

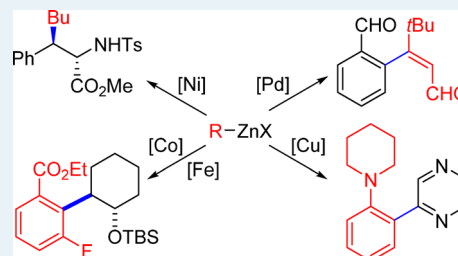
# Recent Developments in Negishi Cross-Coupling Reactions

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**ABSTRACT:** This Perspective describes general methods for the preparation of polyfunctional zinc organometallics and their use in Negishi cross-coupling reactions. Recent advances including new ligands and palladium catalysts are described. Related Negishi cross-coupling reactions involving Ni-, Cu-, Co-, and Fe-catalyzed cross-couplings are covered. The availability of a range of zinc organometallics combined with new efficient catalysts allows for efficient cross-coupling reactions with various organic electrophiles under usually mild conditions.

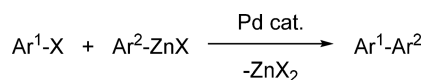
**KEYWORDS:** Negishi cross-coupling, zinc, palladium, nickel, copper, iron



## 1. INTRODUCTION

Pd-catalyzed cross-coupling reactions between unsaturated halides and organometallics have found broad applications. Cross-coupling reactions using boronic acids or esters, known as Suzuki cross-coupling reactions,<sup>1</sup> have been extensively used due to the broad availability and relative air- and moisture-stability of unsaturated boronic derivatives.<sup>2</sup> Nevertheless, the fast transmetalation of organozinc reagents to palladium compared to boronic acids often allows the investigator to achieve Negishi cross-couplings<sup>3</sup> between a broad range of unsaturated halides and zinc organometallics under very mild conditions (Scheme 1).

Scheme 1. General Scheme of the Negishi Reaction



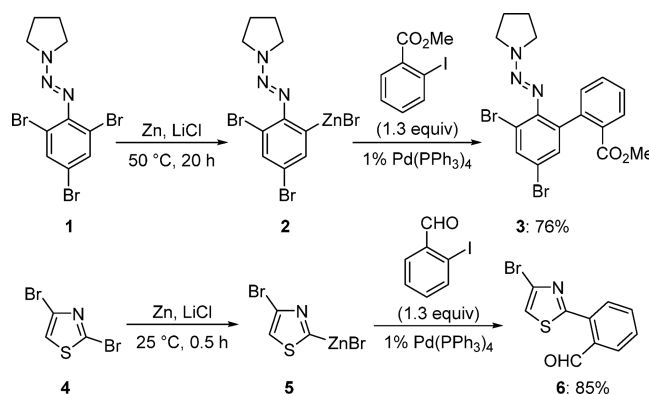
In addition, the low toxicity of zinc salts, as well as the growing number of commercially available zinc reagents has increased their employment in cross-coupling reactions. Furthermore, in several cases, it has been shown that expensive Pd-based catalytic systems can be replaced by alternative metals, such as Ni, Fe, Co, or Cu. In this perspective article, we will summarize methods for the preparation of polyfunctional zinc organometallics and describe the most significant advances in palladium-catalyzed Negishi-reactions. We will also cover Negishi cross-couplings performed with alternative transition-metal catalysts and emphasize some of the most spectacular recent applications of Negishi reactions.

## 2. PREPARATION OF ZINC ORGANOMETALLICS

**2.1. Oxidative Addition of Zinc Powder to Organic Halides.** Organozinc reagents can be prepared directly by the insertion of zinc powder to various aromatic and heterocyclic iodides or bromides.<sup>4</sup> Thus, reduction of zinc chloride in THF using lithium naphthalene provides highly activated zinc (Rieke-zinc).<sup>5</sup> Alternatively, the insertion of commercial zinc

powder in the presence of lithium chloride proceeds readily with aryl iodides and activated aryl or heteroaryl bromides.<sup>6a</sup> Thus, the bromo-triazene (1) inserts Zn in the presence of LiCl providing the zinc reagent (2) that after Negishi cross-coupling with methyl 2-iodobenzoate leads to the biphenyl (3) in 76% yield (Scheme 2).<sup>6b</sup>

Scheme 2. Regioselective Insertion of Zinc in the Presence of LiCl

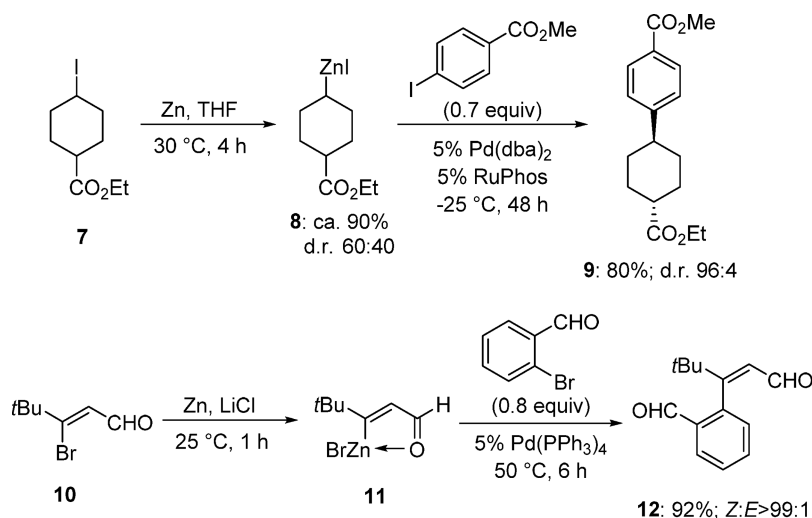


Also, 2,4-dibromothiazole (4) regioselectively inserts zinc dust in the presence of LiCl to afford the zincated thiazole (5), which undergoes a cross-coupling with 2-iodobenzaldehyde furnishing the arylated thiazole (6) in 85% yield.<sup>6b</sup> The addition of LiCl is not required, although it accelerates such Csp<sup>3</sup>-halide insertions<sup>6a</sup> as it plays a multiple role: it removes the oxide impurities on the surface of zinc and solubilizes the newly formed zinc reagent (RZnX) at the active site of the zinc surface by forming complexes of the type RZnX·LiCl. The metal activation effect of LiCl is quite general and other

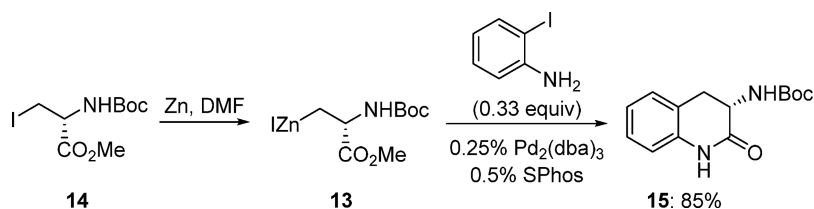
Received: November 30, 2015

Revised: January 15, 2016

Scheme 3. Stereoselective Negishi Cross-Coupling Using Various Zinc Reagents



Scheme 4. Preparation of Jackson's Zinc Reagent in DMF

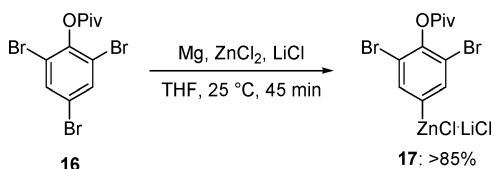


metallic powders such as Mg,<sup>7</sup> In,<sup>8</sup> Mn,<sup>9</sup> and Al<sup>10</sup> are also efficiently activated by LiCl. It should be mentioned that the presence of additional Lewis acids, such as B(OR)<sub>3</sub><sup>11</sup> or electron-transfer acceptors,<sup>12</sup> further accelerates the metal insertion. The intermediate radicals resulting from the zinc insertion do not allow a stereoselective formation of secondary alkylzinc reagents, such as in the case of the substituted cyclohexylzinc (8). However, the Negishi cross-coupling with methyl 4-iodobenzoate is stereoconvergent and produces in the presence of RuPhos (2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl)<sup>13</sup> the *trans*-cyclohexane derivative (9) in 80% yield (d.r. 96:4; Scheme 3).<sup>14</sup>

In the case of the (*Z*)-alkenyl bromide (10), the zinc insertion appears to be stereoselective as a result of the chelate-stabilization as shown in intermediate (11). Subsequent Negishi cross-coupling affords the (*Z*)-cinnamyl aldehyde (12) in 92% yield (*Z*:*E* > 99:1; Scheme 3).<sup>15</sup> Jackson<sup>16</sup> showed that this method allows the preparation of chiral amino-acid derived zinc reagents, such as (13), starting from the readily available iodide (14). Negishi cross-coupling with 2-iodoaniline<sup>17</sup> provides the chiral lactam (15) in 85% yield (Scheme 4).

