

sp³-sp³ Coupling reactions in the synthesis of natural products and biologically active molecules

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 This *Highlight* covers the current status of relatively unexplored sp³-sp³ cross-coupling reactions with particular focus on natural product and related syntheses.

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1 Introduction

Transition metal catalysed cross-coupling reactions have had a huge impact on natural product synthesis and medicinal chemistry. Particularly, cross-coupling methodologies between sp² centred reactants have changed retrosynthetic analysis, because until then no reliable methods were available to construct oligoenes by creating a single bond between alkenes or arenes. Consequently, the Nobel Prize Award for Chemistry in 2010 was given to Suzuki, Negishi and Heck for their pioneering work mainly on palladium-catalysed cross-coupling chemistry.¹

Besides C-H activation, metal catalysed sp³-sp³ cross-coupling reactions are particularly challenging and while what is called C-H activation is currently intensely explored, only slow progress has been made in the latter field. From a historical point of view the Wurtz reaction was one of the first alkyl-alkyl coupling reactions. Unfortunately the Wurtz reaction is limited to the synthesis of symmetric alkanes due to the uncontrolled radical mechanism of the reaction.

In this *Highlight* we provide an overview of sp³-sp³ couplings in the synthesis of natural products and related molecular targets, after some mechanistic considerations on cross-coupling reactions at sp³ centres have been covered.

2 Mechanistic aspects relevant in sp³-sp³ cross-coupling reactions

2.1 Palladium catalysis

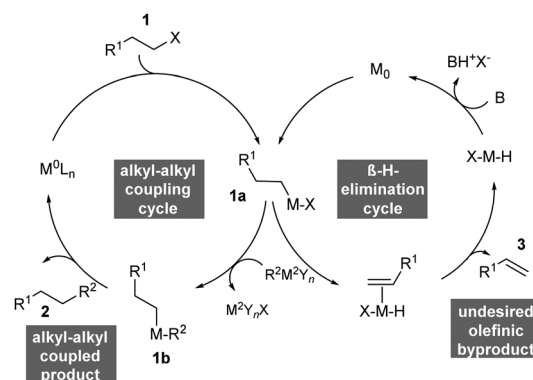
The mechanism for palladium-catalysed Suzuki-Miyaura cross-coupling reactions is well established.¹ The general catalytic cycle for transition metal catalysed C-C cross-coupling proceeds by oxidative addition to the metal centre **1a** followed by

transmetalation **1b** and reductive elimination to the desired product **2**.²

A problem in alkyl-alkyl cross-couplings of non-activated alkyl halides is the undesired β-hydride elimination of the intermediate alkyl-metal complex **1a** if there is a free coordination site on the metal centre. The fast and favoured β-hydride elimination leads to the formation of olefinic by-products **3**. The relatively slow reductive elimination of the cross-coupling product **2** from the catalyst (aryl-aryl > aryl-alkyl > alkyl-alkyl) makes side reactions more probable (Scheme 1).³ This problem can be addressed by the use of bulky electron-rich phosphine ligands^{4,5} or by NHC ligands.⁶

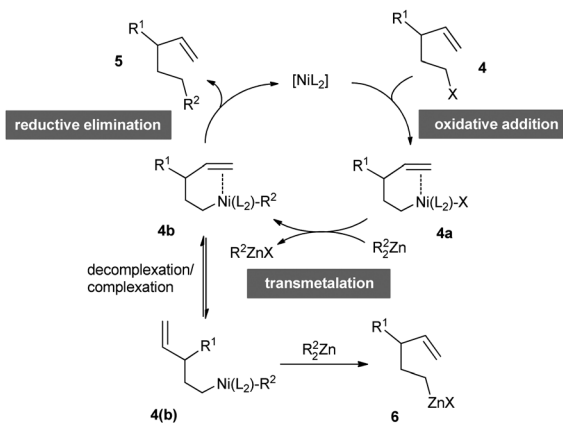
2.2 Nickel catalysis

Unlike palladium chemistry, the mechanism of nickel-catalysed sp³-sp³ cross-coupling reactions is not as well developed. One of the first proposed mechanisms for nickel-catalysed alkyl-alkyl cross-couplings was reported by Knochel and co-workers.⁷ Based on their observations, and further studies by the Yamamoto group,⁸ the following mechanism was proposed (Scheme 2).



