

## New C-O Electrophiles in Cross-Coupling Reactions

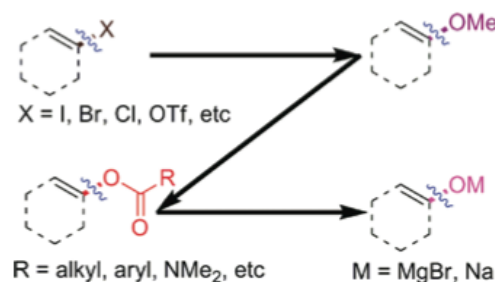
### Introduction

Cross-couplings are ubiquitous in modern synthetic chemistry, becoming one of the most widely used methods to construct C-C and C-heteroatom bonds.<sup>1</sup> In both academic and industrial laboratories, organohalides are typically used as the electrophilic partner. However, the preparation of such halogenated species - especially on a large scale for industrial applications - can often be costly, sluggish and toxic towards the environment.

Whilst organohalides will remain the mainstay of this chemistry for many years to come, this does raise the question: can other functional groups operate as suitable electrophilic components for cross-coupling reactions?

### Triflates

Readily available from alcohol and carbonyl containing compounds, aryl and alkenyl triflates have attracted much attention as viable alternatives to organohalides due to their high reactivity.<sup>2</sup> However, relatively low moisture stability and high cost has hampered their application, with other (less reactive) sulfonates and phosphonates becoming more applicable as more efficient catalysts and ligands have been developed.<sup>3</sup> However, the relatively complex catalyst systems required, allied to poor atom economy remain obstacles to their broader utility.

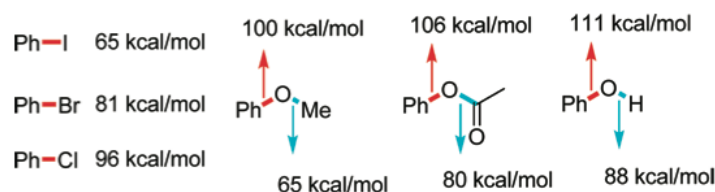


**Scheme 1:** Using C-O functional groups as electrophilic cross-coupling partners

### What about other oxygen-containing functional groups?

Abundant and readily available moieties such as ethers, esters, phenols, alcohols and carbonyl compounds are used much more rarely. The reasons for this include:

1. In general the bond dissociation energy (BDE) of C-O is quite high (see figure 1).
2. Differentiation of the two different bonds to O is difficult.
3. Selective activation of one of (typically) several O-containing groups in a complex molecule is very challenging.



**Figure 1:** BDE of C-X bonds and C-O bonds.

<sup>1</sup> de Meijere, A.; Diederich, F. *Wiley-VCH: Weinheim, Germany*, 2004.

<sup>2</sup> Stille, J. K. *et al. J. Am. Chem. Soc.* **1984**, 106, 4630.

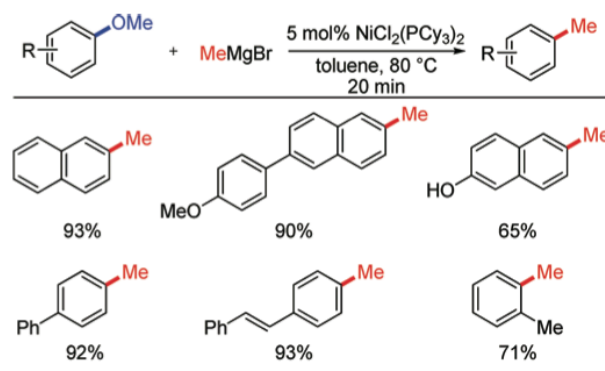
<sup>3</sup> Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2003**, 125, 8704; Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2003**, 125, 11818.

## Ethers

Apart from the relatively active allyl ethers, this functional group is rarely employed as a reagent in synthesis (just solvents).