The reaction scope of such oxidative insertions was increased by replacing Zn with the bimetallic reagent couples Mg, ZnCl<sub>2</sub>,<sup>7,18</sup> or Mg, Zn(OPiv)<sub>2</sub>.<sup>19</sup> Under these conditions, the insertion is fast and highly regioselective. Thus, the tribromoarene (16) reacts solely in *para*-position with the bimetallic-cocktail Mg, ZnCl<sub>2</sub>, LiCl leading to the zinc reagent (17) in high yield (Scheme 5).<sup>7a</sup>

Benzylic zinc reagents are readily prepared by Zn, LiCl insertion,<sup>18a</sup> and this method has been extended to a wide range of heterocyclic systems.<sup>20</sup> The chloromethyl-pyridine (18) is converted to the zinc reagent (19), followed by Pd-PEPPSI-IPr-catalyzed<sup>21</sup> cross-coupling with 2-bromopyridine

Scheme 5. Preparation of a Zinc Organometallic Using Mg, ZnCl<sub>2</sub>, LiCl

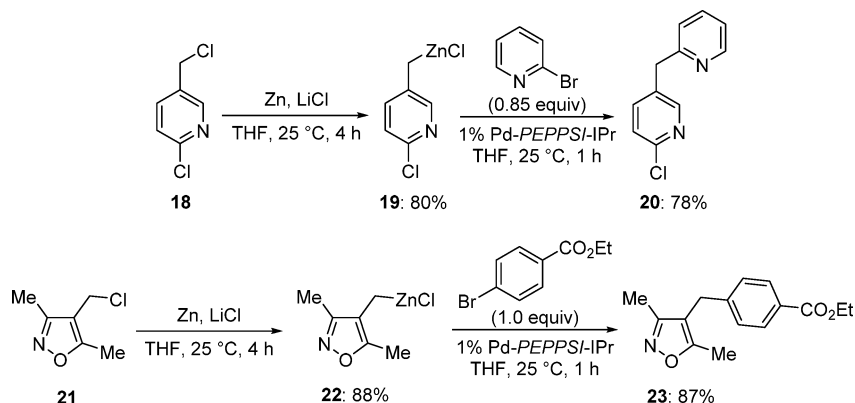
providing the bis-pyridine (20) in 78% yield.<sup>20</sup> Similarly, the chloromethyl isoxazole derivative (21) leads to the zinc reagent (22), and Negishi cross-coupling using Pd-PEPPSI-IPr furnishes the desired product (23) in 87% yield (Scheme 6).<sup>22</sup>

**2.2. Metal-Catalyzed Preparations of Organozinc Reagents.** Gosmini<sup>23</sup> further showed that cobalt halides efficiently catalyze the preparation of various polyfunctional arylzinc reagents. Also, Yoshikai has reported that CoCl<sub>2</sub> catalyzes the zinc insertion into various aryl halides and that Pd-catalyzed cross-couplings can be subsequently achieved with such zinc reagents. Thus, 3-iodobenzonitrile (24) is converted into the corresponding zinc reagent (25) in 89% yield, and subsequent Negishi cross-coupling provides the expected biphenyl (26) in high yield (Scheme 7).<sup>24</sup>

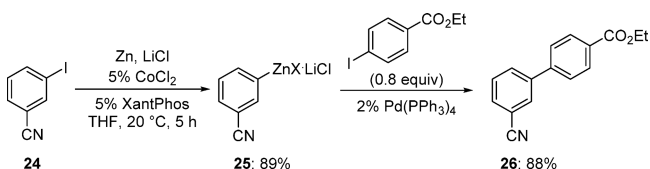
Yoshikai has also achieved impressive cascade reactions involving a 1,4-cobalt migration and subsequent palladium-catalyzed Negishi cross-couplings upon addition to an alkyne. This procedure allows the conversion of *p*-anisylzinc derivative (27) into the styrene derivative (28) in 70% overall yield via the zinc intermediate (29) (Scheme 8).<sup>25</sup>

**2.3. Transmetalations of Organo-magnesium, Aluminum, or Lithium Organometallics.** The transmetalation of lithium, magnesium, or aluminum<sup>10c</sup> organometallics is a well-established method for preparing various organozinc reagents.

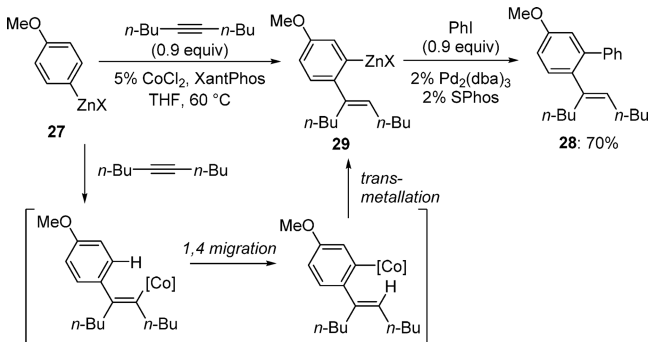
Scheme 6. Preparation and Cross-Coupling of Heterocyclic Benzylic Zinc Reagents



Scheme 7. Cobalt-Catalyzed Zinc Insertion to an Aryl Iodide



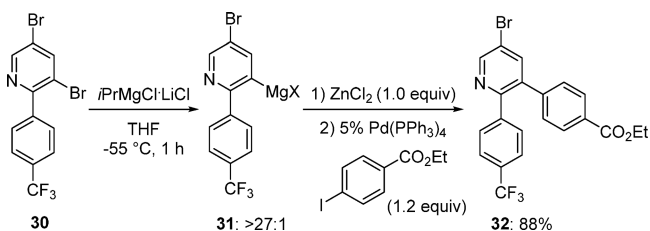
Scheme 8. 1,4-Cobalt Migration and Subsequent Negishi Cross-Coupling



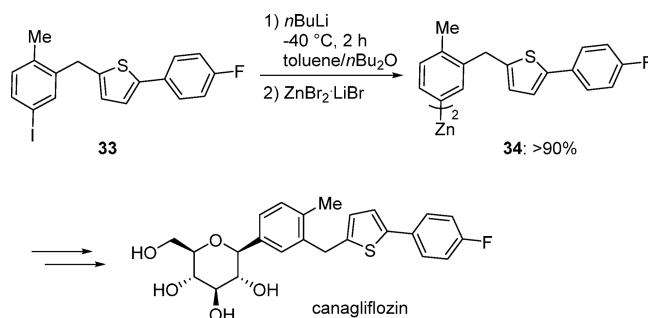
A site-selective Br/Mg-exchange<sup>26</sup> of the 3,5-dibromopyridine (30) using *i*PrMgCl·LiCl leads to the corresponding Grignard reagent (31). Transmetalation with ZnCl<sub>2</sub>, followed by Negishi cross-coupling gives the bis-arylated pyridine (32) in 88% yield (Scheme 9).<sup>27</sup>

A low-temperature I/Li-exchange of the aryl iodide (33) with *n*BuLi provides after transmetalation with the THF soluble salt ZnBr<sub>2</sub>·LiBr, the bis-zinc reagent (34) that is used in a diastereoselective Negishi cross-coupling for the preparation of canagliflozin (Scheme 10).<sup>28</sup>

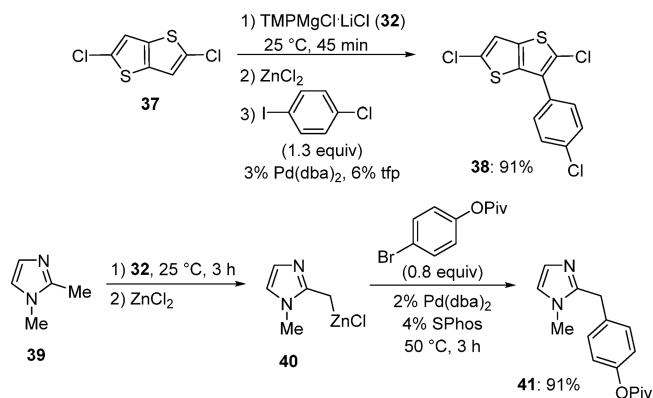
Scheme 9. Regioselective Br/Mg-Exchange on a 3,5-Dibromopyridine



