

Synthesis of Aryl(di)azinylmethanes and Bis(di)azinylmethanes via Transition-Metal-Catalyzed Cross-Coupling Reactions

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Abstract: Aryl(di)azinyl- and bis(di)azinylmethane motifs are important as they are found in a number of pharmaceuticals and their precursors. An exhaustive overview of transition metal-catalyzed cross-coupling reactions for their synthesis has been provided.

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Key words: heterocycles, transition metals, cross-coupling, palladium, nickel

1 Introduction

Transition-metal-catalyzed cross-coupling reactions are nowadays widely accepted as a general tool for the construction of carbon–carbon bonds and already appear in educational chemistry textbooks. Starting from the early 1970s, the cross-coupling reactions (mediated mainly by palladium) evolved from using stoichiometric amounts of

the transition metal to requiring only catalytic amounts. While transition-metal-catalyzed transformations of aryl (pseudo)halides involving formation of (un)symmetrical biaryls have already gained a lot of attention and have been reviewed thoroughly,¹ the synthesis of (un)symmetrical diphenylmethanes has gained less attention. A 2008 review by Bruneau summarized the functionalization of benzylic systems by palladium catalysis.² Diarylmethane skeletons are usually prepared by palladium or nickel catalysis using arylboronic acids and benzyl (pseudo)halides [Suzuki–Miyaura reaction] or with (in situ formed) benzylzinc species and aryl (pseudo)halides [Negishi reaction] as coupling partners. Examples by Bedford and Gosmini have shown that even catalytic amounts of base metals (iron or cobalt catalysts) are applicable as catalysts for the synthesis of diarylmethanes.³

The syntheses of aryl(di)azinylmethanes rely mostly on analogous strategies. Halogenated (di)azines, for instance, react with benzyl organometallic species, such as benzylzinc bromide or benzyltributylstannane. A new and recent approach uses methyl(di)azines as such to prepare aryl(di)azinylmethanes, although (in situ) stoichiometric pre-activation is usually necessary. Stoichiometric pre-activation can involve the use of strong bases (BuLi, TMPZnCl·LiCl) followed by transformation of the carbanion into more stable reagents that can be isolated or, in the case of TMPZnCl·LiCl, directly used in a cross-coupling reaction. However pre-activation can also mean quaternization of the (di)azine nitrogen, like the formation of *N*-oxides or *N*-iminopyridinium ylides. Methyl(di)azines, such as 2- and 4-methylpyridine, are interesting starting materials as they appear in bone oil or can be easily synthesized via condensation reactions of acetaldehyde and ammonia.⁴ Aryl(di)azinylmethane motifs and their methylene substituted derivatives are economically very important as they are found in the structure of a number of pharmaceuticals or their precursors (Figure 1).⁵ Several methylene functionalization protocols starting from aryl(di)azinylmethanes have therefore been developed.⁶ Probably the most known pharmaceutical based on the aryl(di)azinylmethane entity is mefloquine (Lariam®) (**1**), an antimalarial that, despite its known cytotoxicity, is still widely used in malaria prevention.⁵ Other examples containing the aryl(di)azinylmethane skeleton are the 1st and 2nd generation antihistamines carbinoxamine (**2**), bep-otastine (**3**), doxylamine (**4**) and acrivastine (**5**), the β_2 -adrenergic agonist rimiterol (**6**), the anxiolytic bromazepam

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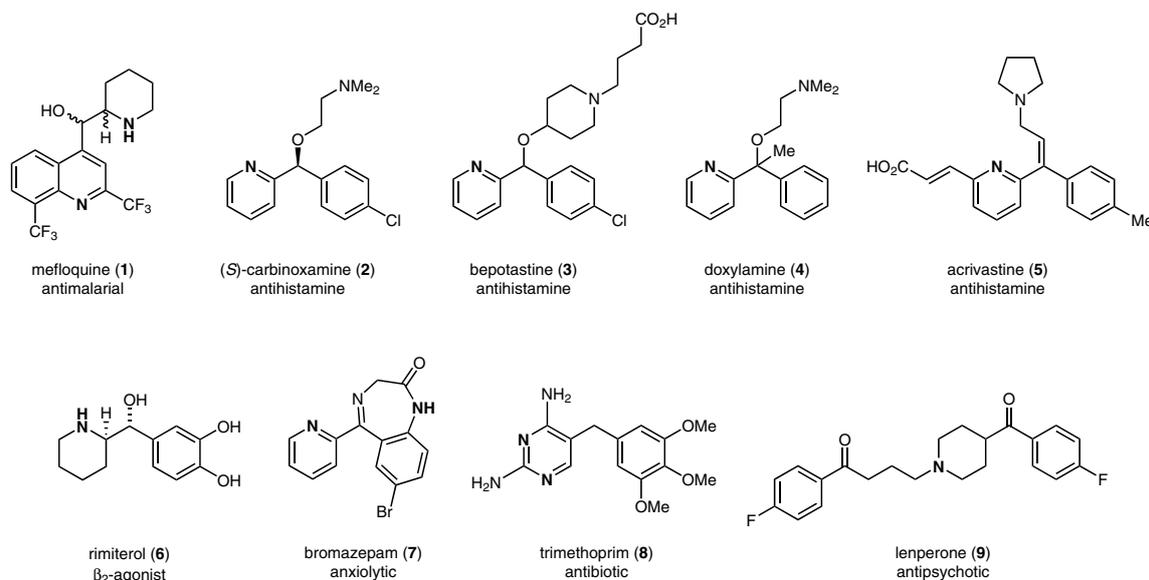


Figure 1

(7), the antibiotic trimethoprim (8) and the anti-psychotic lenperone (9).⁵

This review gives an overview of all transition-metal-catalyzed coupling reactions that provide aryl(di)azinylmethane or bis(di)azinylmethane entities. Their annulated systems, like quinolines, quinazolines, quinoxalines, phthalazines, cinnolines, naphthyridines, purines, etc., are not systematically covered as they mostly rely on protocols analogous to those of the parent (di)azine.

2 Reaction of (Di)azinyl (Pseudo)halides with Benzyl Organometallic Reagents

2.1 Organozinc Reagents – Negishi Reaction

In 1977, Negishi and Jutand independently communicated the first examples of transition-metal-catalyzed cross-coupling reactions using organozinc reagents.⁷ While Jutand used the Reformatsky reagent ethyl bromozincacetate for nickel- and palladium-catalyzed coupling reac-

Biographical sketches



Bert Maes was educated at the University of Antwerp. In 2001 he received a post-doctoral fellowship of the National Science Foundation (FWO) in Belgium to allow his transition to an independent academic career. In 2003 he was appointed as an Assistant Professor (docent) in the Department of

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moted to Professor (hoogleraar) and currently holds a research professorship. His research focuses on heterocyclic chemistry, organometallic chemistry, sustainable chemistry and homogeneous catalysis. He is an author of 95 publications, 4 book chapters and 3 patents.



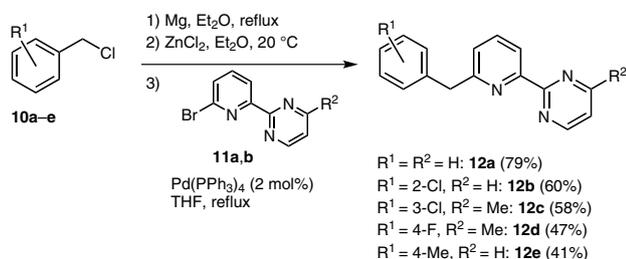
Johan De Houwer obtained his M.Sc. degree (licentiaat) in chemistry at the University of Antwerp in 2007. Under the supervision of Prof. Bert Maes he received his PhD in 2013. His

PhD work was financially supported by a prestigious IWT fellowship. He is currently working as a postdoctoral researcher on an IMI project (Chem21), funded by EU and EFPIA members.

His scientific interests are mainly focused on transition-metal-catalyzed (cross-coupling) reactions and heterocyclic chemistry.

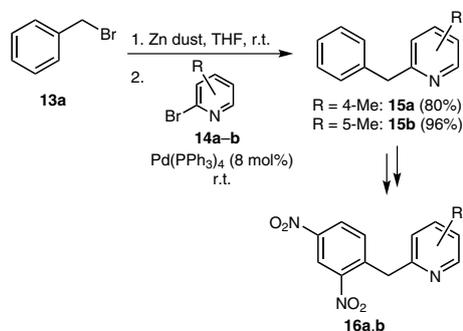
tions with aryl halides, Negishi used aryl- and benzylzinc species for the synthesis of unsymmetrical diaryls and diarylmethanes using the same transition metals as catalysts. Since then, many research groups have adapted the conditions reported by Negishi for the synthesis of (unsymmetrical) diphenylmethanes, as well as arylheteroarylmethanes, including aryl(di)azinylmethanes.

In 2000, Worthington reported the synthesis of 2-(6-benzylpyridin-2-yl)pyrimidines, which can be used as broad-spectrum fungicides.⁸ The key intermediates, 2-(6-bromopyridin-2-yl)pyrimidines **11**, were synthesized in multigram quantities by a palladium-catalyzed Negishi coupling of (6-bromopyridin-2-yl)zinc chloride with a 2-bromopyrimidine. In the next step, **11a** or **11b** was cross-coupled with a benzylzinc reagent (obtained via the direct insertion of magnesium into a functionalized benzyl chloride **10**, followed by transmetalation with zinc chloride) in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium, in tetrahydrofuran under reflux, to afford the required 2-(6-benzylpyridin-2-yl)pyrimidines **12a–e** in moderate to good yields (Scheme 1).



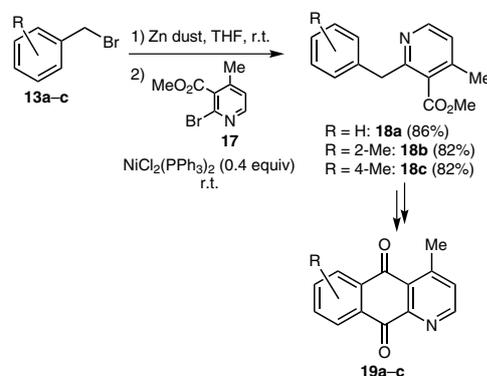
Scheme 1

In their study on thermally activated tautomerization processes in 2-(2,4-dinitrobenzyl)pyridine derivatives, Eichen and co-workers prepared 2-benzylpyridine substrates.⁹ 2-Benzyl-4-methylpyridine (**15a**) and 2-benzyl-5-methylpyridine (**15b**) were prepared by a Negishi coupling of benzylzinc bromide, obtained via the direct insertion of zinc into benzyl bromide (**13a**), with 2-bromo-4-methylpyridine (**14a**) and 2-bromo-5-methylpyridine (**14b**), respectively (Scheme 2). The obtained products **15a,b** were then converted into the required nitro-substituted substrates **16a,b** via electrophilic nitration.