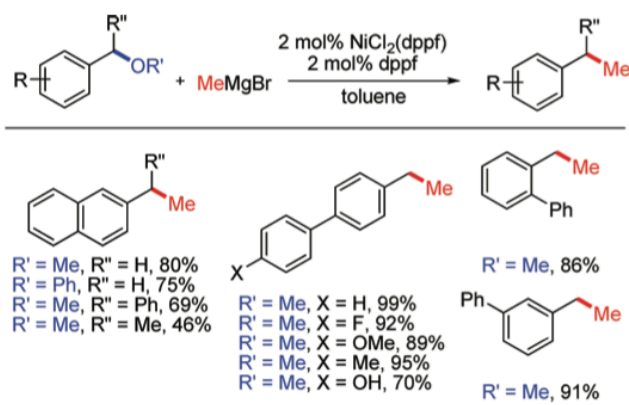
In 1979, Wenkert took aryl/alkenyl methyl ethers as electrophiles in a Ni-catalysed Kumada reaction.<sup>4</sup> This work remained relatively untouched until recently, when the group of Shi optimised and extended the scope of the reaction (see Table 1).<sup>5</sup> Unfortunately, other alkyl Grignard reagents afforded 'complex mixtures'.

**TABLE 1.** Kumada–Tamao–Corriu Reaction of Aryl Methyl Ethers with MeMgBr



By changing the nature of the phosphine ligand (from 2 x PCy<sub>3</sub> to dppf), Shi was able to successfully activate benzyl methyl ethers towards Kumada couplings at room temperature (the first example with a dialkyl ether, see Table 2).<sup>6</sup>

**TABLE 2.** Kumada–Tamao–Corriu Reaction of Benzyl Alkyl Ethers with MeMgBr



Ethyl Grignard reagents also worked well under these conditions, but Ph and i-Pr gave low yields. Substrates bearing β-hydrogens were found to be prone to β-H elimination, affording styrene derivatives (see above when R'' = Me).

Aryl methyl ethers have also been used in Suzuki reactions. Chatani coupled anisoles and phenyl boronic esters with CsF as base.<sup>7</sup>

<sup>4</sup> Wenkert, E. *et al. J. Am. Chem. Soc.* **1979**, *101*, 2246.

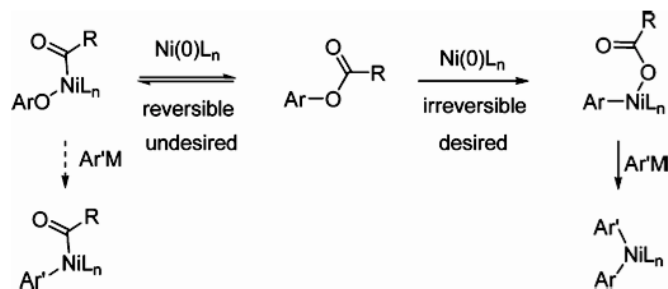
<sup>5</sup> Shi, Z. *et al. Chem. Commun.* **2008**, *12*, 1437; Shi, Z. *et al. Acc. Chem. Res.* **2010**, 1486.

<sup>6</sup> Shi, Z. *et al. J. Am. Chem. Soc.* **2008**, *130*, 3268.

<sup>7</sup> Chatani, N. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 4866.

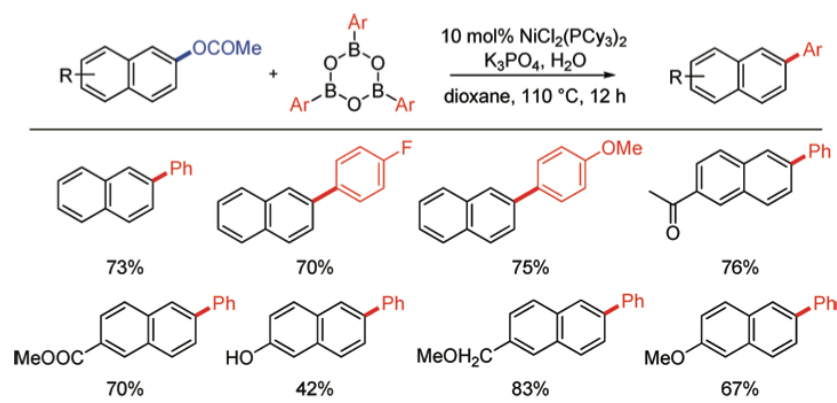
## Carboxylates

Most successfully applied in TM catalysis for Tsuji-Trost chemistry (allylic and benzylic). However, aryl/alkenyl carboxylates require selective cleavage of the C-O bond (see scheme 2).