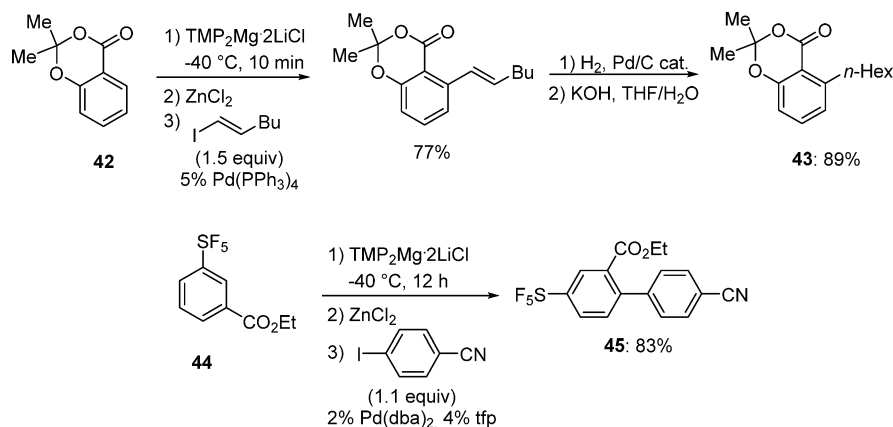
Scheme 10. Preparation of a Bis-Zinc Reagent for the Synthesis of Canagliflozin



**2.4. Preparation of Zinc Reagents by Directed Metalation.** The directed metalation<sup>29</sup> of unsaturated, aromatic, and heterocyclic molecules using various TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl) of magnesium or zinc provides for the general preparation of the corresponding organometallic reagents.<sup>30</sup> The use of TMPMgCl·LiCl (35)<sup>31</sup> and the related zinc base TMPZnCl·LiCl (36)<sup>32</sup> proved to be the most useful. Thus, 2,5-dichlorothiopheno[3,2-*b*]thiophene (37) is readily magnesiated by the addition of TMPMgCl·LiCl (35). Transmetalation with ZnCl<sub>2</sub>, followed by a Negishi cross-coupling reaction with 1-chloro-4-iodobenzene leads to the monoarylated thienothiophene (38) in 41% yield (Scheme 11).<sup>33</sup>

Scheme 11. Directed Magnesiation of Heterocyclic Scaffolds with TMPMgCl·LiCl<sup>a</sup>

<sup>a</sup>32, dba = dibenzylidenacetone, tfp = tris(*o*-furyl)phosphine.<sup>34</sup>

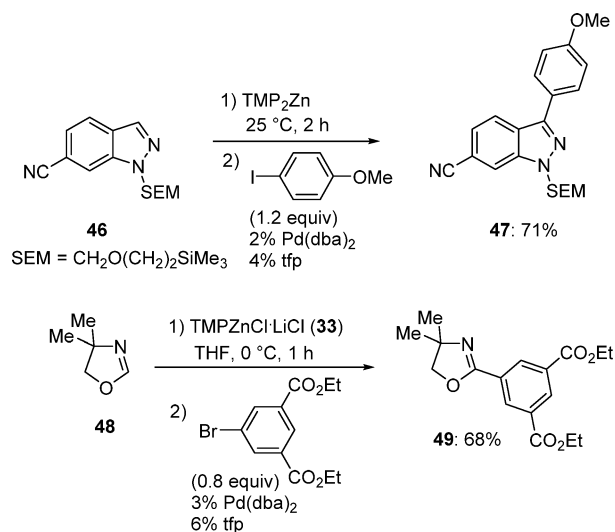
Scheme 12. Magnesiumation of Sensitive Substrates with  $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ 

Interestingly, 1,2-dimethylimidazole (39) is selectively magnesiumated at the lateral methyl group furnishing the zinc reagent (40) after transmetalation with  $\text{ZnCl}_2$ , which then undergoes a smooth cross-coupling with an aryl bromide affording benzylated imidazole (41) in 91% yield (Scheme 10).<sup>35</sup> In the case of aromatic substrates bearing C–H bonds of moderate acidity or sensitive functional groups, the use of  $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$  can be advantageous. Thus, the magnesiumation of the salicylic derivative (42) proceeds with  $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$ , and after transmetalation with  $\text{ZnCl}_2$  and Negishi cross-coupling with (*E*)-1-iodocyclohexene, the natural product (43) present in the essential oil of *Pelargonium sidoides* DC is obtained after deprotection (Scheme 12).<sup>36</sup> Also, the presence of a  $\text{SF}_5$  substituent on ethyl benzoate (44) decreases the metalation rate, and the use of  $\text{TMP}_2\text{Mg}\cdot 2\text{LiCl}$  is required to achieve a smooth magnesiumation.<sup>36</sup> After transmetalation with  $\text{ZnCl}_2$  and Negishi cross-coupling, the desired product (45) is obtained in 83% yield (Scheme 12).<sup>37</sup>

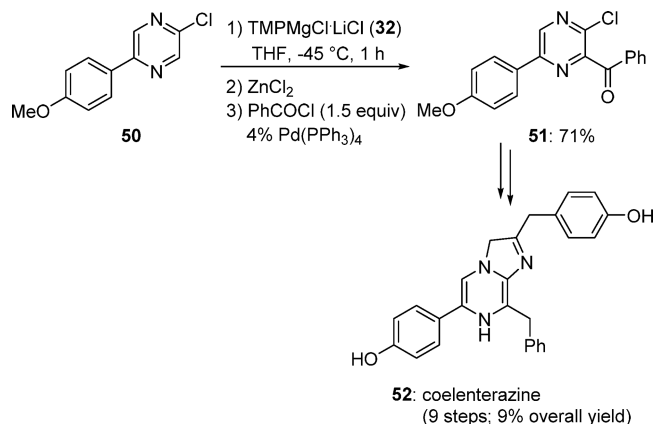
The more covalent Zn–N bond in  $\text{TMPZnCl}\cdot\text{LiCl}$  (36)<sup>32</sup> combined with the high thermal stability of the resulting zinc reagents at up to 120 °C without noticeable decomposition allowed the performance of directed zincations under a wide range of conditions.<sup>38</sup> Thus, indazoles, such as (46), which are prone to undergo fragmentation after lithiation or magnesiumation, are efficiently zincated at the C-3 position using  $\text{TMP}_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$ .<sup>39</sup> After Negishi cross-coupling with an aryl iodide, the desired 3-arylated indazole (47) is obtained in 71% yield (Scheme 13).<sup>40</sup> Similarly, 4,4-dimethyloxazoline (48), which can undergo ring fragmentation after lithiation, is zincated using  $\text{TMPZnCl}\cdot\text{LiCl}$  (36), leading to a 2-zincated oxazoline that reacts in Negishi cross-couplings affording 2-arylated oxazolines, such as (49) in 68% yield (Scheme 13).<sup>41</sup>

Related zincations of the sensitive oxazole scaffold allow a triple regioselective functionalization using multiple Negishi cross-couplings.<sup>42</sup> The zincation of various chlorinated or brominated pyrazines is readily realized using  $\text{TMPZnCl}\cdot\text{LiCl}$ .<sup>43b</sup> However, the arylated pyrazine (50) is metalated best using  $\text{TMPMgCl}\cdot\text{LiCl}$  and after transmetalation with  $\text{ZnCl}_2$  and Pd-catalyzed Negishi acylation,<sup>44</sup> the regioselectively substituted pyrazine (51) is obtained in 71% yield. In a few steps, it is converted into coelenterazine (52), a bioluminescent natural product found in the jellyfish *Aequorea victoria* (Scheme 14).<sup>43a</sup>

A regioselective arylation can be achieved combining the use of the bases (35) or (36) with (or without)  $\text{BF}_3\cdot\text{OEt}_2$ .<sup>45</sup> Extension of such a regioselectivity switch can be extended to other Lewis acids such as  $\text{MgCl}_2$ . This Lewis acid allows a

Scheme 13. Zincation of Sensitive Heterocycles Using  $\text{TMP}_2\text{Zn}$  Zinc Bases

Scheme 14. Total Synthesis of Coelenterazine Using a Negishi Acylation

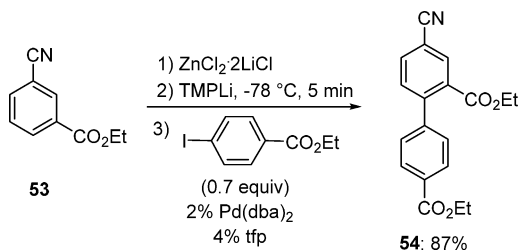


regioselective metalation of the chromone scaffold.<sup>46</sup> The compatibility of a strong Lewis acid with magnesium amides is reminiscent of the concept of frustrated Lewis pairs.<sup>47</sup> This methodology can be extended to lithium amides, and it was recently found that  $\text{TMPLi}$  does not instantaneously react with  $\text{ZnCl}_2$  or  $\text{MgCl}_2$ , allowing the performance of in situ trapping



metalations followed by Negishi cross-couplings.<sup>48</sup> Thus, mixing the cyano-benzoate (**53**) with  $\text{ZnCl}_2 \cdot 2\text{LiCl}$ , cooling the mixture to  $-78^\circ\text{C}$  and adding TMPLi allows a regioselective lithiation at position 6. The lithium intermediate is immediately transmetalated with  $\text{ZnCl}_2$ . After a Negishi cross-coupling, the corresponding arylated product (**54**) is obtained in 87% yield (Scheme 15).

