoramidite as ligand

As aryl iodides are highly reactive in palladium catalysed Heck reactions they are the preferred aryl source for reactions with more sensitive substrates that require low temperatures. Main issues for production are reactivity and stabil-

Table 1  
Palladium-catalysed arylation of olefins with (ArCO)<sub>2</sub>O.<sup>a</sup>

Entry	Ar	Olefin	Time (min)	Yield of arylated olefin (%)
1	Ph	CH <sub>2</sub> =CHCO <sub>2</sub> Bu	90	77
2	Ph	C <sub>8</sub> H <sub>17</sub> CH=CH <sub>2</sub>	90	60
3	Ph	PhCH=CH <sub>2</sub>	120	76 ( $\alpha : \beta = 13 : 87$ )
4	Ph	Cyclooctene	120	54
5	Ph	CH <sub>2</sub> =CHOC <sub>6</sub> H <sub>11</sub>	120	25 <sup>b</sup> $\alpha$
6 <sup>c</sup>	Ph	CH <sub>2</sub> =CHCN	180	60 ( $E : Z = 75 : 20$ )
7	Ph	CH <sub>2</sub> =C(Me)CO <sub>2</sub> Bu	90	62
8 <sup>d</sup>	Ph	Z-BuO <sub>2</sub> CCH=CHCO <sub>2</sub> Bu	90	72 ( $E : Z = 7 : 2$ )
9	Ph	N-vinyl-pyrrolidone	90	25 ( $\alpha : \beta - E = 20 : 5$ )
10 <sup>d</sup>	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> =CHCO <sub>2</sub> Bu	60	75
11	2-furanyl	CH <sub>2</sub> =CHCO <sub>2</sub> Bu	90	77

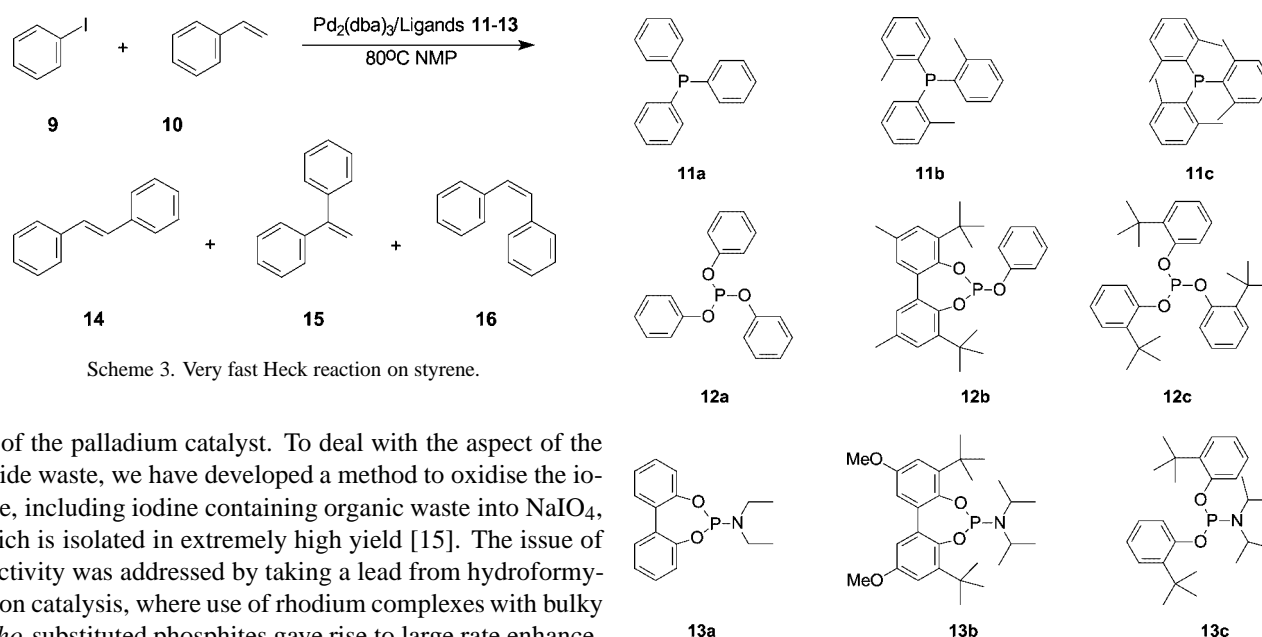
<sup>a</sup> Conditions: aromatic anhydride : olefin : PdCl<sub>2</sub> : NaBr = 100 : 120 : 0.25 : 1 mmol in 100 ml NMP,

*T* = 160 °C unless indicated otherwise.