**Scheme 2:** Designing cross-couplings with aryl carboxylates.

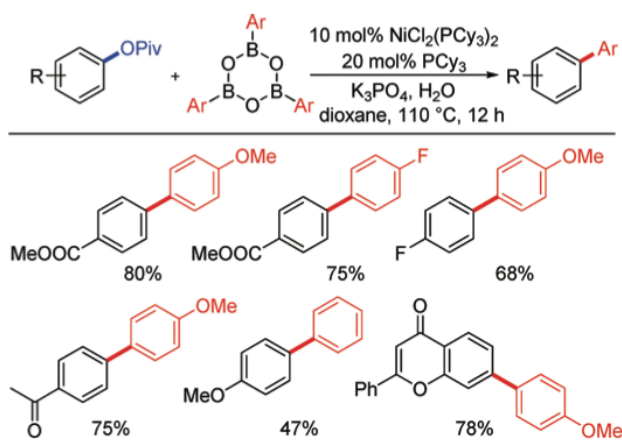
It was found that 2-naphthyl acetate underwent Suzuki coupling with phenylboroxine using NiCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> and K<sub>3</sub>PO<sub>4</sub> in dioxane at 110 °C (see Table 3).<sup>8</sup>



**Table 3:** Suzuki reaction of naphthyl acetates with arylboroxines.

Phenyl acetate was unsuccessful under the same reaction conditions, due to competitive hydrolysis of the acetate, but a change to the bulkier pivalate group addressed this issue (see Table 4).

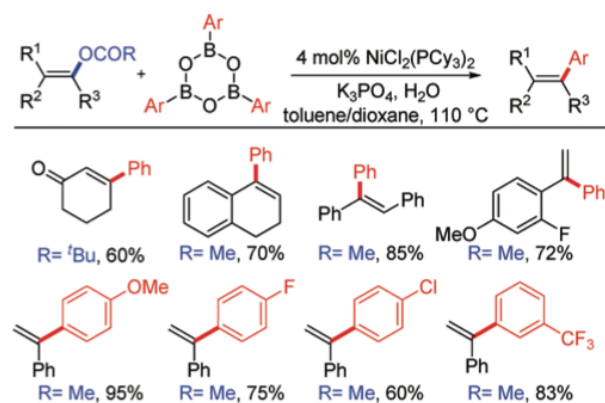
**TABLE 4.** Suzuki–Miyaura Reaction of Phenyl Pivalates with Arylboroxines



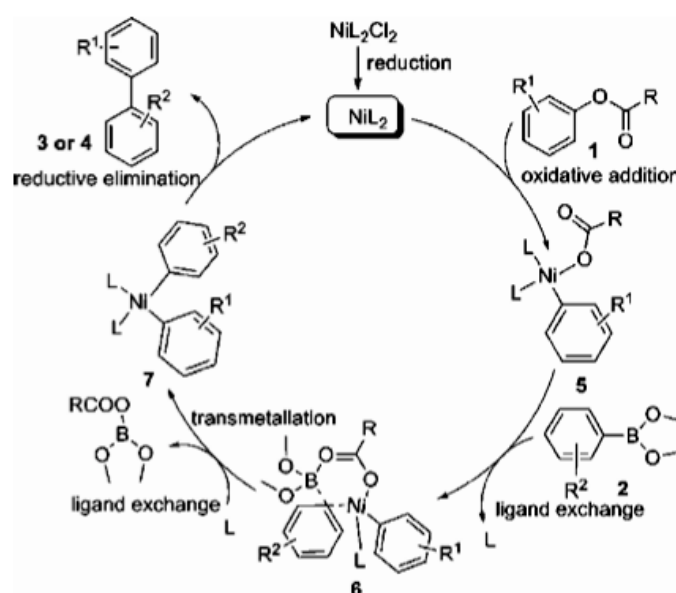
<sup>8</sup> Shi, Z. *et al. J. Am. Chem. Soc.* **2008**, *130*, 14468.

Alkenyl carboxylates were also amenable to Ni-catalysed Suzuki couplings (see Table 5). Various aryl boroxines were tolerated, as well as alkenyl acetates containing other potentially reactive functionality, such as C-F, C-Cl and C-OMe groups.