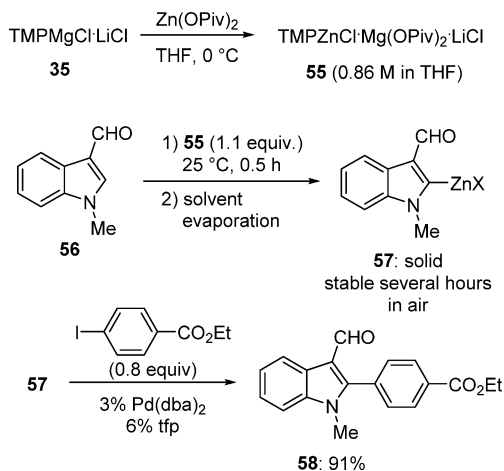
**Scheme 15. In Situ Trapping Metalation and Negishi Cross-Coupling**



However, performing these reactions not in batch but in flow allows to run these in situ trapping reactions at  $0^\circ\text{C}$ .<sup>49</sup> Most organozinc halides are sensitive to water and to moisture, however, tuning of the reaction conditions for preparing unsaturated zinc reagents by the addition of either magnesium salts, such as magnesium pivalate,<sup>50,51</sup> or ligands, such as dioxane<sup>52</sup> or bis-pyridine, this moisture stability can be considerably attenuated.<sup>53</sup> Thus, the treatment of various aromatic or heterocyclic derivatives with  $\text{TMPZnCl} \cdot \text{Mg}(\text{OPiv})_2 \cdot \text{LiCl}$  (**55**), obtained by mixing  $\text{TMPMgCl} \cdot \text{LiCl}$  with  $\text{Zn}(\text{OPiv})_2$ , readily provides solid zinc reagents that display considerable stability toward air and moisture after removal of all solvents.<sup>54</sup> In addition to their improved stability, these solid organozincs react very well in Negishi cross-couplings. Typically, the reaction of the 3-formyl-indole (**56**) with the base (**55**) furnishes the solid zinc reagent (**57**), and after Pd-catalyzed cross-coupling, the polyfunctional 2-arylated indole (**58**) is obtained in 91% yield (Scheme 16).<sup>54,55</sup>

These zinc reagents were also proved to undergo copper-catalyzed acylation reactions and can be prepared from a broad range of polyfunctionalized substrates bearing groups such as nitro, carboxy, cyano, or formyl.<sup>55</sup> It should be mentioned that

**Scheme 16. Preparation and Negishi Cross-Coupling of Solid Air-Stable Zinc Reagents**

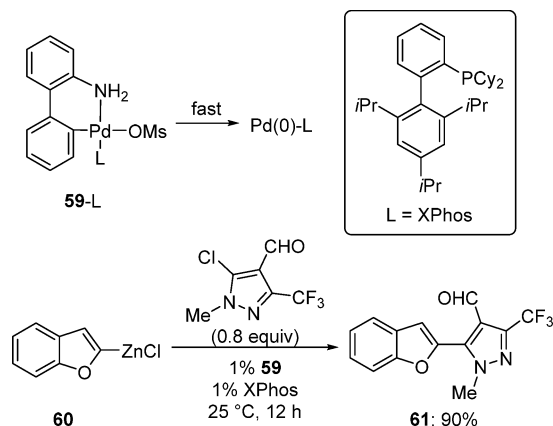


transition-metal-free cross-couplings can be realized with various organozinc reagents especially with the class of reactive benzylic zinc organometallics.<sup>56,57</sup>

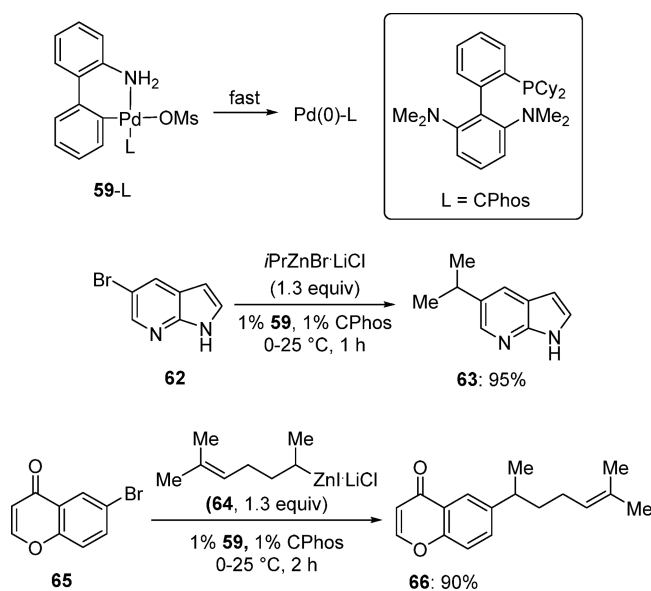
### 3. NEGISHI CROSS-COUPLING USING PALLADIUM CATALYSTS

Negishi cross-couplings involve the use of organozinc reagents, an organic electrophile, and a transition-metal catalyst. The variation of this transition-metal catalyst allowed in recent years a greater expansion in the synthetic scope of this important cross-coupling procedure. The use of palladacycle precatalysts enables the performance of Negishi cross-couplings with a broad range of substrates. Buchwald recently developed a new class of easily prepared, air- and moisture-stable aminobiphenyl-based palladacycle precatalysts capable of rapidly generating the catalytically active  $\text{Pd}(0)\text{-L}$  species under basic conditions, allowing Negishi cross-couplings to proceed at ambient temperature with low catalyst loading. Thus, the precatalyst palladacycle (**59-L**) with  $\text{L} = \text{XPhos}$  considerably facilitates the formation of the highly active catalytic palladium-species  $\text{LPd}(0)$  leading to fast Negishi cross-couplings at room temperature. The 2-zincated benzofuryl derived reagent (**60**) reacts with a chloropyrazole providing the complex polyfunctional heterocyclic compound (**61**) in 90% yield (Scheme 17).<sup>58</sup>

**Scheme 17. Pd-Precatalyst Facilitated Negishi Cross-Coupling**



This strategy has been successfully applied to the performance of highly selective Negishi cross-couplings of secondary alkylzinc species. A major difficulty of this transformation is undesired  $\beta$ -hydride elimination/migratory insertion that competes with the desired reductive elimination leading to isomerized side products. In order to suppress this isomerization, the rate of reductive elimination relative to  $\beta$ -hydride elimination must be enhanced. Several research groups have addressed this issue by employing catalysts containing sterically hindered phosphine ligands. Thus,  $i\text{PrZnBr} \cdot \text{LiCl}$  reacts smoothly with the 7-azaindole (**62**) affording the coupling product (**63**) in 95% yield, without any isomerization of the secondary alkylzinc species using the precatalyst (**59-L**) with  $\text{L} = \text{CPhos}$ . A range of secondary alkylzinc reagents like (**64**) can be used with excellent results for the coupling of the bromochromane (**65**), leading to the alkylated product (**66**) in 90% yield (Scheme 18).<sup>59</sup>

Scheme 18. Pd-Precatalyst for the Cross-Coupling of *sec*-Alkylzinc Reagents

Additionally, Organ<sup>60</sup> and co-workers developed a series of new N-heterocyclic carbene-based Pd-complexes, which were used for the Negishi cross-coupling of aryl and heteroaryl halides with a variety of secondary alkylzinc reagents. It was shown that Pd-PEPPSI-IPent<sup>Cl</sup> (**67**) had unprecedented selectivity, leading to only one single isomer (**68**) for reactions of a variety of alkylzincs, such as (**69**), with highly functionalized (hetero)aromatic halides like (**70**) (Scheme 19).<sup>61</sup>