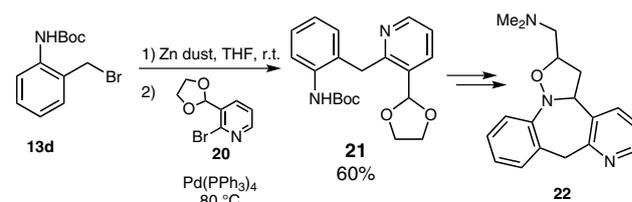
Scheme 2

During the synthesis of the natural product cleistopholine (**19a**) and two closely related analogues (**19b,c**), Krapcho and Ellis performed a nickel-catalyzed Negishi cross-coupling reaction on methyl 2-bromo-4-methylnicotinate (**17**) with benzylzinc bromides prepared by direct zinc insertion in the corresponding benzyl bromides **13a–c**.¹⁰ The benzylpyridines **18a–c** were then further transformed into the natural product and its analogues in four steps (Scheme 3).



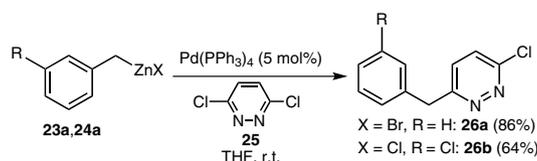
Scheme 3

In a 2002 publication, Andrés et al. reported the synthesis of 2-(dimethylaminomethyl)tetrahydroisoxazolo-pyridobenzazepine derivatives as 5-HT_{2C} antagonists.¹¹ The synthesis of one of these derivatives started with the palladium-catalyzed Negishi coupling of a Boc-protected (2-aminobenzyl)zinc bromide **13d** with 2-bromo-3-(1,3-dioxolan-2-yl)pyridine (**20**) in 60% yield (Scheme 4). Product **21** was then further converted into the desired 2-(dimethylaminomethyl)-2,3,3a,8-tetrahydroisoxazolo[3,2-*a*]pyrido[3,2-*c*][2]benzazepine (**22**) in five consecutive steps.



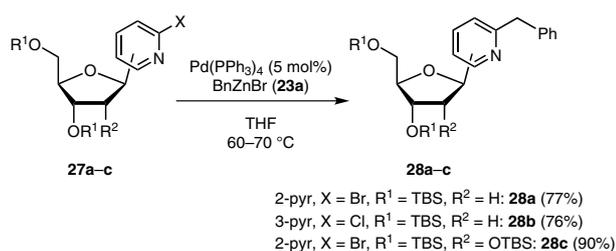
Scheme 4

In 2005, Kasatkin and co-workers noticed that 3,6-dichloropyridazines can react selectively with alkyl-, alkenyl-, aryl- and benzylzinc species to give the corresponding monosubstituted products.¹² When 3,6-dichloropyridazine (**25**) was allowed to react with 1.6 equivalents of benzylzinc bromide (**23a**) or (3-chlorobenzyl)zinc chloride (**24a**) in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium, the resulting 6-benzyl-3-chloropyridazines **26a,b** were obtained selectively in moderate to good yields (Scheme 5).



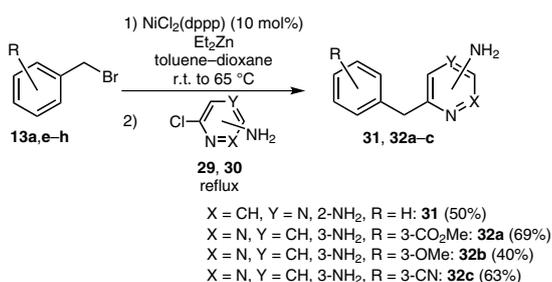
Scheme 5

The Hocek group published multiple papers on the synthesis of 6-substituted 2- and 3-pyridinyl *C*-(ribo)nucleosides.¹³ On 6-halo-2- and -3-pyridinyl *C*-(ribo)nucleoside substrates **27a–c**, they performed a set of transition-metal-catalyzed cross-coupling reactions, including a standard Negishi reaction with benzylzinc bromide (**23a**) (Scheme 6).



Scheme 6

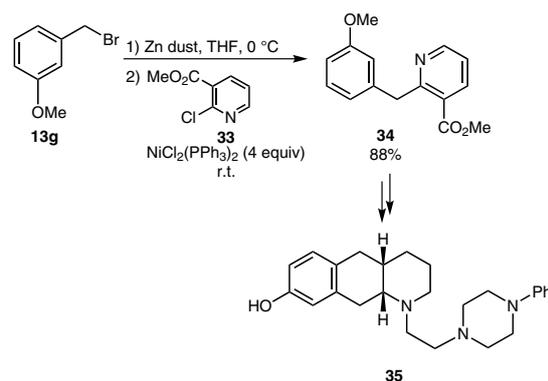
In 2006, Walters reported the nickel-catalyzed Negishi coupling of amino-substituted halodiazines with alkyl- and benzylzinc reagents.¹⁴ The benzylzinc reagents were prepared by a nickel-catalyzed halogen–zinc exchange of the benzyl bromides (**13a,e–h**) with excess diethylzinc, a procedure that was developed earlier by Knochel.¹⁵ Employing these conditions with 2-amino-6-chloropyrazine (**29**; X = CH, Y = N) and 3-amino-6-chloropyridazine (**30**; X = N, Y = CH) afforded the corresponding benzylated products **31** and **32a–c** in moderate yields (Scheme 7).



Scheme 7

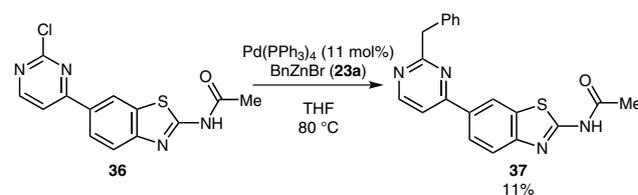
During their studies on selective dopamine receptor agonists, Dutta and co-workers designed and synthesized a series of compounds that contained varying degrees of conformational constraint in the agonist moiety of the hybrid template.¹⁶ The synthesis of one of these compounds started with the nickel-mediated Negishi reaction of (3-methoxybenzyl)zinc bromide, prepared by direct zinc insertion into 3-methoxybenzyl bromide (**13g**), with methyl 2-chloronicotinate (**33**), supplying the benzylated

nicotinate **34** in 88% yield. Product **34** was then further converted into *cis*-1-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,3,4,4a,5,10,10a-octahydrobenzo[*g*]quinolin-8-ol (**35**) in ten steps (Scheme 8).



Scheme 8

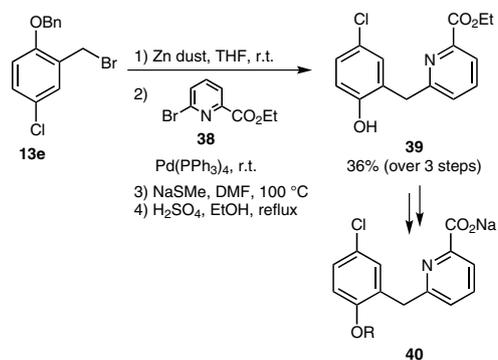
In 2011, D'Angelo et al. reported the discovery and optimization of a series of benzothiazole phosphoinositide 3-kinase inhibitors.¹⁷ During the structure–activity relationship (SAR) study, 4-(benzothiazol-6-yl)pyrimidine **36** was transformed into the benzylated analogue under standard cross-coupling conditions, providing **37** in a mere 11% yield (Scheme 9).



Scheme 9

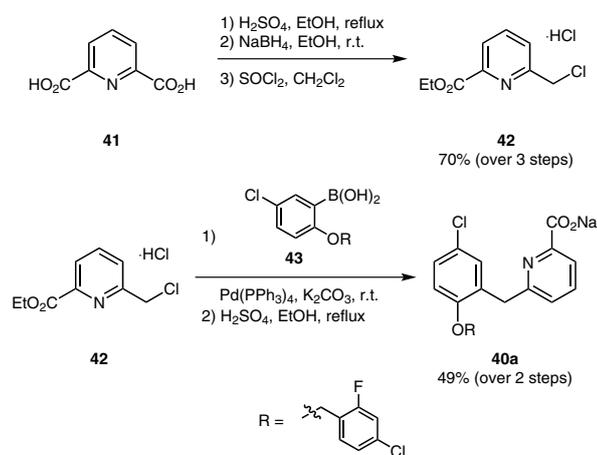
During their efforts to identify novel EP₁ antagonists for the treatment of inflammatory pain, Hall and co-workers reported the synthesis of a series of benzylated sodium picolinates **40**.¹⁸ Ethyl 6-benzyl-2-picolinate **39** was obtained in 36% overall yield by reaction of zinc with benzyl bromide **13e**, followed by a palladium-catalyzed Negishi reaction with ethyl 6-bromo-2-picolinate (**38**), deprotection with sodium methanethiolate and re-esterification. Alkylation of the phenol with different benzyl or alkyl halides followed by ester hydrolysis provided the desired substituted sodium picolinates **40** (Scheme 10).

After initial testing, the most active compound (**40a**) was subjected to more elaborate testing. Since the synthetic route depicted above was not suitable for large-scale synthesis of **42**, an alternative route, applying a Suzuki–Miyaura reaction as the key step, was developed. 2,6-Pyridinedicarboxylic acid (**41**) was first transformed in three steps into ethyl 6-chloromethyl-2-picolinate (**42**) in 70% overall yield; **42** was then further converted into the desired sodium picolinate **40a** in 49% overall yield by a palladium-catalyzed Suzuki–Miyaura cross-coupling



Scheme 10

reaction with boronic acid **43**, followed by hydrolysis of the ester (Scheme 11).

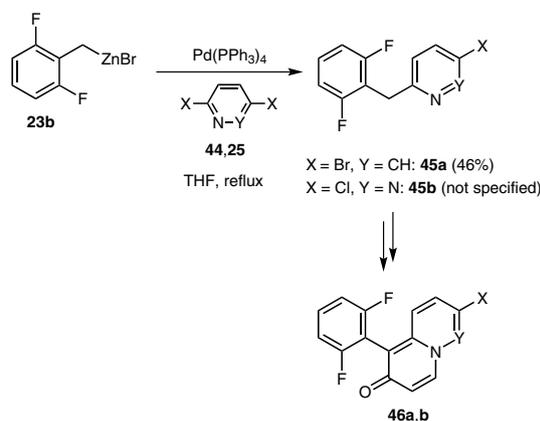


Scheme 11

During their research on 6*H*-pyrido[1,2-*b*]pyridazin-6-ones as potential p38 MAP kinase inhibitors, Tynebor et al. performed palladium-catalyzed Negishi reactions on 2,5-dibromopyridine (**44**) and 3,6-dichloropyridazine (**25**), employing (2,6-difluorobenzyl)zinc bromide (**23b**) as the organometallic reagent.¹⁹ The obtained halogenated benzylic coupling products **45a,b** were then transformed into the corresponding bromo- and chlorobicyclics **46a,b** in three steps. Displacement of the chloro or bromo substituent by nucleophilic substitution or by transition-metal-catalyzed reactions provided a set of functionalized products, thereby allowing a SAR study (Scheme 12).

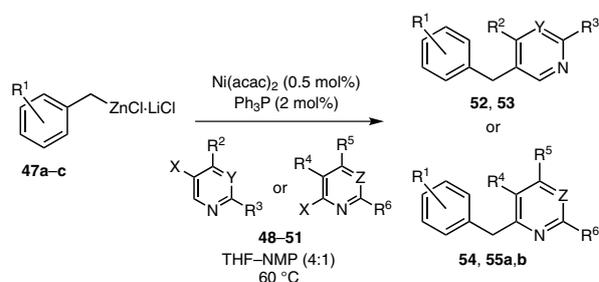
During the last decade, Knochel has published numerous papers on Negishi cross-coupling reactions in organic synthesis, including the use of benzylzinc reagents for the synthesis of diphenylmethanes, benzylated (di)azines and bis(heteroaryl)methanes.