Scheme 1 Catalytic cycle of transition metal-catalysed cross-couplings and competitive β-hydride elimination.

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Scheme 2 Proposed mechanism of nickel-catalysed cross-coupling reactions.

The active catalyst $[L_2Ni^0]$ is generated *in situ* and undergoes oxidative addition to the alkyl halide **4** to provide the nickel(II) complex **4a**. A π -system, such as an olefin, has to be present and in close vicinity so that coordination with the metal centre **4b**

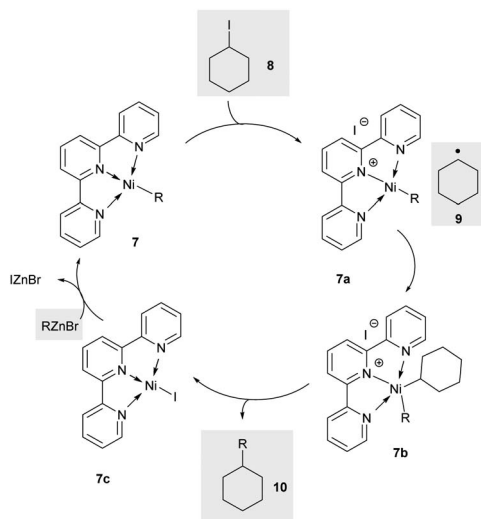


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Andreas Kirschning studied chemistry at the University of Hamburg and at Southampton University (UK). In Hamburg, he joined the group of Prof. Ernst Schaumann and received his PhD in 1989 working in the field of organosilicon chemistry. After a postdoctoral stay at the University of Washington (Seattle, USA) with Prof. Heinz G. Floss, he started his independent research at the Clausthal

University of Technology in 1991, where he finished his habilitation in 1996. In 2000 he moved to the Leibniz University of Hannover. His research interests cover structure elucidation as well as the semi-, total and mutasynthesis of natural products, biomedical biopolymers, and synthetic technologies (solid-phase assisted synthesis, microreactors and inductive heating).



Scheme 3 Proposed radical mechanism of nickel-catalysed cross-couplings.

occurs, blocking the coordination site. Transmetalation with the organo-zinc species and reductive elimination to follow yields the cross-coupled product **5**. Coordination to the organo-nickel species is essential because it reduces the electron density at the metal centre, which otherwise favours reductive elimination.⁸ As known from palladium-catalysed alkyl-alkyl cross-couplings, β -hydride elimination is also a favourable process in nickel-catalysed cross-couplings. The undesired β -hydride elimination can be suppressed by coordinative saturation of the metal centre.⁹

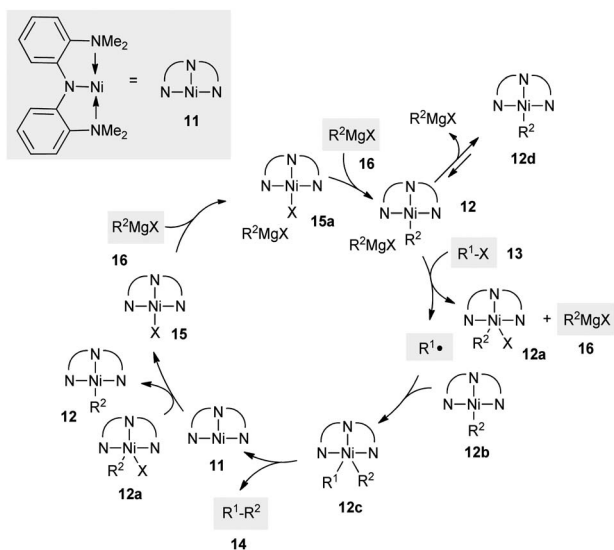
Vicic and co-workers proposed an alternative mechanism for the nickel-catalysed Negishi alkyl-alkyl coupling (Scheme 3).¹⁰

The proposed catalytic cycle begins with the reaction of a (terpyridyl)Ni(alkyl) complex **7**, with an alkyl halide (here cyclohexyl iodide) (**8**) to form complex **7a** and alkyl radical **9**.