**TABLE 5.** Suzuki–Miyaura Reaction of Alkenyl Acetates with Arylboroxines

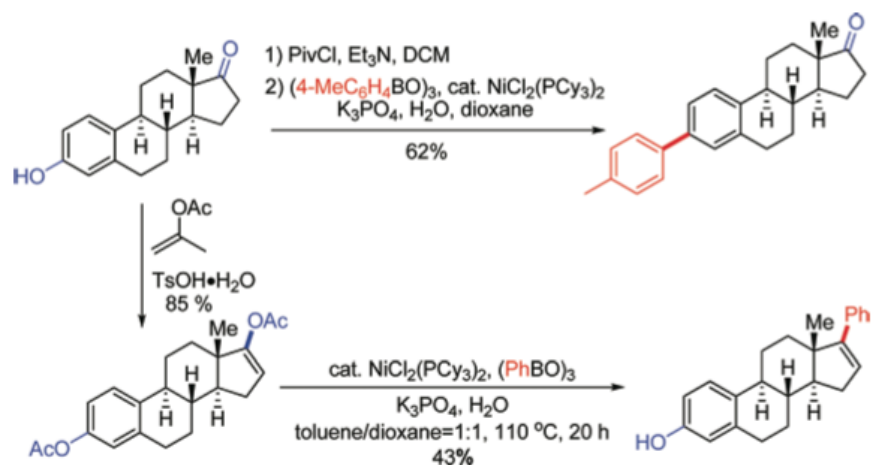


A general mechanism for these couplings is proposed in scheme 3.



**Scheme 3:** Proposed catalytic cycle for the cross-coupling of aryl/alkenyl carboxylates.

The potential orthogonality of the aryl and alkenyl carboxylate methodology has been shown by the selective arylation of C<sub>sp<sup>2</sup></sub>-O bonds of different carboxylates in estrone (see scheme 4).



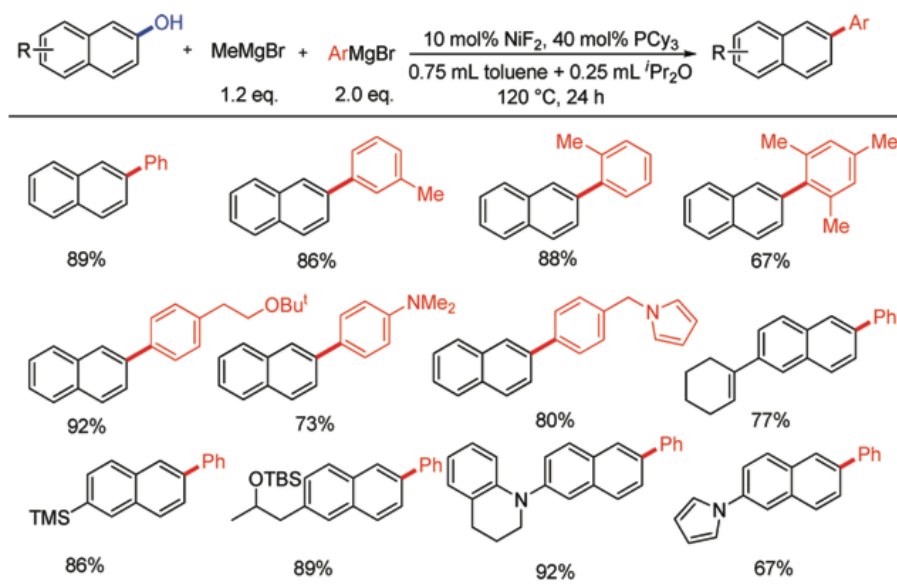
**Scheme 4:** Selective functionalisation of estrone.

Carboxylates have also been employed as coupling partners in Negishi and Kumada reactions.<sup>9</sup>

### Aryl alcohols

Eliminate any need for prefunctionalising the oxygen-containing moiety by using free aryl alcohols or alkoxyates. However, high BDE makes OH<sup>-</sup> and especially MO<sup>-</sup> poor leaving groups, whilst the phenolate anion is a good ligand for TM's thus further impeding the cleavage.

With a few hints towards possible reactivity from other work, Shi found that 2-naphthol derivatives could be coupled *via* a Kumada reaction with various aryl Grignards. The method requires formation of the 2-naphthol magnesium salt (upon addition of methyl Grignard), which then undergoes an oxidative addition with Ni(0) and subsequent transmetalation with the appropriate aryl Grignard. Reductive elimination then generates the biaryl species (see Table 6).



**Table 6:** Kumada reaction of naphtholate salts with ArMgBr

<sup>9</sup> Shi, Z. *et al. Angew. Chem. Int. Ed.* **2008**, 47, 10124; Shi, Z. *et al. J. Am. Chem. Soc.* **2009**, 131, 14656.