In 2008, the Knochel group published their first communication on transition-metal-catalyzed cross-coupling reactions of benzylzinc reagents with (hetero)aromatic (pseudo)halides.²⁰ Functionalized benzylzinc chlorides



Scheme 12

47a–c were cross-coupled with (hetero)aryl chlorides, bromides and tosylates **48–51** using nickel catalysis. The benzylzinc chlorides **47** were obtained from the corresponding benzyl chlorides by direct insertion with zinc in the presence of lithium chloride.²¹ The corresponding benzylated pyridines and pyrimidines **52–55** were obtained in moderate to excellent yields (Scheme 13).

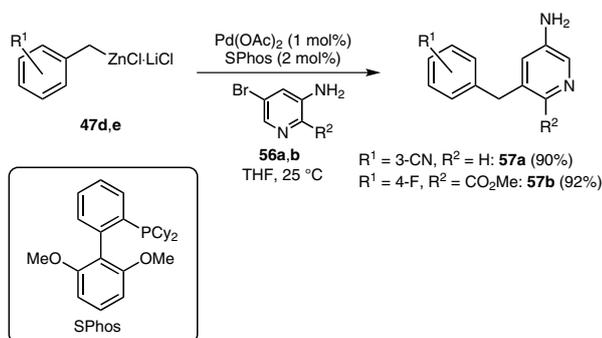


R¹ = 3,4,5-(OMe)₃, X = Br, Y = N, R² = R³ = OMe: **52** (63%)
R¹ = 3-COBu, X = OTs, Y = CH, R² = H, R³ = Me: **53** (84%)

R¹ = 3,4,5-(OMe)₃, X = Cl, Z = N, R⁴ = H, R⁵ = R⁶ = OMe: **54** (98%)
R¹ = 3-COBu, X = Cl, Z = CH, R⁴ = CO₂Et, R⁵ = R⁶ = H: **55a** (90%)
R¹ = 3-COMe, X = Cl, Z = CH, R⁴ = CO₂Et, R⁵ = R⁶ = H: **55b** (68%)

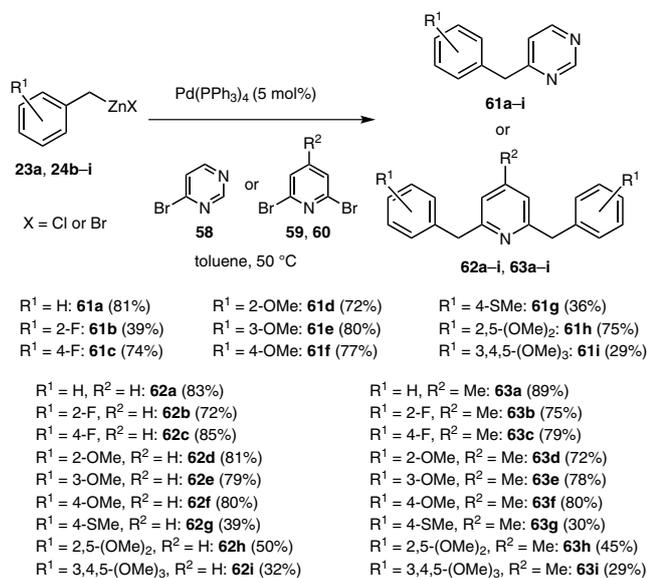
Scheme 13

In the same year, a full paper was published regarding palladium- and nickel-catalyzed cross-couplings of unsaturated halides bearing functional groups with relatively acidic protons with organozinc reagents.²² Alkyl-, aryl- and benzylzinc reagents were, for instance, allowed to react with halogenated anilines, phenols, benzylamines and benzyl alcohols in the presence of catalytic amounts of palladium or nickel. In this manner, 3-amino-5-bromopyridine (**56a**; R = H) and methyl 3-amino-5-bromopicolinate (**56b**; R = CO₂Me) reacted with (3-cyanobenzyl)zinc chloride (**47d**) and (4-fluorobenzyl)zinc chloride (**47e**), respectively, in excellent yields (Scheme 14).



Scheme 14

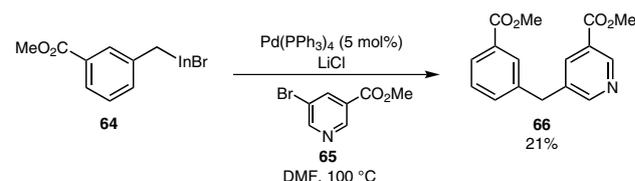
More recently, Czarnocki and co-workers reported the synthesis of a series of substituted 4-benzylpyrimidines **61** and 2,6-dibenzylpyridines **62** and **63**.²³ These compounds are well known as synthetic by-products in the illegal synthesis of amphetamine and its ring-substituted analogues. Commercially available benzylzinc reagents [$\text{R}^1 = \text{H}, 4\text{-F}, 2\text{-OMe}, 3\text{-OMe}, 4\text{-OMe}, 2,5\text{-(OMe)}_2$] and benzylzinc reagents [$\text{R}^1 = 2\text{-F}, 4\text{-SMe}, 3,4,5\text{-(OMe)}_3$] that were prepared according to the method of Knochel²¹ were cross-coupled with 4-bromopyrimidine (**58**), 2,6-dibromopyridine (**59**) and 2,6-dibromo-4-methylpyridine (**60**), respectively, using catalytic amounts of tetrakis(triphenylphosphine)palladium in toluene. The resulting (di)benzylated (di)azines were obtained in low to good yields (Scheme 15).



Scheme 15

2.2 Organoindium Reagents

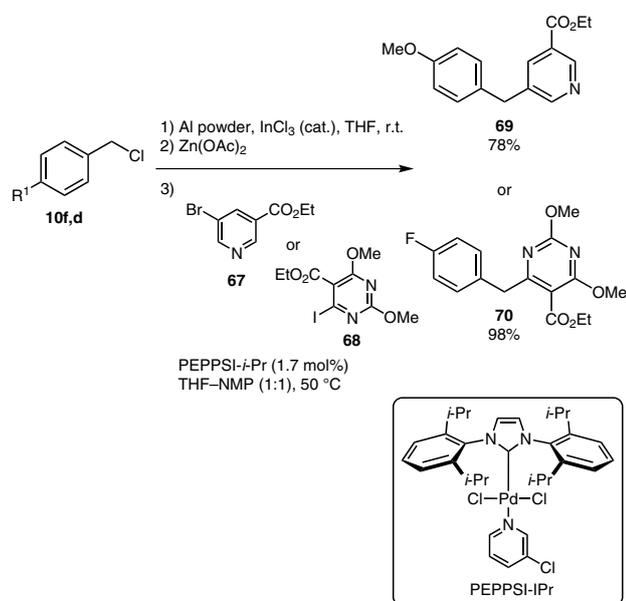
In a 2009 communication, Chupak et al. reported a palladium-catalyzed cross-coupling reaction of benzylindium reagents with aryl iodides.²⁴ The benzylindium reagents were prepared by direct insertion of indium into benzyl bromides in *N,N*-dimethylformamide at room temperature and were then coupled with a range of substituted aryl iodides by using a catalytic amount of tetrakis(triphenylphosphine)palladium, giving rise to a series of functionalized diphenylmethanes. In only one example, a heteroaryl bromide was used. In this particular case, (3-methoxycarbonylbenzyl)indium bromide (**64**) was coupled with methyl 5-bromonicotinate (**65**), providing benzylpyridine **66** in a poor 21% isolated yield (Scheme 16).



Scheme 16

2.3 Organoaluminum Reagents

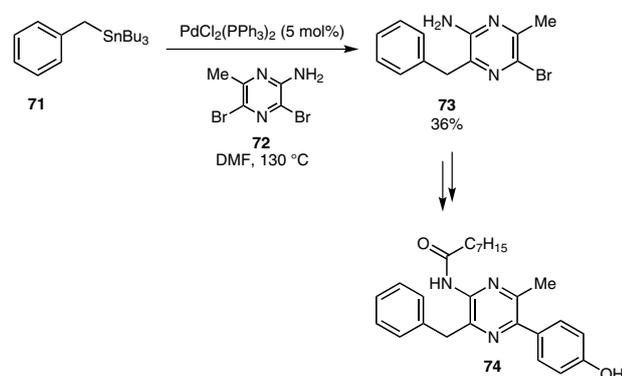
A 2011 publication by Knochel and co-workers reported the use of organoalanes in cross-coupling reactions. Functionalized benzyl chlorides were transformed into benzyl aluminum sesquichlorides by reaction with aluminum powder in the presence of catalytic amounts (3 mol%) of a metal chloride.²⁵ From the metal chlorides that were tested (PbCl_2 , BiCl_3 , TiCl_4 , InCl_3), indium(III) chloride proved to be superior in terms of yield of the aluminum sesquichlorides, without formation of benzil (1,2-diphenylethane) dimers. These new benzyl organometallic species were then, for instance, cross-coupled with (hetero)aryl and allyl halides using a PEPPSI-*i*Pr catalyst with zinc acetate as additive. The authors stated that the addition of stoichiometric amounts of zinc acetate appeared to be crucial in obtaining a cross-coupling reaction. They speculated that the acetate anion reduces the Lewis acidity of the aluminum species whereas the zinc cation favors the transfer of the aryl group to palladium. Under these conditions, (4-methoxybenzyl) chloride (**10f**) and (4-fluorobenzyl) chloride (**10d**) were first converted into the corresponding benzyl aluminum sesquichlorides and were then cross-coupled with ethyl 5-bromopyridine-3-carboxylate (**67**) and ethyl 4-iodo-2,6-dimethoxypyrimidine-5-carboxylate (**68**), respectively, giving rise to the benzylated products **69** and **70** in good to excellent yields (Scheme 17).



Scheme 17

2.4 Organotin Reagents – Migita–Kosugi–Stille Reaction

In 2006, Hirano and co-workers reported the bioluminescence of the calcium-activated photoproteins aequorin and obelin.²⁶ They used a palladium-catalyzed Migita–Kosugi–Stille reaction for the chemoselective coupling of 3,5-dibromo-6-methylpyrazin-2-amine (**72**) with benzyltributylstannane (**71**). The resulting benzylpyrazine **73** was obtained in 36% isolated yield and was then further converted into the desired pyrazine amide **74** in three steps (Scheme 18).