Thomas Schmidt studied chemistry at the Leibniz University of Hannover. In 2006 he spent a research internship in the group of Prof. Barry M. Trost at Stanford University (USA). In Hannover, he joined the group of Prof. Andreas Kirschning and received his PhD degree in 2012 after having successfully achieved the first total synthesis of carolacton. After a postdoctoral stay with Prof. Janine Cossy at the

ESPCI ParisTech in 2013 he joined Boehringer Ingelheim GmbH & Co. KG where he works in the area of process development.



Scheme 4 Mechanism for the nickel-catalysed sp^3 - sp^3 Kumada cross-coupling.

Conceptually different from common mechanistic considerations, Vicic and co-workers assumed that complex **7** undergoes a single electron transfer to give oxidised complex **7a** and an alkyl radical. This process is believed to be ligand driven.

The resulting alkyl radical **9** stays in close proximity to the metal centre, so that an oxidative radical addition ensues to afford a nickel(III)-dialkyl species **7b**. If the ligand is chiral, chirality transfer can occur. Fast reductive elimination provides a nickel-complex **7c** and product **10**.¹⁰ In fact, this mechanistic pathway may explain the excellent stereoconvergence found for asymmetric versions of Negishi alkyl-alkyl cross-coupling reactions (*vide supra*).

Kinetic investigations and DFT calculations by Hu reveals that a bimetallic radical mechanism for the nickel-catalysed alkyl-alkyl Kumada cross-coupling may be operating (Scheme 4).¹¹ The key intermediate is the $[(N_2N)Ni-alkyl^2](alkyl^2-MgCl)$ complex (**12**), its formation is the turnover-determining step of the catalytic cycle. The $[(N_2N)Ni-alkyl^2](alkyl^2-MgCl)$ (**12**) stands in an equilibrium with the non-coordinated $[(N_2N)Ni-alkyl^2]$ complex (**12d**).

Oxidative addition of the alkyl halide **13** to the nickel complex **12** generates an alkyl radical that reacts with a second nickel alkyl complex (**12b**) to form complex **12c**. Reductive elimination generates the sp^3 - sp^3 cross-coupled product **14**. The nickel catalyst is regenerated by comproportionation of the nickel(I) species **11** and the nickel(III) species **12a** to give the nickel(II) species **12** and **15**. Then the $[(N_2N)Ni-X]$ complex (**15**) gets coordinated by $alkyl^2-MgCl$ (**16**) and undergoes transmetalation to $[(N_2N)Ni-alkyl^2](alkyl^2-MgCl)$ (**12**) to close the catalytic cycle. The highest formal oxidation state of nickel in the intermediates is +3.¹¹

3 sp^3 - sp^3 Cross-coupling reactions

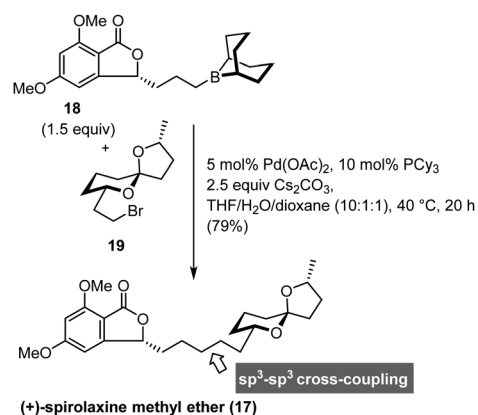
In the following, examples of palladium- and nickel-catalysed cross-coupling reactions will be covered in separate chapters

due to their importance. Subsequently other metals known to promote sp^3 - sp^3 cross-coupling reactions will be covered.

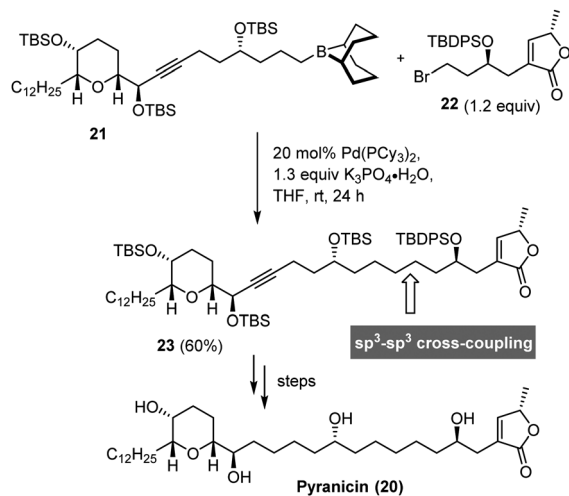
3.1 Palladium-catalysed coupling reactions