<sup>b</sup> GC yield.

<sup>c</sup> *T* = 140 °C.

<sup>d</sup> *T* = 190 °C.



Scheme 3. Very fast Heck reaction on styrene.

Figure 2. Bulky ligands for very fast Heck reactions at moderate temperatures.

ity of the palladium catalyst. To deal with the aspect of the iodide waste, we have developed a method to oxidise the iodide, including iodine containing organic waste into NaIO<sub>4</sub>, which is isolated in extremely high yield [15]. The issue of reactivity was addressed by taking a lead from hydroformylation catalysis, where use of rhodium complexes with bulky *ortho*-substituted phosphites gave rise to large rate enhancements [16]. Presumably, this is due to the large cone-angle, which allows only a single phosphite ligand to coordinate to the metal. We applied this concept to the Heck reaction of iodobenzene (**9**) with styrene (**10**) (scheme 3) and screened three each of phosphines (**11**), phosphites (**12**) and phosphoramidites (**13**) of increasing bulkiness (figure 2). The use of bulky phosphites to accelerate the Heck reaction has been reported by other groups [7k,9c]. In this series we found bulky phosphoramidite (**13b**) to lead to the most active catalyst in combination with Pd<sub>2</sub>(dba)<sub>3</sub> (table 2) [17]. In fact, the reaction was complete after 45 min under conditions where palladacycle (**17**) (figure 3) gave 8% conversion and Pd(OAc)<sub>2</sub> 5% conversion. Selectivity to *trans*-stilbene (**14**) is around 90% with 1,1,-diphenylethene (**15**) (9%) and *cis*-stilbene (**16**) (1%) as side products. Using lower amounts of catalyst turnover numbers up to 500 000 were measured. With this ligand no precipitate of Pd-black occurred, not even at the end of the reaction.

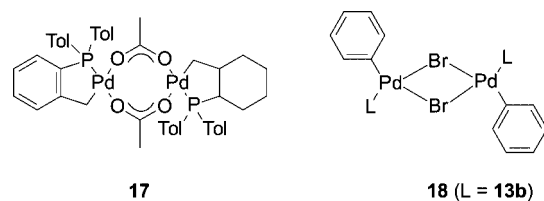


Figure 3. Palladium catalysts for Heck reaction on styrene.

Kinetic measurements of the Heck reaction are complicated by the fact that usually an induction phase occurs, due to slow formation of the active catalyst by displacement of dba with the ligand or by reduction of Pd(II) to Pd(0) in case a Pd(II) salt is used as precursor. For this reason we made a pre-formed complex (**18**) from Pd, ligand (**13b**) and

Table 2  
Heck reaction between iodobenzene and styrene.<sup>a</sup>

Run	Catalyst	Conversion after 45 min (%)	Selectivity to trans-stilbene (%)
1	Pd(OAc) <sub>2</sub>	5	90
2	Pd(dba) <sub>2</sub>	7	90
3	Pd(dba) <sub>2</sub> /11a	6	90
4	Pd(dba) <sub>2</sub> /11b	12	90
5	Pd(dba) <sub>2</sub> /11c	1	89
6	Pd(dba) <sub>2</sub> /12a	8	90
7	Pd(dba) <sub>2</sub> /12b	48	90
8	Pd(dba) <sub>2</sub> /12c	6	85
9	Pd(dba) <sub>2</sub> /13a	18	90
10	Pd(dba) <sub>2</sub> /13b	100	90
11	Pd(dba) <sub>2</sub> /13c	6	88
12	17	8	90

<sup>a</sup> Conditions: Pd : L : ArI : styrene : Et<sub>3</sub>N = 0.05 : 0.1 : 4.9 : 5.5 : 5.4 mmol in 5 ml CH<sub>3</sub>CN at 80 °C.

bromobenzene. Very satisfactory kinetic data were obtained showing the reaction to be first order in styrene and half-order in palladium. Presumably, the rate determining step is reaction of the olefin with monomeric [ArPd(13b)Br], which is in equilibrium with dimeric 18.