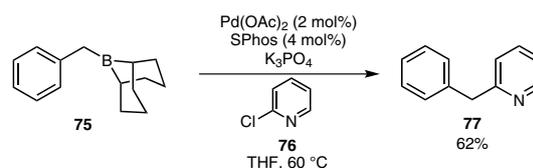


Scheme 18

2.5 Organoboron Reagents – Suzuki–Miyaura Reaction

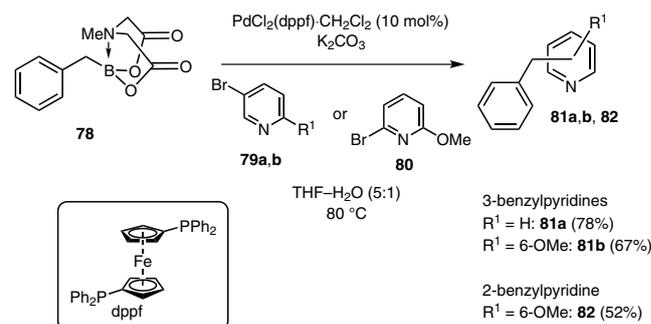
In 2005, Flaherty et al. reported the use of commercially available *B*-benzyl-9-BBN (**75**) as the coupling partner in a palladium-catalyzed Suzuki–Miyaura reaction.²⁷ Besides the synthesis of a range of substituted diphenylmethanes, 2-benzylpyridine (**77**) and 2-benzylquinoline were also prepared. 2-Chloropyridine (**76**) was coupled with **75**

in the presence of a catalytic amount of palladium(II) acetate and SPhos under anhydrous conditions, resulting in 2-benzylpyridine (**77**) in 62% isolated yield (Scheme 19).



Scheme 19

Very recently, in 2014, Yudin and co-workers used benzylic and aliphatic *N*-methyliminodiacetyl (MIDA) boronates in a palladium-catalyzed Suzuki–Miyaura cross-coupling reaction with functionalized (hetero)aryl bromides.²⁸ Tetrahedral boronates, like MIDA boronates and potassium trifluoroborates, circumvent possible side reactions (e.g., protodeborylation and β -hydride elimination) by coordinative saturation of the vacant p-orbital of boron. 3-Bromo- and 5-bromo-2-methoxypyridine (**79a,b**) and 2-bromo-6-methoxypyridine (**80**) were coupled with *B*-benzyl MIDA boronate **78** in moderate to good yields (Scheme 20).

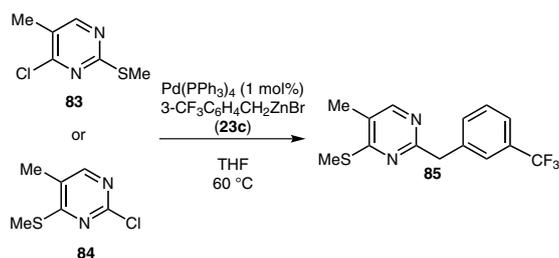


Scheme 20

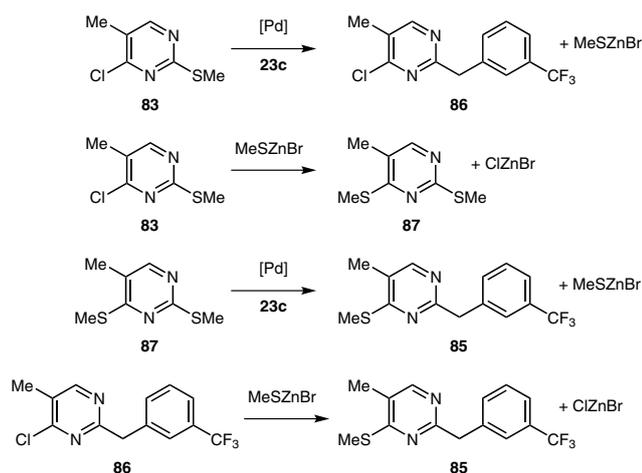
2.6 (Di)azinyl Methyl Thioether Reagents

In 2000, Casalnuovo and co-workers found that methylthio-substituted nitrogen heteroarenes are viable substrates for palladium-catalyzed cross-coupling reactions with benzylzinc species.²⁹ During their research on cereal herbicides, they envisioned that it should be possible for 4-chloro-2-(methylthio)pyrimidines to react chemoselectively with benzylzinc species, with the methylthio blocking group kept intact during the catalysis. Subsequently, this group would be oxidized to the sulfone and displaced with various nucleophiles. Much to their surprise, however, they noticed that the palladium-catalyzed benzylation of either 4-chloro-5-methyl-2-(methylthio)pyrimidine (**83**) or 2-chloro-5-methyl-4-(methylthio)pyrimidine (**84**) gave the same major 2-benzylpyrimidine regioisomer **85** (Scheme 21), although yields were not specified. In both cases the C-2 position proved to be more reactive towards oxidative addition than the C-4 position, also in the case of the methylthio substituent. Gas chromatographic anal-

ysis of the Negishi reaction of **83** revealed two intermediate compounds **86** and **87**, which explains the outcome of the reaction (Scheme 22).



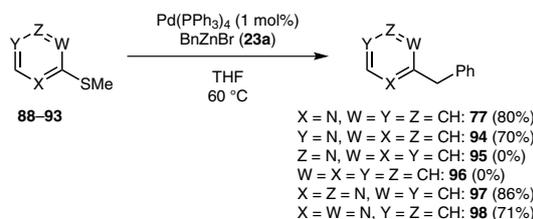
Scheme 21



Scheme 22

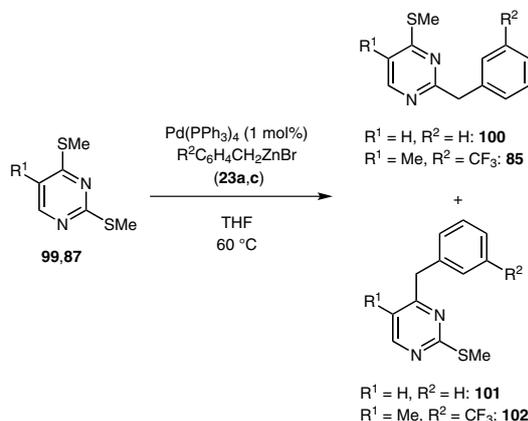
While the related nickel- and palladium-catalyzed cross-coupling of Grignard reagents with methylthio-substituted nitrogen heteroarenes was already known at that time, this Negishi cross-coupling was unprecedented. After the necessary control experiments, the reaction scope was explored. In contrast to the aforementioned Kumada reactions, the authors noticed that the methylthio group must occupy a position activated for nucleophilic substitution in order for cross-coupling to occur. While 2- and 4-(methylthio)pyridine (**88** and **89**) underwent the cross-coupling with benzylzinc bromide (**23a**) smoothly, 3-(methylthio)pyridine (**90**) and thioanisole (**91**) gave no cross-coupled product. Other methylthio-substituted nitrogen heteroarenes like (methylthio)pyrazine (**92**) and 2-(methylthio)pyrimidine (**93**), were readily converted into the corresponding benzylated products in good yields (Scheme 23).

To further investigate the unexpected regioselectivity of 4-chloro-5-methyl-2-(methylthio)pyrimidine (**83**), the authors treated 2,4-bis(methylthio)pyrimidine (**99**; $R^1 = H$) with an excess of benzylzinc bromide (**23a**) (Scheme 24). By performing gas chromatographic analysis of the initially formed products (i.e., at low conversion), they observed that the 2-methylthio group was 30 times more reactive than the 4-methylthio group (formation of **100** >

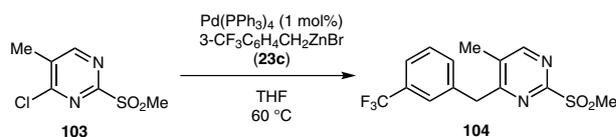


Scheme 23

101). With the methyl substituent *ortho* to the 4-methylthio group, for instance in the cross-coupling of 5-methyl-2,4-bis(methylthio)pyrimidine (**87**; $R^1 = Me$) with an excess of 3-(trifluoromethyl)benzyl zinc bromide (**23c**), the regioselectivity was increased even further, favoring benzylation in the C-2 position in a 500:1 ratio (formation of **85** >> **102**). Interestingly, when the Negishi reaction was applied to sulfone **103**, benzylation only took place at the 4-chloro group, even in the presence of two equivalents of the benzylzinc reagent (Scheme 25). These results offer new flexibility in designing regioselective synthesis routes for substituted heterocycles.



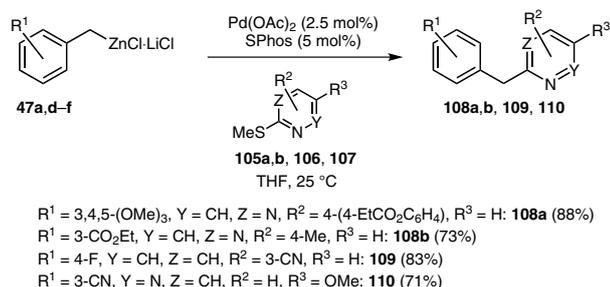
Scheme 24



Scheme 25

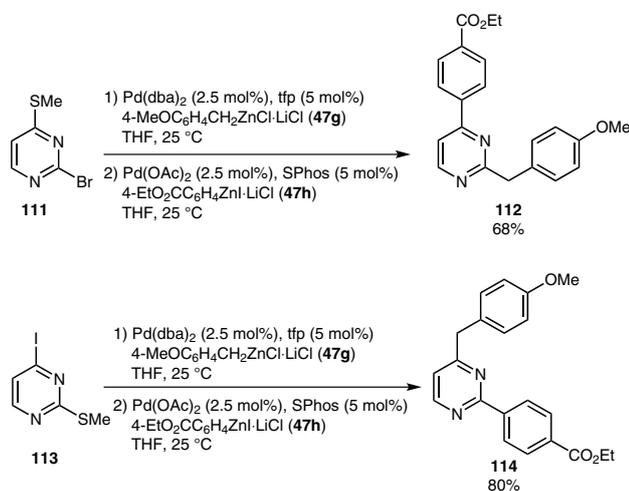
In 2009, the Knochel team reported a catalytic system that allowed for a palladium-catalyzed Negishi cross-coupling reaction with thiomethyl-substituted nitrogen heteroarenes at room temperature.³⁰ A set of substituted (benzo)(di)azinyl and (benzo)azolyl methyl thioethers were allowed to react with functionalized aryl-, alkyl- and benzylzinc reagents in tetrahydrofuran in the presence of catalytic amounts of palladium(II) acetate and SPhos. In this fashion, ethyl 4-[2-(methylthio)pyrimidin-4-yl]benzoate (**105a**), 4-methyl-2-(methylthio)pyrimidine (**105b**), 2-(methylthio)nicotinonitrile (**106**) and 3-methoxy-6-

(methylthio)pyridazine (**107**) were cross-coupled with functionalized benzylzinc reagents **47**, affording the benzylated (di)azines **108a,b**, **109**, and **110** in good yields (Scheme 26).



Scheme 26

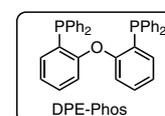
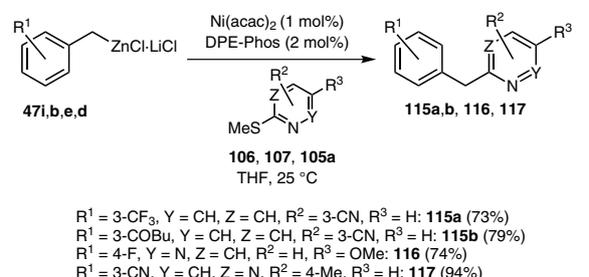
The authors were also able to do selective one-pot cross-coupling reactions at room temperature. Similar to the chemoselectivity observed by Casalnuovo, 2-bromo-4-(methylthio)pyrimidine (**111**) reacted selectively with (4-methoxybenzyl)zinc chloride (**47g**) at room temperature, with bis(dibenzylideneacetone)palladium(0) and tris(2-furyl)phosphine (tfp) as precatalyst system, then underwent a second Negishi reaction with 4-(ethoxycarbonyl)phenylzinc iodide (**47h**), with a palladium(II) acetate and SPhos precatalyst (Scheme 27). In this way the resulting 2,4-difunctionalized pyrimidine **112** was obtained regioselectively in 68% overall yield. Alternatively, under the same conditions, 4-iodo-2-(methylthio)pyrimidine (**113**) was transformed in the regioisomeric pyrimidine **114** in 80% yield over the two steps.