A survey of the literature reveals that the use of palladium in sp^3 - sp^3 cross-coupling reactions is less common compared to nickel. The Phillips group probably published the most impressive examples of palladium catalysed sp^3 - sp^3 cross-coupling chemistry in the field of natural product total synthesis. In 2007 the group based their total synthesis of the polyketide (+)-spiroloxine methyl ether (**17**) on a late stage alkyl-alkyl Suzuki cross-coupling key step.¹² The class of the spiroloxines are produced by the white-rod fungi *Sporotrichum* and *Phanerochaetei* and show potential as antibiotics against *Helicobacter pylori*. Additionally, it was reported that (+)-spiroloxine methyl ether (**17**) inhibits the growth of multiple cell lines and lowers cholesterol levels. In Phillips group's total synthesis, borane **18** was generated by treating the olefin precursor with 9-BBN at 25 °C. The Suzuki-Miyaura cross-coupling of borane **18** with alkyl bromide **19** followed an original report by Fu *et al.*¹³ In the presence of aqueous Cs_2CO_3 , $Pd(OAc)_2$ and PCy_3 in dioxane the coupling partners were converted to spiroloxine methyl ether (**17**) in remarkably good yield (Scheme 5). According to Fu the use of the bulky, electron-rich phosphine ligand PCy_3 is crucial for cross-coupling reactions with alkyl bromides that are usually prone to β -hydride elimination.

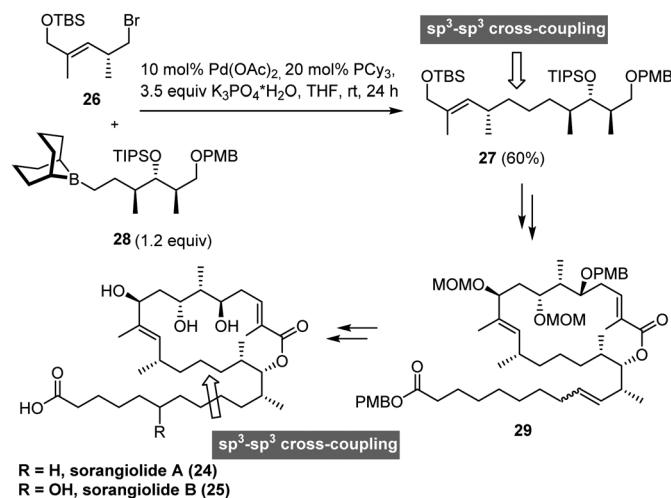
In 2008, the Phillips group made use of the alkyl-alkyl Suzuki coupling for merging two advanced fragments in the synthesis of pyranicin (**20**).¹⁴ Pyranicin was first isolated from the stem bark of *Goniothalamus giganteus*.¹⁵ It exhibits anti-proliferative activity against a number of cancer cell lines ($ED_{50} < 1 \mu g mL^{-1}$). It belongs to the annonaceous acetogenins, a class of polyketide metabolites, that among other structural features have tetrahydropyran rings in common.¹⁶ A key step in the synthesis relies on borane **21**, which was generated *in situ* by chemoselective hydroboration of the terminal double bond in the precursor of **21** in the presence of the alkyne moiety. The alkyl-alkyl cross-coupling between borane **21** and only 1.2 equiv. of bromide **22** furnished the complete carbon backbone



Scheme 5 Key step in the Phillips group's total synthesis of (+)-spiroloxine methyl ether (**17**).¹²



Scheme 6 Key step in the total synthesis of pyranicin (20).



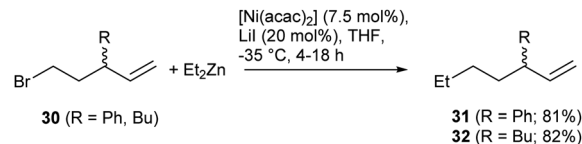
Scheme 7 Key step in the total synthesis of sorangiolides A (24) and B (25).