Further experiments with catalyst 18 showed that it is active in a range of solvents; even in toluene excellent rates were obtained. NMP gave the highest rates: at a styrene concentration of 1 M a TOF of 8000 was obtained at 100% conversion.

### 2.3. A very effective palladium recycle for ligand-free palladium

It is a well-known phenomenon that at the end of Heck reactions with ligand-free palladium the catalyst precipitates in the form of palladium black. We measured the palladium content of the remaining solution of the Heck reaction between iodobenzene and *n*-butyl acrylate catalysed by Pd(OAc)<sub>2</sub> after filtering the deposited palladium over celite. Fortunately, more than 99% of the palladium is precipitated and no more than 5.5 ppb of palladium was found in the filtrate. When the recovered palladium is reused for a second run the activity is greatly diminished. As this might well be due to the reduced surface area of the catalyst we studied the effect of deposition on carrier materials, but even these recovered catalysts were on average ten times less active as the original Pd(OAc)<sub>2</sub>. Analysis with TEM revealed that the deposited palladium on the carrier materials is in the form of fairly large crystals. This means that most of the palladium is locked up inside the crystals and cannot actively participate in the catalysis. The only manner in which the palladium can be restored to its original activity would be to oxidise it back to a monomeric species. A range of common oxidising agents failed to perform the oxidation, only HNO<sub>3</sub> being effective. However, Pd(NO<sub>3</sub>)<sub>2</sub> is not active in the Heck reaction. Surprisingly, we found that oxidation with mild oxidants such as Br<sub>2</sub> or I<sub>2</sub> rapidly dissolved the precipitated palladium. This gave rise to a protocol where we add just 2 equivalents of I<sub>2</sub> to the recovered Pd on Celite in NMP just

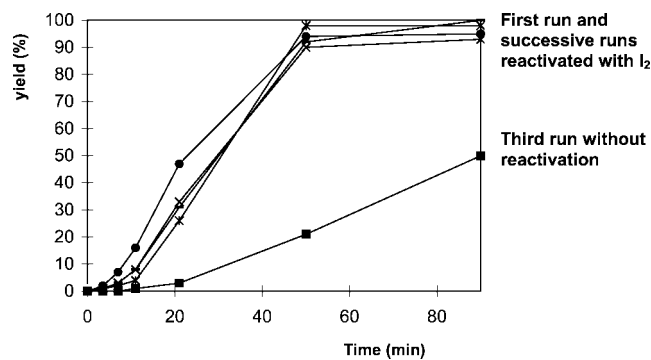


Figure 4. Reactivation of precipitated palladium with I<sub>2</sub> and re-use in the Heck reaction of iodobenzene with butyl acrylate.

prior to the next run, leading to fully restored activity in the Heck reaction [18]. In this manner we have performed four consecutive runs without loss of activity (figure 4).

### 3. Biaryl couplings

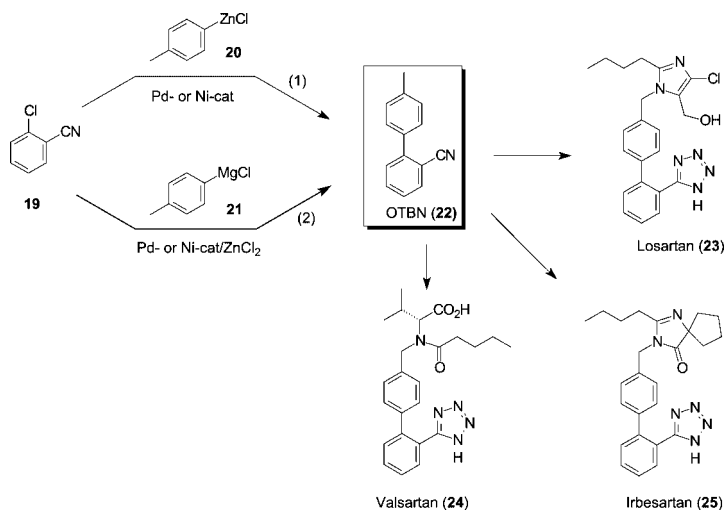
Biaryl compounds play an important role in industrial chemistry, appearing in commercially attractive targets ranging from liquid crystals [19] to pharmaceuticals. Much research has been published on synthetic routes towards *ortho*-tolyl-benzonitrile, a common intermediate for a number of *Sartan* type blood-pressure lowering agents [3,20] (scheme 4).