Scheme 27

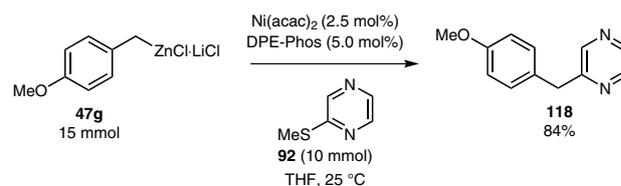
One year later, a follow-up paper was published by the same research group regarding the use of a less expensive nickel catalyst in place of the palladium(II) acetate and SPhos catalyst system.³¹ Optimization of the reaction conditions revealed that nickel(II) acetylacetonate in combination with DPE-Phos gave the best results. With a low catalyst loading of 1 mol%, and 2 mol% of the ligand, sev-

eral substituted (di)azinyl and azoyl methyl thioethers were allowed to react with functionalized aryl-, alkyl- and benzylzinc reagents in tetrahydrofuran at room temperature. Under the optimized conditions, 2-(methylthio)nicotinonitrile (**106**), 3-methoxy-6-(methylthio)pyridazine (**107**) and 4-methyl-2-(methylthio)pyrimidine (**105a**) were cross-coupled with functionalized benzylzinc reagents **47**, affording the benzylated (di)azines **115a,b**, **116** and **117** in good to excellent yields (Scheme 28).



Scheme 28

In the same year, Knochel and co-workers also published a study regarding the scalability of the Negishi cross-coupling protocol with thiomethyl-substituted nitrogen heteroarene substrates.³² For instance, using the nickel-catalyzed protocol mentioned above, the authors carried out the reaction of (4-methoxybenzyl)zinc chloride (**47g**) with (methylthio)pyrazine (**92**) using 2.5 mol% nickel(II) acetylacetonate and 5.0 mol% DPE-Phos in tetrahydrofuran at room temperature on a 10 mmol scale. The resulting (4-methoxybenzyl)pyrazine (**118**) was obtained in 84% isolated yield (Scheme 29).



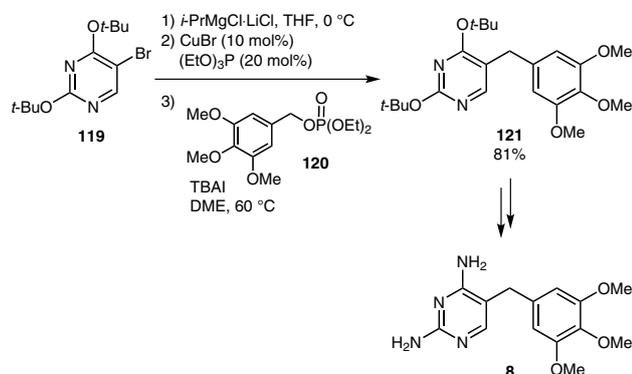
Scheme 29

3 Reaction of (Di)azinyl Organometallic Reagents with Benzyl (Pseudo)halides

3.1 Organomagnesium Reagents – Kumada Reaction

In 2006, Knochel's research group reported a copper-catalyzed cross-coupling reaction of arylmagnesium reagents with benzyl phosphates.³³ A range of unsymmetrical diphenylmethanes were prepared, as well as the synthetic antibiotic drug trimethoprim (**8**). For this purpose,

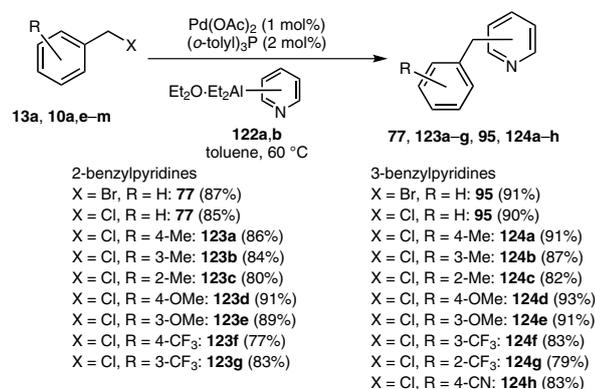
5-bromo-2,4-di(*tert*-butoxy)pyrimidine (**119**) was first magnesiated with isopropylmagnesium chloride–lithium chloride complex, then underwent a copper-catalyzed cross-coupling reaction with diethyl 3,4,5-trimethoxybenzyl phosphate (**120**). The resulting benzylated pyrimidine **121** was obtained in 81% yield and was then further transformed into antibiotic **8** in three steps (Scheme 30).



Scheme 30

3.2 Organoaluminum Reagents

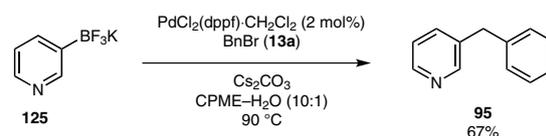
Early in 2014, Zhou published a paper on the palladium-catalyzed cross-coupling of heteroaromatic dialkylalane etherates [ArAlR₂(OEt₂)] with (hetero)aromatic (R = Me) and benzylic halides (R = Et).³⁴ The organoaluminum compounds **122a,b** were prepared by lithiation of the corresponding heteroaryl bromide with butyllithium in diethyl ether, followed by quenching with dimethyl- or diethylaluminum chloride. For simplicity reasons, the organoalanes are represented as (heteroaryl)Al(alkyl)·Et₂O, although the compounds exist as four different species [heteroaryl_x(alkyl)_{3-x}·Et₂O, with x = 0–3] in solution. A combination of 1 mol% palladium(II) acetate and 2 mol% tri(*o*-tolyl)phosphine proved to be optimal for the cross-coupling of diethylpyridin-2-yl- and diethylpyridin-3-ylalane etherates **122** with a range of substituted benzyl chlorides **10a,e–m** and benzyl bromide (**13a**) in good to excellent yields (Scheme 31).



Scheme 31

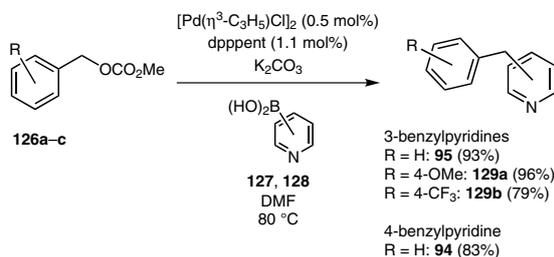
3.3 Organoboron Reagents – Suzuki–Miyaura Reaction

In 2006, Molander and Elia disclosed the use of potassium (hetero)aryltrifluoroborates in combination with benzyl halides for the synthesis of diphenylmethanes using PdCl₂(dppf)·CH₂Cl₂ as pre-catalyst.³⁵ An example of the synthesis of a benzylpyridine is the coupling of benzyl bromide (**13a**) with potassium pyridin-3-yltrifluoroborate (**125**) in a mixture of cyclopentyl methyl ether (CPME) and water (Scheme 32). In this fashion, 3-benzylpyridine (**95**) was obtained in 67% isolated yield.



Scheme 32

One year later, Kuwano and Yu reported a palladium-catalyzed decarboxylative Suzuki–Miyaura reaction of benzyl carbonates with heteroarylboronic acids.³⁶ A small set of functionalized benzylcarbonates **126** was, for instance, coupled with pyridin-3-yl- and pyridin-4-ylboronic acids (**127** and **128**) in the presence of a catalytic amount of allylpalladium chloride dimer with 1,5-bis(diphenylphosphino)pentane (dppppent) as the ligand, thereby providing the corresponding 3- and 4-benzylpyridines in good to excellent yields (Scheme 33).

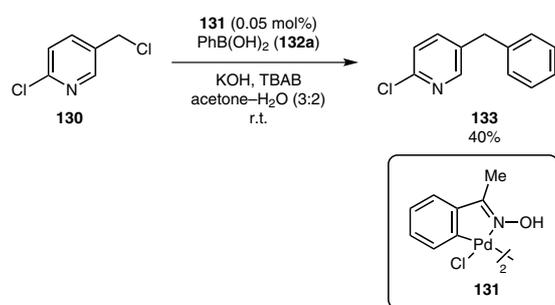


Scheme 33

4 Reaction of (Di)azinylmethyl Halides with Aryl Organometallic Reagents

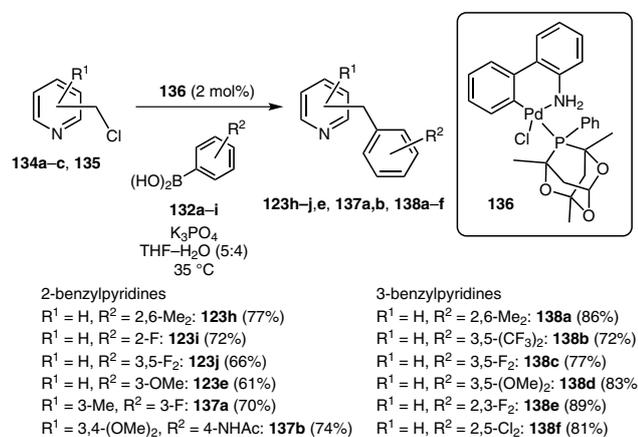
4.1 Organoboron Reagents – Suzuki–Miyaura Reaction

In 2002, Nájera and Botella reported the use of oxime-derived palladacycles for Suzuki–Miyaura cross-coupling reactions in acetone–water mixtures.³⁷ A range of chloro(methyl)- and bromo(methyl)(hetero)arenes were coupled with aromatic and aliphatic boronic acids in the presence of a catalytic amount of the palladacycle. In one example, 2-chloro-5-(chloromethyl)pyridine (**130**) reacted with phenylboronic acid (**132a**), with only 0.05 mol% of palladacycle **131**, to provide 5-benzyl-2-chloropyridine (**133**) in 40% isolated yield (Scheme 34).



Scheme 34

More recently, in 2013, Tudge and Schmink published a paper on the use of a palladium aminobiphenyl pre-catalyst³⁸ **136** for the Suzuki–Miyaura cross-coupling of arylboronic acids with chloromethylpyridines and chloromethylazoles (not shown).³⁹ For example, a series of functionalized 2- and 3-chloromethylpyridines **134** and **135** were coupled with different arylboronic acids **132** in moderate to good yields (Scheme 35).