Interestingly, alkyl iodides such as *i*PrI were found to accelerate Negishi cross-couplings.<sup>62</sup> The reaction of the diarylzinc (**71**), prepared by a Br/Mg exchange, with an aniline derivative (**72**) bearing a free NH<sub>2</sub>-group leading to the biphenyl (**73**) in 97% yield. In absence of *i*PrI, a conversion of only 37% is observed (Scheme 20).<sup>62</sup>

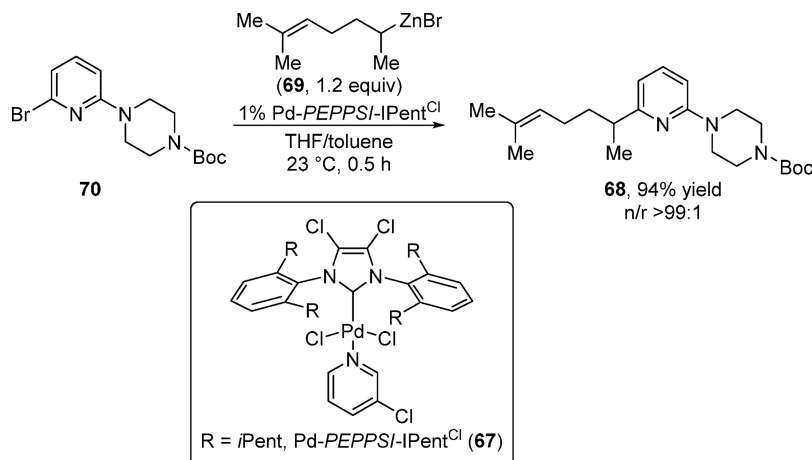
The mechanism of the Negishi cross-coupling has been carefully studied by Espinet<sup>63</sup> and Koszinowski<sup>64</sup> using a combination of kinetic measurements, mass-spectrometry, and NMR methods. A structure–reactivity relationship in Negishi

cross-coupling reactions by Mayr<sup>65</sup> showed that this reaction is accelerated by the presence of electron-acceptor substituted aryl bromides. On the other hand, the presence of an electron-acceptor substituent on the arylzinc halide diminishes the reaction rates. Additionally, Organ and co-workers<sup>66</sup> investigated the role of halide salt additives in the Negishi reaction involving arylzinc reagents. It was shown that diarylzincs easily transmetallate to palladium in THF with no salt present, leading to the corresponding coupling products. In contrast, arylzinc halides fail to couple in THF without additional salt. However, unlike alkylzincs that form higher-order zincates<sup>67</sup> in order to facilitate transmetalation, all that is needed for arylzincs is an increase in the solvent dielectric constant, which completely hampers the alkylzinc cross-coupling.

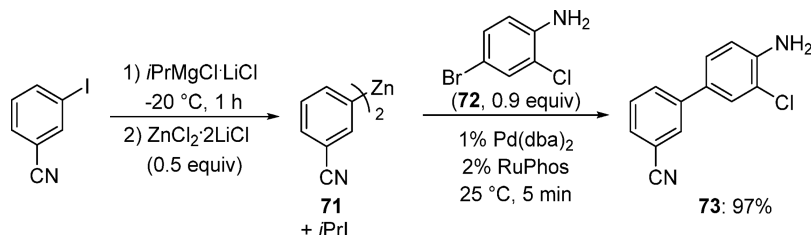
The original reaction scope has been considerably extended, as the excellent functional group tolerance of zinc reagents allows the Negishi cross-coupling of various bromo-substituted alkoxy-carbene complexes of chromium, molybdenum, or tungsten complexes, as shown by Dvorak.<sup>68</sup> Also, Dughera reported Negishi cross-couplings with arenediazonium *o*-benzenedisulfonimides.<sup>69</sup> The combination of a Zr-catalyzed asymmetric carboalumination of alkenes (ZACA-reaction) with the Negishi cross-coupling allowed Negishi to prepare various chiral 1-alkanol derivatives in high enantiomeric purity.<sup>70</sup> Remarkable cross-couplings between heterocyclic moieties could be achieved with the Negishi cross-coupling. Thus, Zhang showed that 3-amino-1*H*-1,2,4-triazoles, such as (**74**), were readily zincated with TMPZnCl·LiCl (**35**) and underwent a smooth Negishi cross-coupling with various aryl or alkenyl bromides enabling a smooth conversion of the aminotriazole (**74**) into the arylated derivative (**75**) in 85% yield (Scheme 21).<sup>71</sup>

Gosselin showed that TMPZnCl·LiCl can also be employed for the zincation of pyridine oxides, such as (**76**). After a cross-coupling with a bromopyridine, the desired bis-pyridine (**77**) was obtained in high yield (Scheme 21).<sup>72</sup> The zincation of pyridazine-3(2*H*)-ones, such as (**78**), with TMPZnCl·LiCl allows for the preparation of highly functionalized heterocycles that are of high interest as pesticides (Scheme 22).<sup>73</sup>

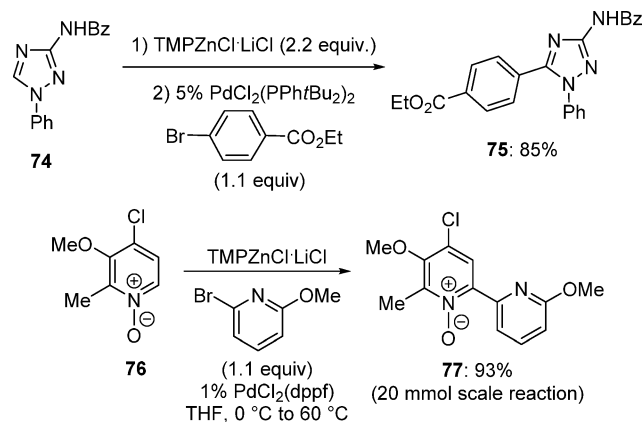
Highly diastereoselective Negishi cross-couplings have been achieved by the treatment of various cyclic organozinc reagents, such as (**81a–c**), with a range of aryl iodides in the presence of

Scheme 19. Negishi Cross-Coupling of Secondary Alkylzincs Using Pd-PEPPSI-IPent<sup>Cl</sup><sup>a</sup>

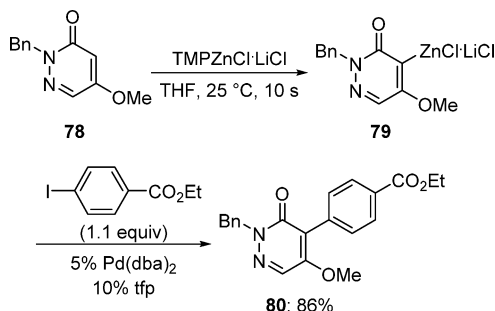
<sup>a</sup>n/r = ratio of normal and rearranged product.

Scheme 20. *i*PrI-Accelerated Negishi Cross-Coupling

Scheme 21. Negishi Cross-Couplings of N-Heterocycles



Scheme 22. Zincation and Negishi Cross-Coupling of Pyridazinones

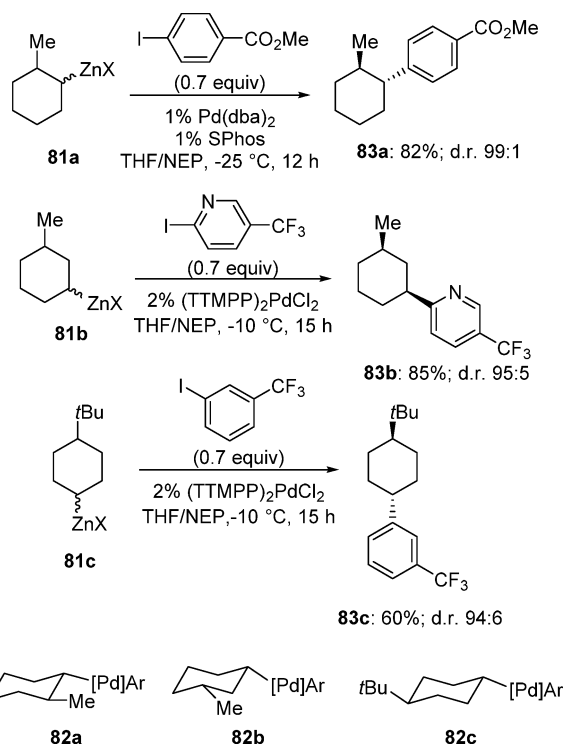


a palladium catalyst. The new carbon–carbon bond is formed preferentially via an intermediate having the C–Pd bond in an equatorial position, such as (**82a–c**), leading in the case of 1,2- and 1,4-disubstituted zinc reagents to the *trans*-disubstituted products (**83a**) and (**83c**) and in the case of 1,3-disubstituted zinc reagents to the *cis*-1,3-disubstituted product (**83b**) (Scheme 23).<sup>74</sup>