During the last three decades, there have been a number of significant advances in biaryl coupling technology that have really broadened the scope over previous methods (*i.e.*, Ullmann coupling) In multi-step synthetic schemes [21]. These technological advances are represented by the following reactions:

- (1) Kumada coupling [22] (ArX/ArMgBr, Ni or Pd cat.);
- (2) Stille coupling [23] (Ar-X/Ar-SnR<sub>3</sub>, Pd cat.);
- (3) Negishi coupling [24] (Ar-X/Ar-ZnX, Ni or Pd cat.);
- (4) Suzuki coupling [3,25] (Ar-X/Ar-B(OR)<sub>2</sub>, Pd cat.).

These types of biaryl coupling have numerous examples in the literature and are widely used because of their generally good yields and their high tolerance of other functional groups. Recently, the driving force in research of new biaryl couplings has been the inclusion of aryl chlorides as substrates, as the aryl chlorides are much more likely to be commercially available, and at a much lower cost than the corresponding aryl iodides or bromides.

Our recent research has been directed at the adaptation of the Negishi coupling to the synthesis of biaryls from aryl chlorides. The original efforts were directed at the coupling of alkylzinc reagents with aryl chlorides, catalysed by palladium salts (specifically, PdCl<sub>2</sub>(dppf)), and it was shown that these reactions proceeded as expected, but were rather sluggish (72 h at reflux). Further investigation showed that the corresponding Ni-based catalysts (Ni(acac)<sub>2</sub>/dppf) also facilitated this coupling. Interestingly, while Pd(0)/PPh<sub>3</sub> catalysts were not suitable catalysts, the corresponding Ni-based



Scheme 4. Use of the Negishi (1) and “double metal catalysis” (2) cross-coupling for production of the Sartan intermediate OTBN.

Table 3  
The cross-coupling of arylzinc reagents with aryl chlorides.

Entry	Aryl chloride	ArZnX	Catalyst	(mol%)	Reaction conditions	Product	Yield (%)
1		PhZnCl	Ni(acac) <sub>2</sub> dppf	2.0 2.2	25 °C, 18 h		86
2		<i>p</i> -TolZnCl	Ni(acac) <sub>2</sub> ( <i>i</i> -PrO) <sub>3</sub>	7.5 15.0	40 °C, 6 h		89
3		<i>p</i> -TolZnCl	PdCl <sub>2</sub> (dppf)	5.0	Reflux, 72 h		82
4		<i>p</i> -TolZnCl	Ni(acac) <sub>2</sub> PPh <sub>3</sub>	5.0 20.0	50 °C, 1.5 h		81
5		<i>p</i> -TolZnCl	Ni(acac) <sub>2</sub> PPh <sub>3</sub>	5.0 20.0	25 °C, 1 h		85
6		PhZnCl	Ni(acac) <sub>2</sub> PPh <sub>3</sub>	5.0 20.0	25 °C, 1 h		81
7		<i>p</i> -TolZnCl	Ni(acac) <sub>2</sub> PPh <sub>3</sub>	5.0 20.0	25 °C, 1 h		63
8		PhZnCl	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	6.0	25 °C, 3 h		72
9		PhZnCl	NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> PPh <sub>3</sub>	2.0 4.0	50 °C, 24 h		75
10			NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> PPh <sub>3</sub>	7.5 15.0	55 °C, 5 h		75


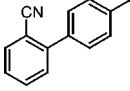

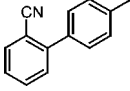

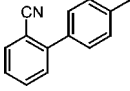

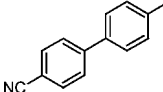
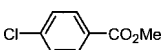
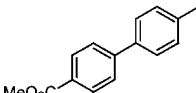
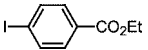
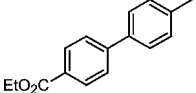
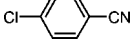
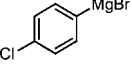
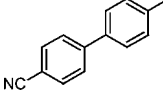
catalyst (NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>) was a superb catalyst. With this catalyst system, coupling proceeded under very mild conditions, requiring only a few hours at 25 °C (table 3).