Scheme 35

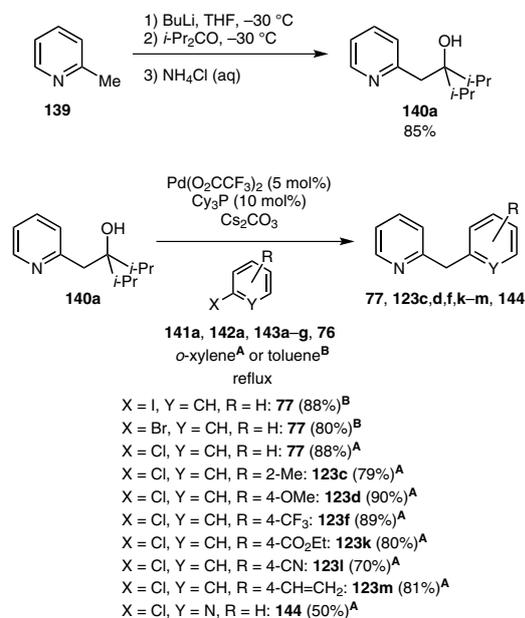
5 Reaction of Methyl(di)azine Reagents with Aryl Halides

This section, covering the reaction of methyl(di)azines with aryl (pseudo)halides, is divided into three parts. In cases where the pre-activated methyl(di)azines are isolated, they are considered under the category of pre-activation. On the other hand, where the pre-activation takes place in situ, without intermediate isolation, this is treated as in situ pre-activation. Finally, where the methyl(di)azines are arylated as such, they are labeled as direct arylation.

5.1 Pre-activation of Methyl(di)azines

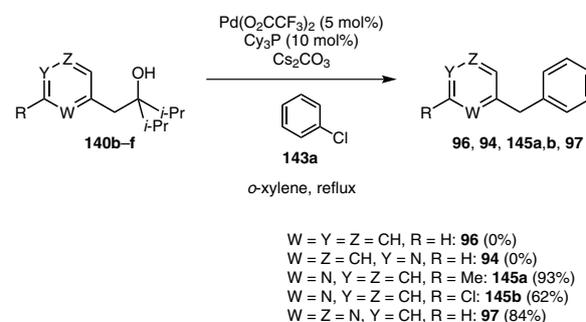
The first publication on the use of methyl(di)azines as reagents for the synthesis of aryl(di)azinylmethanes appeared in 2007. In it, Oshima reported the palladium-catalyzed pyridin-2-ylmethyl transfer from 2-(pyridin-2-yl)ethanol derivatives to organic halides by chelation-

assisted cleavage of unstrained C_{sp3}–C_{sp3} bonds.⁴⁰ 2-Methylpyridine (**139**) was first activated by being transformed into 2,4-dimethyl-3-(pyridin-2-ylmethyl)pentan-3-ol (**140a**) in 85% yield. Then **140a** was subjected to reaction with a series of substituted (hetero)aryl halides, in the presence of 5 mol% of palladium(II) trifluoroacetate, 10 mol% tricyclohexylphosphine and 1.2 equivalents of cesium carbonate in refluxing *o*-xylene (Scheme 36). The resulting (aryl)(di)azinylmethanes were obtained in good to excellent yields.



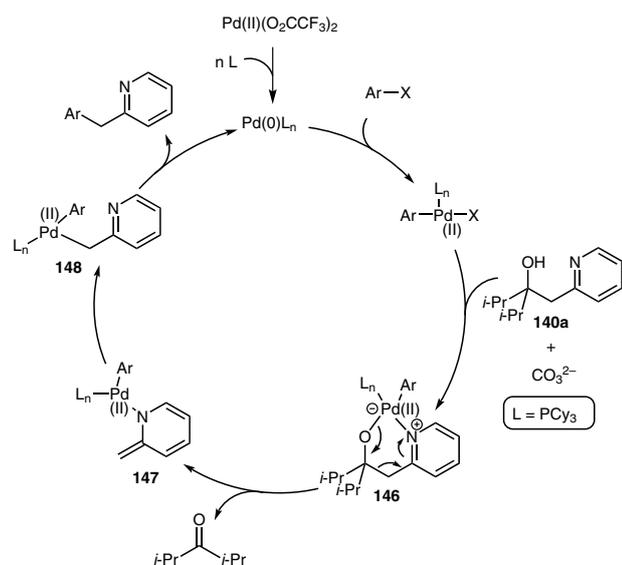
Scheme 36

During the investigation of the reaction scope, it became apparent that the presence of the α -nitrogen was crucial for the cross-coupling to take place. The use of 2,4-dimethyl-3-(benzyl)pentan-3-ol (**140b**) and 2,4-dimethyl-3-(pyridin-4-ylmethyl)pentan-3-ol (**140c**) resulted only in the recovery of starting alcohols, while other α -nitrogen-containing substrates like 2,4-dimethyl-3-(6-methylpyridin-2-ylmethyl)pentan-3-ol (**140d**), 2,4-dimethyl-(6-chloropyridin-2-ylmethyl)pentan-3-ol (**140e**), and 2,4-dimethyl-3-(pyrazinylmethyl)pentan-3-ol (**140f**) underwent the reaction readily, providing the corresponding benzyl(di)azines in good to excellent yields (Scheme 37).



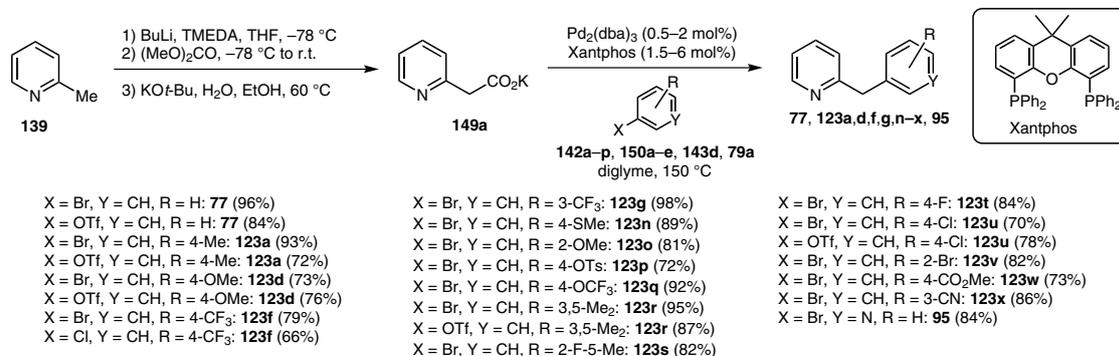
Scheme 37

Based on these results, a mechanistic pathway was proposed (Scheme 38). After in situ reduction of the palladium pre-catalyst and oxidative addition to the aryl halide, ligand exchange takes place to afford the palladium-alkoxide complex **146** through coordination of the basic nitrogen to the palladium center. Coordination facilitates the cleavage of the C_{sp3}-C_{sp3} bond, which affords palladium amide **147**. After isomerization, driven by re-aromatization of the pyridine moiety, complex **148** undergoes reductive elimination, providing the desired product as well as simultaneous regeneration of the palladium catalyst.



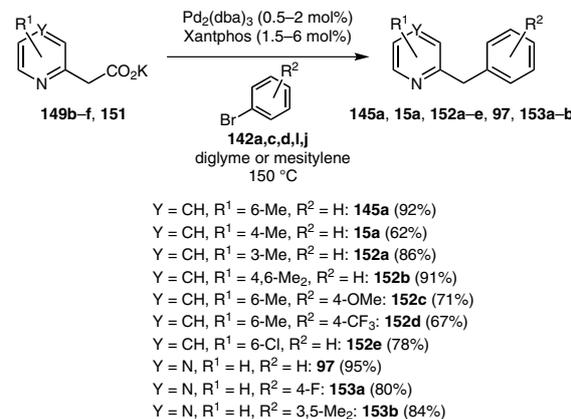
Scheme 38

In 2010, a communication by the Liu research group⁴¹ appeared, following a strategy similar to that used by Oshima.⁴⁰ While the latter used di(isopropyl) ketone as a leaving group, the Liu process involved expulsion of carbon dioxide. 2-Methylpyridine (**139**) was first transformed into potassium 2-(pyridin-2-yl)acetate (**149a**) in two steps and was then coupled with a range of (hetero)aryl bromides and -triflates (Scheme 39). The resulting (aryl)(di)azinylmethanes were obtained in good to excellent yields.



Scheme 39

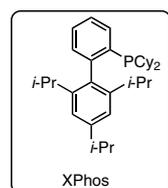
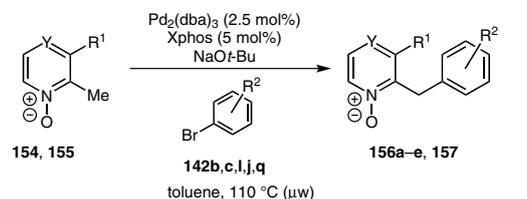
The advantages associated with this coupling protocol, in comparison to the Oshima strategy, are the lower catalyst loading [0.5–2 mol% of Pd₂(dba)₃, with 1.5–6 mol% of Xantphos] and the fact that no base is required in the palladium-catalyzed cross-coupling reaction. Using this procedure, a range of substituted potassium 2-(pyridin-2-yl)-, pyrazinyl- and (quinolin-2-yl)acetates as well as sodium benzoxazol-2-yl- and benzothiazol-2-ylacetates were smoothly coupled with substituted aryl bromides. The 2-benzylpyridine and benzylpyrazine products were obtained in good to excellent yields (Scheme 40).



Scheme 40

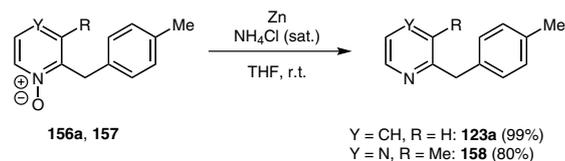
In 2008, Fagnou and co-workers communicated on a site-selective sp² and/or benzylic sp³ palladium-catalyzed arylation of 2-methyl(di)azine *N*-oxides.⁴² During this research, the authors noticed that lower yields were encountered with substrates bearing methyl substituents adjacent to the *N*-oxide moiety. By careful choice of the conditions [5 mol% Pd(OAc)₂, 5 mol% (*t*-Bu)₃P, 1.05 equiv K₂CO₃, toluene, reflux], sp³ arylation could be avoided and only (hetero)arylated 2-picoline *N*-oxides were obtained. The authors envisioned that it also should be possible to reverse the sp²-sp³ selectivity by re-optimizing the catalyst/ligand system and the base. Indeed, the use of 2.5 mol% Pd₂(dba)₃, 5 mol% XPhos and 3 equivalents of sodium *tert*-butoxide in refluxing toluene under microwave heating gave exclusively sp³-arylation.

Under these conditions, a set of substituted aryl halides **142** were coupled with 2-methylpyridine *N*-oxide (**154**) and 2,3-dimethylpyrazine *N*-oxide (**155**). The corresponding 2-benzyl(di)azine *N*-oxides (**156a–e**, **157**) were obtained in good yields (Scheme 41). The 2-benzyl(di)azine *N*-oxides could be deoxygenated easily, as exemplified by the reduction of **156a** and **157** (Scheme 42).