This method can be extended to the stereoselective preparation of several types of piperidines,<sup>75</sup> such as (**84**), and to achieve a regioselective arylation of allylic amines as shown by Baudoin (Scheme 24).<sup>76</sup>

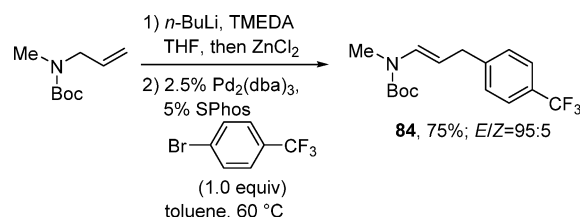
A broad range of catalytic systems are available, and new catalysts and ligands are constantly reported. Thus, the simple N-heterocyclic precatalyst (**85**) proves to be especially efficient as it allows for Negishi cross-coupling reactions of alkylzinc reagents, such as (**86**), or (hetero)arylzinc reagents with various (hetero)aryl halides like (**87**) under mild reaction conditions with low catalyst loading (Scheme 25).<sup>77</sup>

A range of important findings and mechanistic studies with practical applications have been reported, and the difference observed in the role of salts in Negishi cross-couplings of

Scheme 23. Diastereoselective Arylation of Cyclohexane Derivatives<sup>a</sup>

<sup>a</sup>TTMPP = tris(2,4,6-trimethoxyphenyl)phosphine.

Scheme 24. Regioselective Arylation of Allyl amines

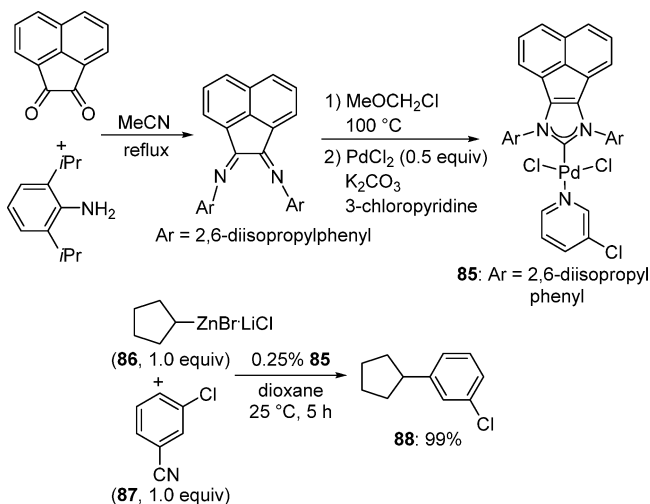


arylzincs compared to alkylzincs has been studied in depth by Organ.<sup>78</sup>

#### 4. NEGISHI CROSS-COUPPLINGS USING NICKEL CATALYSTS

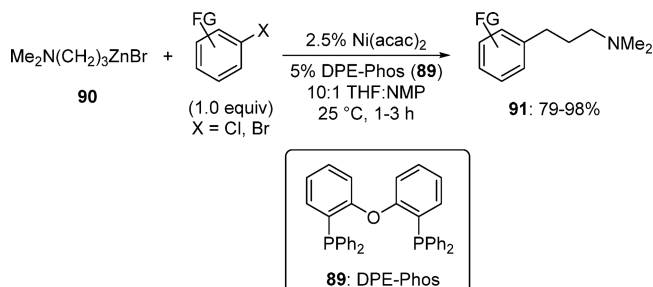
Although the use of palladium catalysts ensures a broad applicability of the Negishi cross-coupling, environmental sustainability and cost concerns have led to the examination of other transition metal catalysts for these cross-couplings, and the use of nickel has led to the most impressive developments. Standard nickel complexes, such as Ni(acac)<sub>2</sub> in combination with DPE-Phos (**89**),<sup>79</sup> were found to catalyze cross-couplings

### Scheme 25. N-Heterocyclic Carbenes for Negishi Cross-Couplings



under milder conditions and a range of amino-substituted zinc reagents, such as (**90**), afforded polyfunctional amines of type (**91**) (Scheme 26).<sup>80</sup>

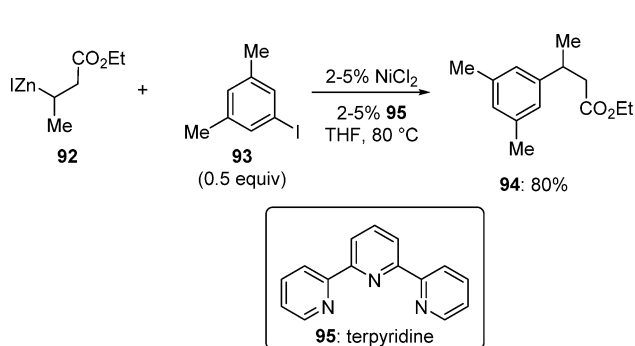
### Scheme 26. Nickel-Catalyzed Negishi Cross-Couplings



Other ligands besides phosphines also show high efficiency especially for the cross-coupling of secondary alkylzinc reagents as shown by Biscoe.<sup>81</sup> Thus, the cross-coupling of the functionalized zinc reagent (**92**) with 1-iodo-3,5-dimethylbenzene (**93**) provides the cross-coupling product (**94**) in 80% yield (Scheme 27).

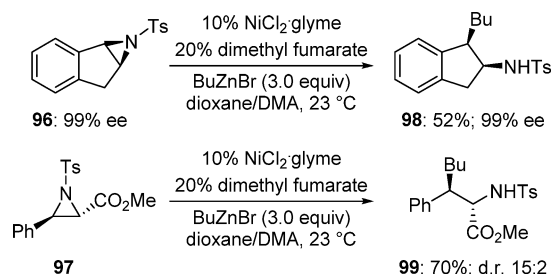
Low-valent nickel readily inserts into the C–N bond of aziridines, and they undergo smooth arylation with organozinc halides. This method can be applied to chiral aziridines, such as (**96**), or disubstituted aziridines like (**97**) providing stereo-

### Scheme 27. Nickel-Catalyzed Negishi Cross-Coupling Using Secondary Alkylzinc Reagents



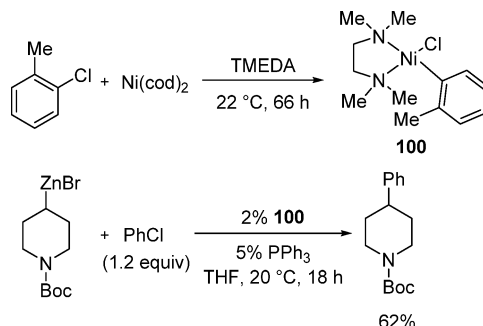
selectively polyfunctional amines, such as (**98**) and (**99**), in satisfactory yields and stereoselectivity (Scheme 28).<sup>82</sup>

### Scheme 28. Stereoselective Negishi Cross-Couplings with Aziridines



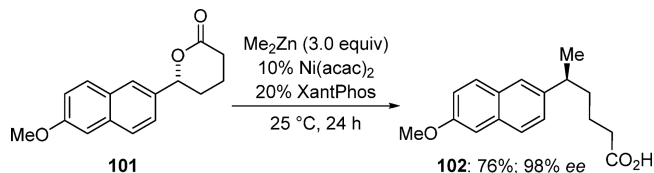
Furthermore, the above method allows for the generation of molecules with quaternary centers.<sup>83</sup> A remarkably simple and practical catalyst has been developed by Monfette<sup>84</sup> simply by treating Ni(cod)<sub>2</sub> and TMEDA with 2-chlorotoluene (**100**). This catalyst undergoes smooth Negishi cross-coupling reactions (Scheme 29).<sup>85</sup>

### Scheme 29. Convenient Nickel Catalyst for Negishi Cross-Couplings



Pincer ligands are also popular ligands in the synthesis of Ni-complexes with good activity in Negishi cross-couplings even with unusual electrophiles, such as aryltrimethylammonium iodide.<sup>85</sup> Remarkable cross-couplings of aryl-substituted tetrahydrofurans, tetrahydropyrans, as well as lactones have been reported by Jarvo.<sup>86</sup> Thus, the ring opening of (**101**) in the presence of Me<sub>2</sub>Zn provides (**102**) in 98% ee, which can be converted in two subsequent steps to an antidyslipidemia agent (Scheme 30).