While these results are interesting, a significant increase in the usefulness of this method was made when it was discovered that the reaction proceeded in the presence of only

a catalytic amount of a zinc salt. Further, the coupling reaction was fast enough that, under controlled addition of the Grignard reagent, a wide variety of functional groups could be tolerated in the substrate (table 4).

Thus, the cross-coupling of *p*-TolMgCl with *o*-chlorobenzonitrile, with catalytic amounts of nickel and zinc

Table 4  
Nickel-catalyzed cross-coupling of grignard reagents with aryl chlorides with catalytic zinc salts.

Entry	Aryl chloride	ArMgX	Catalyst components	(mol%)	Reaction conditions	Product	Yield (%)
1		<i>p</i> -TolMgCl	Ni(acac) <sub>2</sub> P(O <i>i</i> -Pr) <sub>3</sub> Water ZnCl <sub>2</sub> MeMgCl	6.0 13.0 6.0 6.0 11.0	55 °C 1.25 h		82
2		<i>p</i> -TolMgCl	Ni(acac) <sub>2</sub> P(O <i>i</i> -Pr) <sub>3</sub> Water MeMgCl	6.0 13.0 6.0 11.0	55 °C 1.25 h		44
3		<i>p</i> -TolMgCl	Ni(acac) <sub>2</sub> P(O <i>i</i> -Pr) <sub>3</sub> Zn <sup>0</sup> MeMgCl	6.0 13.0 6.0 11.0	55 °C 1.25 h		72
4		<i>p</i> -TolMgCl	Ni(acac) <sub>2</sub> P(O <i>i</i> -Pr) <sub>3</sub> Water ZnCl <sub>2</sub> MeMgCl	6.0 13.0 6.0 6.0 11.0	55 °C 1.25 h		75
5		<i>p</i> -TolMgCl	Ni(acac) <sub>2</sub> PPh <sub>3</sub> Water ZnCl <sub>2</sub> Vitride	5.0 20.0 5.0 5.0 10.0	55 °C 1.25 h		59
6		<i>p</i> -TolMgCl	Ni(acac) <sub>2</sub> PPh <sub>3</sub> Water ZnCl <sub>2</sub> Vitride	5.0 20.0 5.0 5.0 10.0	55 °C 1.25 h		46
7			Ni(acac) <sub>2</sub> P(O <i>i</i> -Pr) <sub>3</sub> Water ZnCl <sub>2</sub> MeMgCl	4.0 8.0 4.0 4.0 8.0	55 °C 1.25 h		75

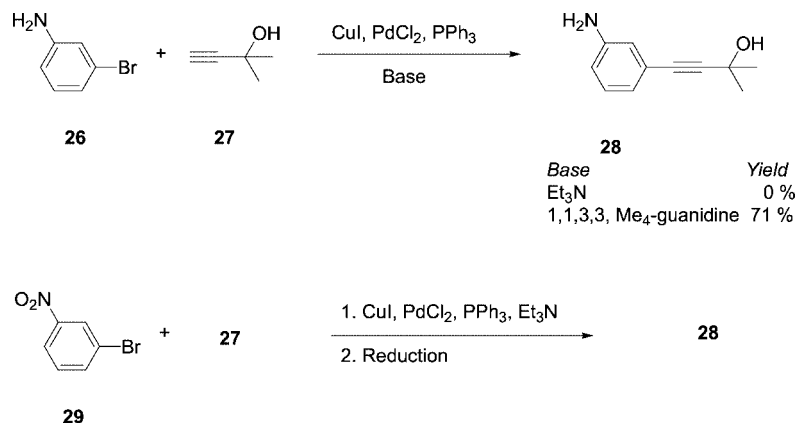
gave very clean conversion and yielded the expected biaryl product in ~82% yield. However, several aspects of the catalyst system should be noted. First, the optimum catalyst system was composed of Ni(acac)<sub>2</sub> with triisopropylphosphite as the ligand (1:2), along with ZnCl<sub>2</sub>. However, the coupling proceeded much more smoothly when both water and a reducing agent (either MeMgCl or Vitride [Li(MeOCH<sub>2</sub>CH<sub>2</sub>O)<sub>2</sub>AlH<sub>2</sub>]) were present. The addition of water is thought to form a Zn-μ-oxo-Ni bridged complex, which appears to be a better catalyst for this system. When water was strenuously removed from the system, little cross-coupling was observed. Further, the exclusion of zinc from the catalyst system greatly reduces the observed yield (82 vs. 44%, entries 1 and 2).