Y = CH, R¹ = H, R² = 4-Me: **156a** (89%)
Y = CH, R¹ = H, R² = 4-OMe: **156b** (72%)
Y = CH, R¹ = H, R² = 4-F: **156c** (72%)
Y = CH, R¹ = H, R² = 3,5-Me₂: **156d** (64%)
Y = CH, R¹ = H, R² = 3,5-(OMe)₂: **156e** (70%)
Y = N, R¹ = Me, R² = 4-Me: **157** (79%)

Scheme 41

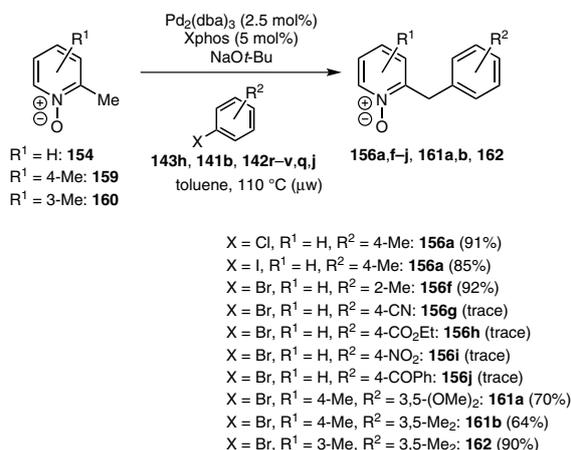


Scheme 42

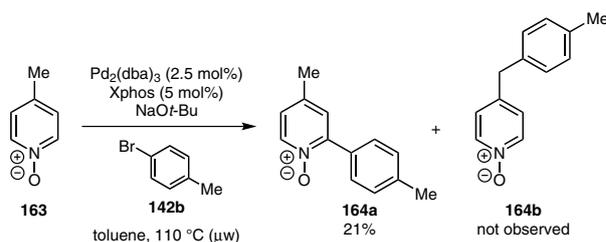
One year later, the same authors published a follow-up paper on the site-selective sp^3 -arylation.⁴³ It was found that besides aryl bromides, aryl chlorides and iodides could also be used as coupling partners. While electron-donating groups (e.g., Me, OMe) on the aryl halide were well tolerated, the presence of electron-withdrawing groups (e.g., CN, CO₂Et, NO₂, C₆H₄) on the aryl halide led to only traces of the benzylated products. Methyl substituents on the picoline *N*-oxide did not hamper the reaction (Scheme 43).

Notably, in the case of **159**, where the methyl substituents are in positions α and γ to the nitrogen, the reaction proceeds exclusively on the C-2 methyl group, suggesting the influence of the *N*-oxide moiety on the regioselectivity (Scheme 43). In a control experiment, where 4-picoline *N*-oxide (**163**) was subjected to the optimized conditions, only sp^2 -arylated product **164a** was observed (Scheme 44).

Based on these results and on the observation that the choice of base (K₂CO₃ vs. NaOt-Bu) has a great influence on the site-selectivity of the reaction, the authors proposed a mechanism (Scheme 45). The active palladium(0) catalyst oxidatively inserts into the aryl halide bond, providing intermediate **165**. The next step, palladation of the



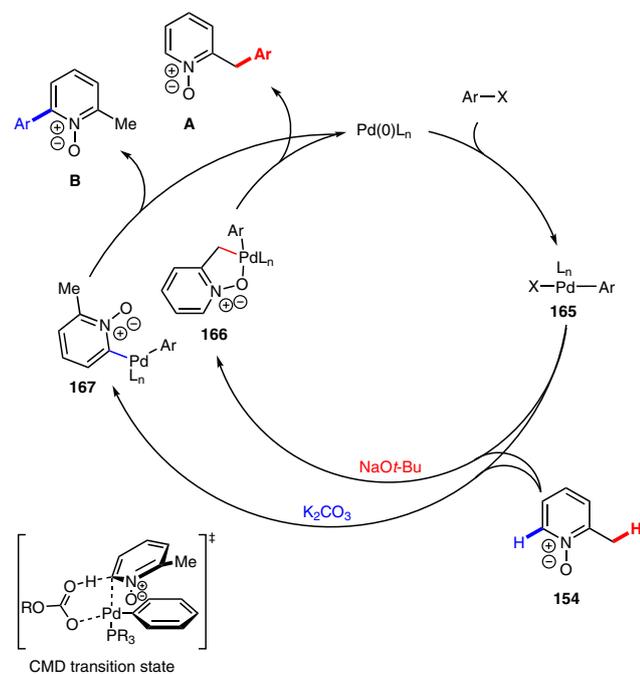
Scheme 43



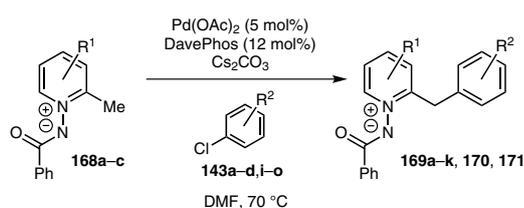
Scheme 44

N-oxide, determines the site-selectivity and is base-dependant. With sodium *tert*-butoxide, the stronger base, the most acidic sp^3 2-methyl position is deprotonated to yield palladacycle **166**. Potassium carbonate, on the other hand, is not strong enough to deprotonate the 2-methyl position, but it does allow a six-membered transition state (concerted metalation–deprotonation pathway) to activate the sp^2 position, which gives rise to complex **167**. Both intermediates **166** and **167** undergo reductive elimination to form products **A** and **B**, respectively, as well as the palladium(0) catalyst.

During the same period, a paper by the Charette research group was published on the sp^3 arylation of *N*-imino-2-methylpyridinium ylides.⁴⁴ In the course of their research on the sp^2 arylation of *N*-iminopyridinium ylides, the authors had made the same observation as Fagnou.⁴² When a methyl group adjacent to the quaternized nitrogen was present, the yields of sp^2 arylation dropped and those of sp^3 arylation increased. The optimal conditions for the sp^3 arylation were found to be 5 mol% palladium(II) acetate, 12 mol% DavePhos and 3 equivalents of cesium carbonate in *N,N*-dimethylformamide at 70 °C. The use of a carbonate base is in contrast to Fagnou's work, where a stronger base was needed for sp^3 arylation and potassium carbonate promoted sp^2 arylation. A series of (substituted) *N*-imino-2-methylpyridinium ylides **168a–c** were coupled in this way with functionalized aryl halides **143**, giving rise to the corresponding benzylated products in moderate to excellent yields (Scheme 46).

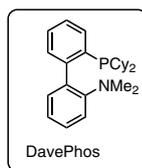


Scheme 45



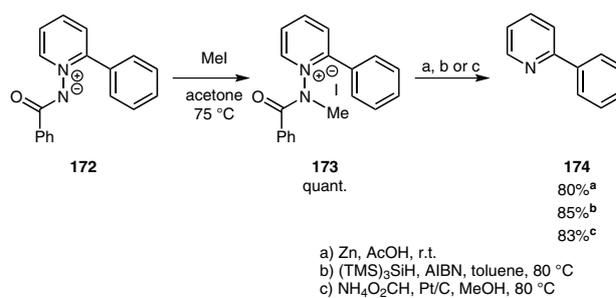
R¹ = H, R² = H: **169a** (86%)
 R¹ = H, R² = 2-Me: **169b** (93%)
 R¹ = H, R² = 4-OMe: **169c** (69%)
 R¹ = H, R² = 4-CF₃: **169d** (64%)
 R¹ = H, R² = 4-Me: **169e** (72%)
 R¹ = H, R² = 4-NHBoc: **169f** (48%)
 R¹ = H, R² = 3-Me: **169g** (76%)

R¹ = H, R² = 4-F: **169h** (94%)
 R¹ = H, R² = 4-CO₂Me: **169i** (72%)
 R¹ = H, R² = 2-CO₂Me: **169j** (43%)
 R¹ = H, R² = 4-COPh: **169k** (71%)
 R¹ = 5-Me, R² = H: **170** (43%)
 R¹ = 3-Me, R² = H: **171** (92%)



Scheme 46

Reduction of the *N*-imino-2-benzylpyridinium ylide was not shown in that report. The authors only mentioned the reduction of an *N*-imino-2-arylpicolinium ylide in their previous paper on sp² arylation.⁴⁵ Quantitative methylation of the imino nitrogen of **172** with iodomethane, followed by treatment of the obtained salt **173** with zinc dust in acetic acid, with tris(trimethylsilyl)silane and azobisisobutyronitrile, or with ammonium formate and platinum on carbon, afforded the desired product **174** in good yield (Scheme 47).



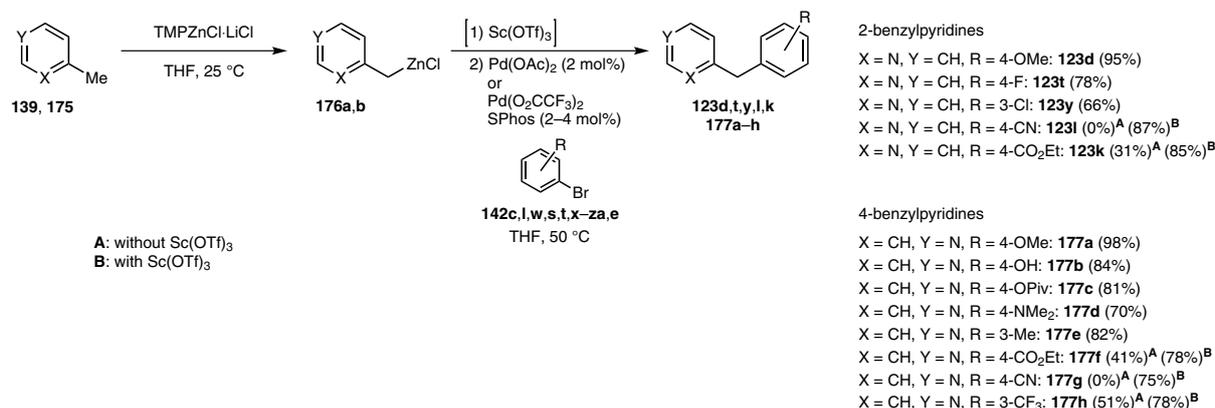
Scheme 47

5.2 In Situ Pre-activation of Methyl(di)azines

In 2011, Knochel and co-workers reported the Lewis acid promoted benzylic cross-couplings of in situ activated methylpyridines with aryl bromides.⁴⁶ The authors stated that one of the problems regarding the direct arylation of 2-picoline (**139**) may be the structure of the oxidative addition complex: chelation of the heterocyclic sp² nitrogen to the electrophilic palladium(II) center might hamper the reductive elimination step. It was anticipated that the presence of a Lewis acid complexing the nitrogen would lead to a faster reductive elimination, providing the cross-coupled products.

For this purpose, 2-picoline (**139**) was first zincated with two equivalents of TMPZnCl·LiCl, a base bearing a Lewis acidic metal center which was already known to be compatible with other strong Lewis acids like magnesium chloride and boron trifluoride diethyl etherate, giving rise to pyridin-2-ylmethylzinc chloride (**176a**; X = N, Y = CH). This organozinc compound was then cross-coupled with a series of functionalized aryl bromides **142** using 2 mol% palladium(II) acetate and 2–4 mol% SPhos in tetrahydrofuran at 50 °C. While the aryl bromides bearing electron-donating substituents (R = OMe, F, Cl) were coupled in good to excellent yields, those bearing electron-withdrawing substituents (CN, CO₂Et) gave unsatisfactory yields of the functionalized 2-benzylpyridines **123** (Scheme 48). The use of 10 mol% of the stronger Lewis acid scandium(III) triflate gave a more efficient reaction, presumably due to the aforementioned acceleration of the reductive elimination. In this fashion, aryl bromides **142s,t** bearing electron-withdrawing substituents (**142s,t**) were also coupled in good to excellent yields (Scheme 48).