### Scheme 30. Nickel-Catalyzed Negishi Cross-Coupling

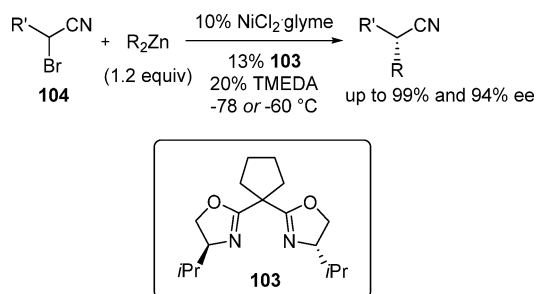


Jarvo has also shown that these Ni-catalyzed cross-couplings of benzylic ethers and esters are general and are part of the modern tool-box for Negishi or Kumada cross-couplings.<sup>87</sup> A range of catalytic asymmetric syntheses using Pfaltz's chiral bis(oxazoline)-type ligand<sup>88</sup> (**103**) are known and allow for stereoconvergent Negishi arylations and alkenylations of



racemic  $\alpha$ -bromonitriles<sup>89</sup> of type (104) and other carbonyl derivatives,<sup>90</sup> as well as benzylic alcohols<sup>91</sup> or propargylic bromides (Scheme 31).<sup>92</sup>

**Scheme 31. Enantioselective Negishi Cross-Couplings**



Remarkably, Fu also reported an enantioselective cyclization/Negishi cross-coupling reaction with alkyl electrophiles.<sup>93</sup> The use of strongly donating bis-dialkylphosphine nickel moieties efficiently promotes the Negishi cross-coupling reactions under practical and mild conditions as demonstrated by Gosmini and Mézailles.<sup>94</sup> Interestingly, it has been shown that Ni(II)-complexes that are relevant to Negishi cross-coupling reactions can be characterized both structurally and spectroscopically.<sup>95</sup>

## 5. NEGISHI CROSS-COUPPLINGS WITH OTHER TRANSITION-METAL CATALYSTS

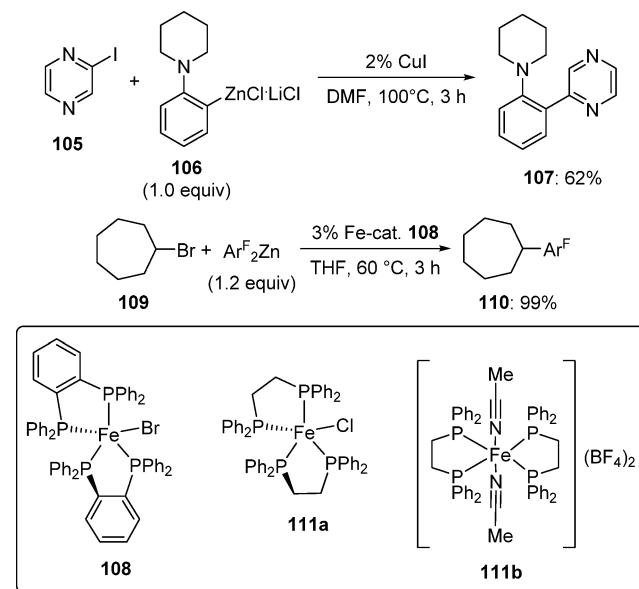
Although palladium and nickel are by far the most used metal catalysts for Negishi cross-couplings, a few other metallic salts, such as Cu, Fe, and Co derivatives have been reported to promote efficiently Negishi cross-couplings. A quite general Negishi cross-coupling procedure involving the coupling between alkyl-, aryl-, and alkynyl-zinc reagents with a range of heteroaryl iodides has been reported by Giri.<sup>96</sup> Thus, reaction of iodopyridazine (105) with the amino-substituted zinc compound (106) provides the desired coupling product (107) in 62% yield. Also, iron-catalyzed cross-couplings have been reported using organozinc reagents, showing that monophosphines are excellent ligands for coupling alkyl bromides with diphenylzinc derivatives.<sup>97</sup> Of special interest is the Fe(I)-catalyzed cross-coupling procedure described by Bedford.<sup>98</sup> The readily available catalyst (108) allows a smooth cross-coupling between cycloheptyl bromide (109) and fluoroarylzinc reagents providing the coupled product (110) in quantitative yield (Scheme 32). More convenient catalysts, such as (111a,b), have been used especially for the cross-coupling of benzylic halides and cycloalkyl bromides with arylzinc derivatives with great success.<sup>99</sup>

Cobalt salts have been used in Negishi cross-couplings as well, and Gosmini has shown that the treatment of CoBr<sub>2</sub> with zinc and allyl bromide in MeCN and TFA, followed by the addition of the coupling partners, provides the cross-coupling products, such as (112), in good yields (Scheme 33).<sup>100</sup>

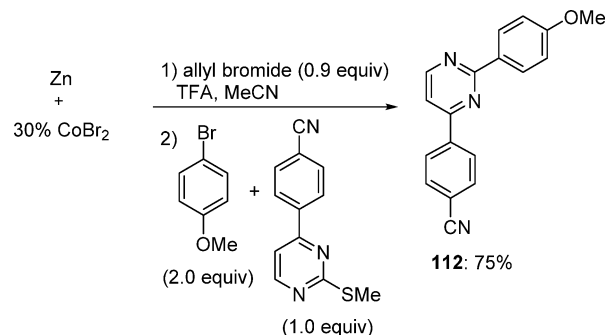
The methodology developed by Gosmini can be efficiently used to couple various organozinc halides with bromoalkynes.<sup>101</sup> Thus, the treatment of functionalized aryl bromides such as (113) with CoBr<sub>2</sub>(phen) and zinc dust produces a zinc reagent that smoothly reacts with various bromoalkynes, such as (114), to afford the desired cross-coupling product (115) in 85% yield (Scheme 34).

Recently, it was shown that various functionalized arenes are zincated with TMP<sub>2</sub>Zn and undergo an efficient cross-coupling

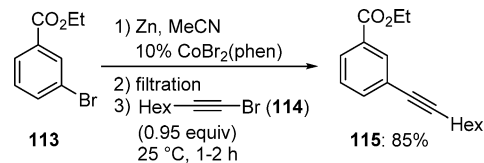
**Scheme 32. Negishi Cross-Couplings Catalyzed by Iron and Copper Catalysts**



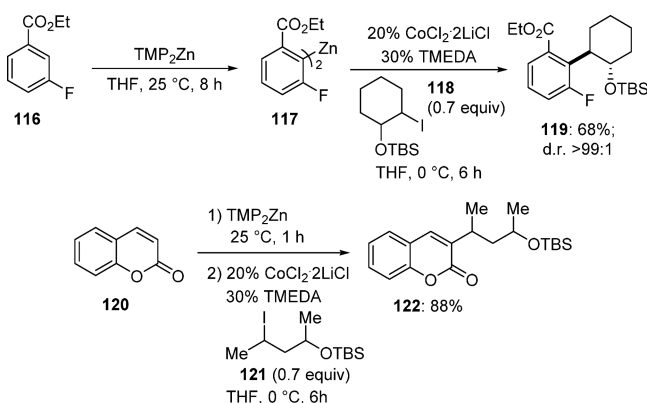
**Scheme 33. Negishi Cross-Couplings Catalyzed by Cobalt(II) Bromide**



**Scheme 34. Cobalt-Catalyzed Formation of Zinc Organometallics and Negishi Cross-Couplings**



with secondary or primary alkyl iodides in the presence of CoCl<sub>2</sub>·2LiCl and TMEDA.<sup>102</sup> Thus, the treatment of ethyl 3-fluorobenzoate (116) with TMP<sub>2</sub>Zn·2MgCl<sub>2</sub>·2LiCl provides the corresponding zinc reagent (117), which reacts with the functionalized alkyl iodide (118) furnishing the cross-coupling product (119) in 68% yield (d.r. > 99:1). This reaction can be readily applied to the alkylation of heterocycles and the cross-coupling of coumarine (120) with the alkyl iodide (121) furnishes the expected product (122) in 88% yield (Scheme 35).