This type of coupling has advantages over other types of coupling in that it avoids protection and deprotection steps, stoichiometric amounts of zinc, tin, or boron salt wastes, and avoids the isolation of an intermediate boron or tin organometallic reagent.

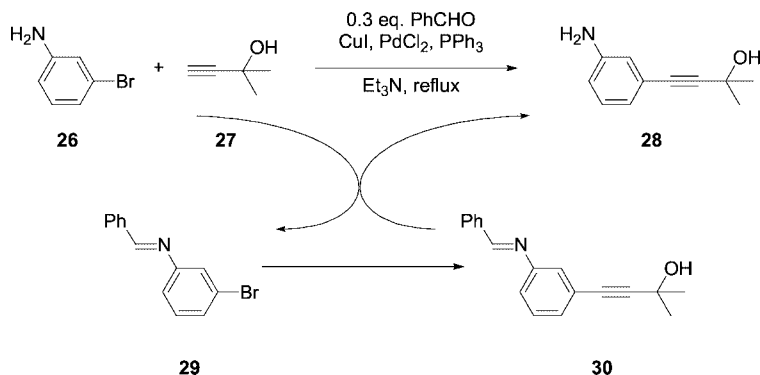
#### 4. Sonogoshira coupling

Another of the powerful C-C bond forming reactions currently in use is the Sonogoshira coupling [26], and related coupling reactions [27]. While numerous examples of this type of aryl-acetylene coupling have been reported [28], one recent case is shown below. The direct Sonogoshira coupling of the 2-methyl-3-butyn-2-ol with 3-bromoaniline under the standard reaction conditions does not proceed satisfactorily, presumably because of the increased electron density on the aniline reducing the rate of the oxidative insertion of the Pd into the C-Br bond (scheme 5).

However, several groups have published routes that allow the target compound to be prepared. The earliest preparations were based on the Sonogoshira coupling of the acetylene with 3-bromonitrobenzene, followed by selective reduction of the nitro group over the acetylene [29]. The two more direct approaches involve modifying the aniline



Scheme 5. Sonogashira coupling of 2-methyl-3-butyn-2-ol on 3-bromoaniline and 3-bromonitrobenzene.

Scheme 6. Sonogashira reaction of 2-methyl-3-butyn-2-ol on 3-bromoaniline using *in situ* protection with benzaldehyde.

*in situ* in such a way as to allow the direct coupling to proceed [30,31]. The first coupling of the acetylene with 3-bromoaniline is facilitated through the addition of an excess of a strong, albeit somewhat expensive base (*e.g.*, 1,1,3,3-tetramethylguanidine or DBU) in place of the customary triethylamine (scheme 5) [30]. While the guanidine is a strong enough base to deprotonate the aniline, this would only decrease the rate of oxidative addition, making the reaction proceed more slowly. An alternative explanation could be that the guanidine is acting as a ligand for the Pd, thereby facilitating the insertion.

The second *in situ* approach is outlined in scheme 6. In this approach, catalytic amounts of the aniline are converted to the imine (allowing oxidative addition by the Pd), which readily undergoes the coupling with the acetylene. Under the reaction conditions, the imine is transferred back to the 3-bromoaniline, and thus a catalytic cycle is established, and all of the starting material is consumed. At the end of the reaction, *n*-butylamine is added and the desired product precipitates out of the reaction mixture, thus avoiding the traditional neutralisation/distillation of the triethylamine and aqueous workup.

## 5. Conclusion

Homogeneous catalysis will only be able to compete successfully with classical organic chemistry for the production

of fine chemicals when it shows clear advantages. In this article we have shown examples of these such as:

- (1) Lowering production costs by:
  - reducing the amount of catalyst;
  - eliminating use of ligands or use of cheaper phosphite or phosphoramidite ligands;
  - replacing palladium by nickel;
  - replacing aryl bromides or iodides with the cheaper chlorides;
  - simplified work-up.
- (2) Waste free production methods by using aromatic anhydrides as aryl donor in the Heck reaction.
- (3) The ability to effect an aromatic substitution without or with facile protection of functional groups.

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