While none of the previous methods based on the arylation of pre-activated methyl(di)azines were able to perform a cross-coupling γ to the heterocyclic nitrogen, the present procedure does allow the use of 4-picoline (**175**) as a substrate. Under the optimized conditions, **175** could be efficiently zincated by 1.5 equivalents of TMPZnCl·LiCl, followed by cross-coupling with a range of substituted aryl bromides **142** (Scheme 48). In the case of electron-deficient aryl bromides, the use of scandium(III) triflate again had a beneficial effect on the isolated yield.



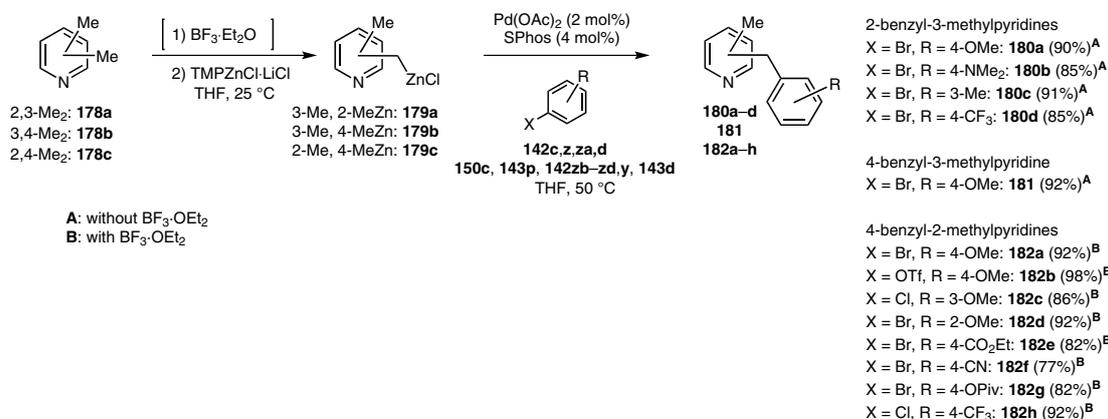
Scheme 48

The authors subsequently studied the regioselective arylation of lutidines. In the case of 2,3-lutidine (**178a**) and 3,4-lutidine (**178b**), zincation with TMPZnCl·LiCl occurred exclusively at the 2- and 4-position, respectively, leading to the corresponding disubstituted pyridines **180a–d** and **181** after palladium-catalyzed arylation with functionalized aryl bromides **142** (Scheme 49). With 2,4-lutidine (**178c**), the zincation produced a 2:1 mixture of regioisomers. The addition of 1.1 equivalents of boron trifluoride diethyl etherate prior to that of the zincating reagent directs the zincation only at the 4-position, since the complexation of boron trifluoride diethyl etherate at the sp² nitrogen hampers the metalation at the 2-position for steric reasons. The resulting (2-methylpyridin-4-yl)methylzinc chloride (**179c**) was then cross-coupled with a series of functionalized aryl bromides **142**, chlorides **143** and triflate **150c**, providing the 4-benzyl-2-methylpyridines **182a–h** regioselectively in good to excellent yields (Scheme 49).

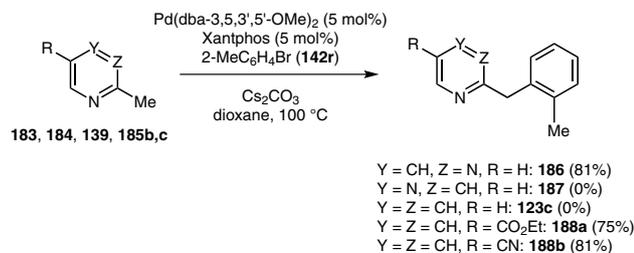
5.3 Direct Arylation of Methyl(di)azines

The first direct arylation (without pre-activation of the substrate) of methyl(di)azines was established by Morris

and Burton in 2010.⁴⁷ During their ongoing research on naphthyridines, the authors sought to prepare 2-benzyl-1,8-naphthyridines at a late stage in the synthesis. After promising exploratory studies, the authors performed an optimization of the coupling conditions. It was found that 2.5–5 mol% of the Fairlamb pre-catalyst Pd[3,5,3',5'-(MeO)₄-dba]₂, 2.5–5 mol% Xantphos and 2 equivalents of cesium carbonate in dioxane at 100 °C gave the best results with regard to reactivity and selectivity between mono- and bisarylation. A range of (substituted) 2-methyl-1,8-naphthyridines were coupled in this way, with (functionalized) aryl iodides, bromides and triflates, while aryl chlorides gave no reaction. In another phase, it was tested whether methyl(di)azines would undergo the same reaction. While 4-methylpyrimidine (**183**) was coupled efficiently with 2-bromotoluene (**142r**) in 81% isolated yield, 2-methylpyrazine (**184**) and methylpyridine (**139**) gave none of the desired benzylated product (Scheme 50). Introduction of an electron-withdrawing group at the 5-position of the 2-methylpyridine allowed the reaction to proceed well, providing the substituted 2-benzylpyridines **188a,b** in good yields. Apparently, the acidity of the methyl C–H is crucial for the reaction to take place.



Scheme 49



Scheme 50

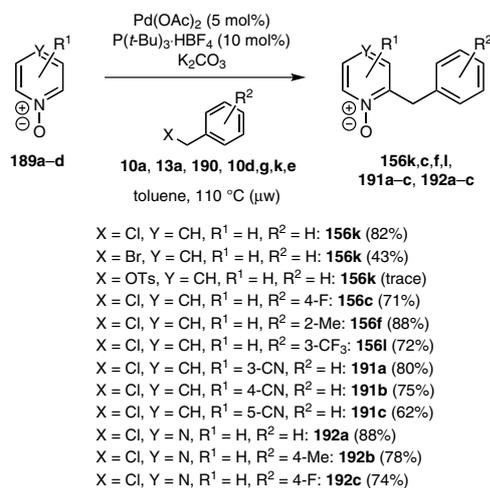
One year later, Li and co-workers reported the palladium-catalyzed arylation of methylbenzazoles (benzimidazole, benzoxazole and benzothiazole) and methyl(benzo)(di)azines (pyridine, pyrazine, pyrimidine, pyridazine and quinoline),⁴⁹ based on the same principle as Morris.⁴⁷ With a stronger base (NaOt-Bu vs Cs₂CO₃) in *o*-xylene at 130 °C, predominantly diarylation occurred. This was later optimized to provide only diarylation, resulting in the corresponding diaryl(di)azinylmethanes. Although a stronger base principally allows for the arylation of less acidic methylenes, overarylation unfortunately becomes the major reaction.

6 Reaction of (Di)azine *N*-Oxides with Benzyl (Pseudo)halides

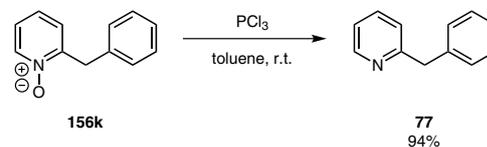
Based on the work of the Fagnou team (vide supra),⁴² Mai prepared a set of benzylated (di)azine *N*-oxides by the coupling of (di)azine *N*-oxides with benzyl halides.⁵⁰ During the optimization, the authors noticed that benzyl chloride (**10a**) as coupling partner gave a superior isolated yield (82%) in comparison with benzyl bromide (**13a**, 43%), while benzyl tosylate (**190**) only gave a trace amount of product (Scheme 51). The combination of 5 mol% palladium(II) acetate, 10 mol% P(*t*-Bu)₃·HBF₄ and potassium carbonate in refluxing toluene proved to be the optimal coupling conditions. In this manner, a range of (substituted) (di)azine *N*-oxides **189** were coupled with functionalized benzyl chlorides **10**. The corresponding 2-benzyl(di)azine *N*-oxides **156**, **191** and **192** were obtained in good yields (Scheme 51). A control experiment, where the coupling conditions were applied to pyridine, gave no 2-benzylpyridine (**77**), proving the necessity of the activating *N*-oxide moiety. The coupled products were easily deoxygenated as exemplified in Scheme 52 by the reduction of **156k** into 2-benzylpyridine (**77**).

7 Conclusion

In the last decade, many efforts have been made regarding the synthesis of functionalized aryl(di)azinylmethanes via transition-metal-catalyzed cross-couplings, with the majority of them based on the Negishi reaction. A great contribution to this field was made by the Knochel group, with a number of important publications on the practical preparation of (highly) functionalized benzylzinc halides



Scheme 51



Scheme 52

as well as their further palladium- or nickel-catalyzed cross-coupling with a variety of (di)azinyll (pseudo)halides and (di)azinyll methyl thioethers. This makes the Negishi reaction attractive for library build-up. On the other hand, the Negishi reaction demands anhydrous conditions, which is not required for the more stable, less demanding organometallics based on, for example, boron and tin. However, reports on the use of the latter two metals to prepare the aryl(di)azinyllmethane motif are surprisingly scarce, consequently their (general) applicability remains unfortunately unknown. It should also be noted that all transition-metal-catalyzed cross-couplings for aryl(di)azinyllmethane synthesis are based on palladium or nickel catalysts, with only one exception based on copper.

The coupling of (in situ) pre-activated methyl(di)azines with aryl halides provides a more straightforward approach to the desired aryl(di)azinyllmethanes. As mentioned in the introduction, a range of methyl(di)azines are easily accessible from condensation reactions or from natural feedstocks, making them valuable alternatives to their halogenated counterparts. Moreover, this approach easily allows the synthesis of bis(di)azinyllmethanes, while no other transition-metal-catalyzed reactions are reported to construct these scaffolds. If one compares the different coupling strategies from (in situ) pre-activated methyl(di)azines, the procedures published by Fagnou, Charette and Mai are generally the least attractive. The substrates, α -methyl(di)azines, have to be activated, cross-coupled and then de-activated to yield the desired

aryl(di)azinylmethanes. On the other hand, the (di)azine *N*-oxides can be deoxygenated via simultaneous (di)azine functionalization providing an extra derivatization tool which can be advantageous in specific cases.⁵¹ The procedures published by Oshima and Liu are mechanistically closely related to each other and offer good functional group tolerance, making them well-suited for the synthesis of functionalized aryl(di)azin-2-ylmethanes and bis(di)azinylmethanes, with the disadvantage that here, also, a separate activation step is required and an α -nitrogen atom is an essential structural element. The protocol proposed by Knochel definitely has the best generality, in terms of substrate scope and availability (α - and γ - to nitrogen; use of aryl chlorides, bromides and tosylates) and functional group tolerance. Nevertheless, in situ pre-activation still requires stoichiometric metalating agents, Lewis acids and anhydrous conditions. The protocol reported by Morris is methodologically by far the most appealing as it is the only 'true' direct arylation protocol hitherto available. It is, however, not general as the substrates need a certain degree of electron deficiency for the reaction to take place, and this limits its scope significantly. Although a lot has already been achieved in this field, the authors believe that there is still room for further improvement in the direct arylation of methyl(di)azines. Extending the scope of the Morris procedure to more electron-rich methyl(di)azines, avoiding overarylation, would have the largest impact on aryl(di)azinylmethane and bis(di)azinylmethane formation.

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