Scheme 35. Negishi Cross-Couplings Performed Using  $\text{CoCl}_2 \cdot 2\text{LiCl}$ 

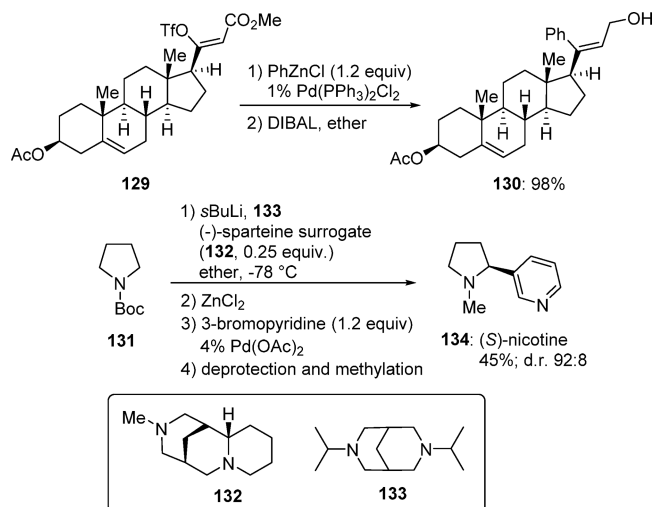
## 6. SOME APPLICATIONS OF NEGISHI CROSS-COUPLING REACTIONS IN NATURAL PRODUCT SYNTHESIS

In a total synthesis of isodesmosine, the use of a regioselective Negishi cross-coupling proved to be critical.<sup>103</sup> The readily prepared thiodopyridine (**123**) undergoes a selective Negishi cross-coupling with Jackson's zinc reagent (**124**) leading to the desired product (**125**) in 46% yield. A Sonogashira cross-coupling converts (**125**) into the monoiodide (**126**), and a subsequent Negishi cross-coupling with (**124**) provides the trisubstituted product (**127**) that was further converted to isodesmosine (**128**) in a few steps (Scheme 36).

Mazet used Negishi cross-couplings in an impressive way for the preparation of complex steroid derivatives.<sup>104</sup> The alkenyl triflate (**129**) was phenylated using  $\text{PhZnCl}$  to provide the trisubstituted alcohol (**130**) in 98% yield after DIBAL-reduction (Scheme 37).

The enantioselective construction of pyrrolidines is important due to the range of highly pharmaceutically active molecules bearing such a ring system. O'Brien and Campos have developed a quite general methodology<sup>105</sup> for the preparation of various chiral pyrrolidines using  $s\text{BuLi}$ /(-)-sparteine or its surrogate to obtain a chiral pyrrolidylzinc reagent, which is readily employed in a Negishi cross-coupling with retention of configuration. This general method is illustrated in a synthesis of (*S*)-nicotine. The metalation of the pyrrolidine (**131**) with  $s\text{BuLi}$  in the presence of the chiral

Scheme 37. Applications of Negishi Cross-Couplings

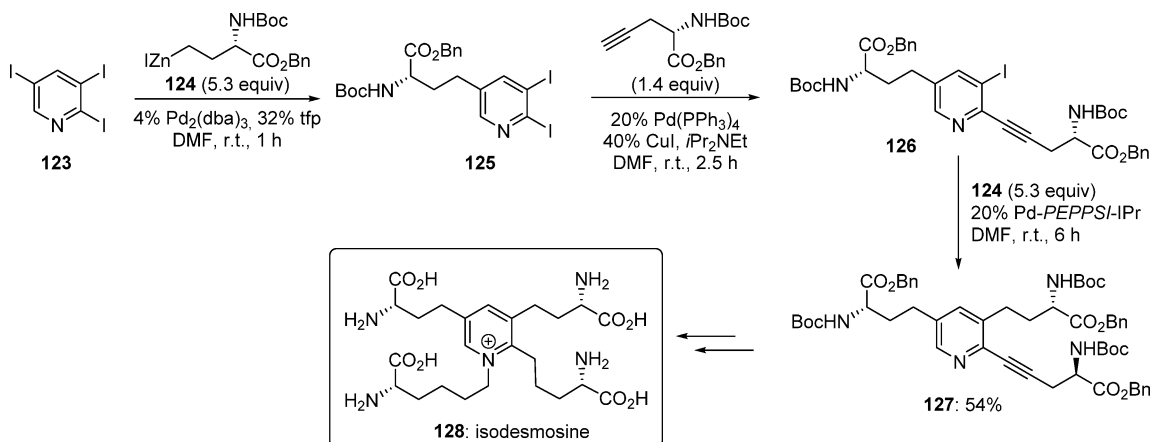


surrogate (**132**) and the diamine (**133**), followed by transmetalation to zinc and cross-coupling with 3-bromopyridine, provides (*S*)-nicotine (**134**) after deprotection and methylation (Scheme 33).<sup>105</sup> Gademann used a Negishi cross-coupling with success to perform the first total synthesis of the ptericidin related natural products Mer-A2026B and JBIR-02.<sup>106</sup> Thus, the reaction of the complex carbonate (**135**) with the pyridylzinc reagent (**136**) leads to the desired Negishi cross-coupling product (**137**) in 69% yield. Finally, the synthesis of the anti-inflammatory pro-resolving lipid (**138**) has been achieved using a Negishi cross-coupling between two  $\text{Csp}^3$ -bonds. Thus, the cross-coupling between the unsaturated bromide (**139**) and the zinc reagent (**140**) provides the desired cross-coupling product (**141**) in 70% yield, affording the drug (**138**) after a few steps (Scheme 38).<sup>107</sup>

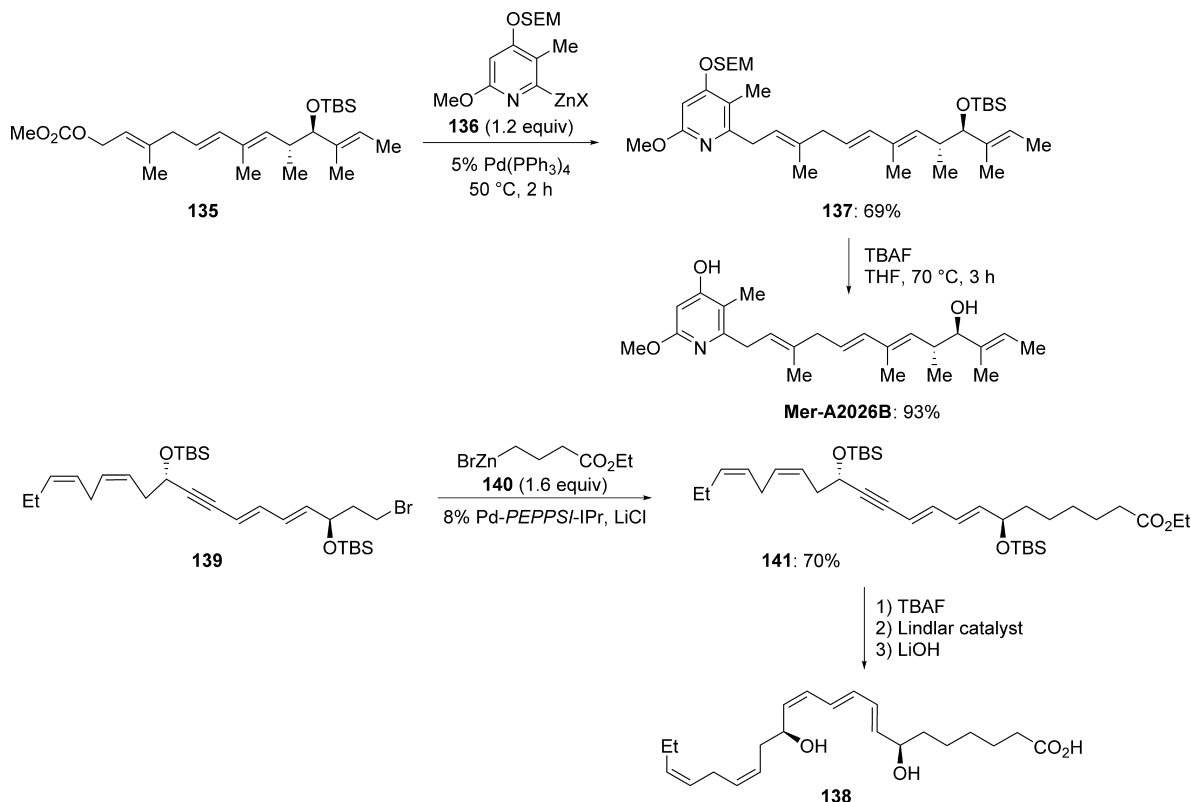
## 8. CONCLUSION

Due to the mild conditions required to form new carbon-carbon bonds, the Negishi cross-coupling has found an increased number of synthetic applications. Although palladium is still the most commonly used metal catalyst for these cross-couplings, alternative metals, such as nickel, cobalt, and iron, may be useful complement methodologies in the future regarding toxicity, as well as ecological and price aspects. The

Scheme 36. Preparation of Isodesmosine via Negishi Cross-Couplings



Scheme 38. Complex Negishi Cross-Coupling Reactions in Natural Product Synthesis



broad and constantly increasing availability of zinc organometallics should further expand the use of the Negishi cross-coupling in organic synthesis.

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### Notes

The authors declare no competing financial interest.

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