23 of pyranicin (20) in 60% yield. However, a high catalyst loading of 20 mol% Pd(PCy₃)₂ was necessary to obtain the best yield (Scheme 6).

A Fu-type Suzuki cross-coupling reaction also found use in the synthesis of sorangiolide A.¹⁷ The sorangiolides A (24) and B (25) are secondary metabolites from the myxobacterium *Sorangium cellulosum*. They possess weak antibiotic activity (MIC = 5–20 μg mL⁻¹) against Gram-(+) bacteria like *Staphylococcus aureus*.¹⁸ Borane 28 had to be prepared *in situ* prior to cross-coupling with bromide 26 to furnish fragment 27.¹⁴ This intermediate was further advanced to the fully protected macrocyclic lactone 29 and then to sorangiolide A (24) (Scheme 7).

3.2 Nickel-catalysed coupling reactions

For the reasons discussed in chapter 2, nickel catalysts have advantages in *sp*³-*sp*³ coupling reactions over their palladium counterparts. In 1995, Knochel and co-workers⁷ reported high

Scheme 8 Nickel-catalysed *sp*³-*sp*³ cross-coupling of terminal bromides.

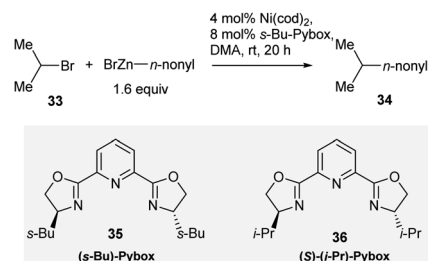
yielding cross-coupling reactions of unsaturated alkyl bromides 30 with Et₂Zn in the presence of catalytic amounts of [Ni(acac)₂] and LiI to yield cross-coupling products 31 and 32, respectively (Scheme 8). Further investigations showed the need of a double bond in the γ-position, otherwise only nickel catalysed bromine–zinc exchange took place.³

Later the same group could by-passed the need of a γ-positioned double bond by using an unsaturated additive, such as styrenes, that contained an electron-deficient substituent in the *meta*-position. These studies gave a strong hint on the necessity of π donor ligands for nickel-catalysed *sp*³-*sp*³ cross-coupling reactions.¹⁹

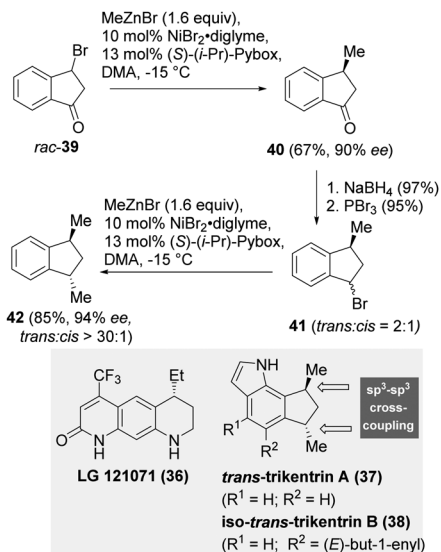
In 2003 Fu and co-workers reported a Negishi coupling of non-activated secondary alkyl halides, such as bromopropane 33, in the presence of catalytic amounts of Ni(cod)₂ and Pybox ligands (Scheme 9). The method covers a broad substrate scope, as far as both electrophiles and nucleophiles are concerned. Among several ligands and metal complexes screened, Ni(cod)₂ and (*s*-Bu)-Pybox (35) showed the most promising results.²⁰ In fact, these studies led to the first stereoconvergent *sp*³-*sp*³ nickel-catalysed Negishi cross-coupling reaction of non-activated secondary alkyl halides. A catalytic amount of NiBr₂·diglyme and (*R*)-(i-Pr)-Pybox in DMA served for the synthesis of (*R*)-3-ethylindanone, a synthetic intermediate of LG 121071 (36), a nonsteroidal androgen receptor agonist. Using these conditions (*R*)-3-ethylindanone was obtained from commercially available 1-indanone in two steps in 92% ee and in moderate yield.

Furthermore, the same protocol was used for the synthesis of *trans*-1,3-dimethylindanes 42, that served as intermediates for *trans*-trikentrin A (37) and *iso-trans*-trikentrin B (38), natural products from marine natural sources (Scheme 10).²¹

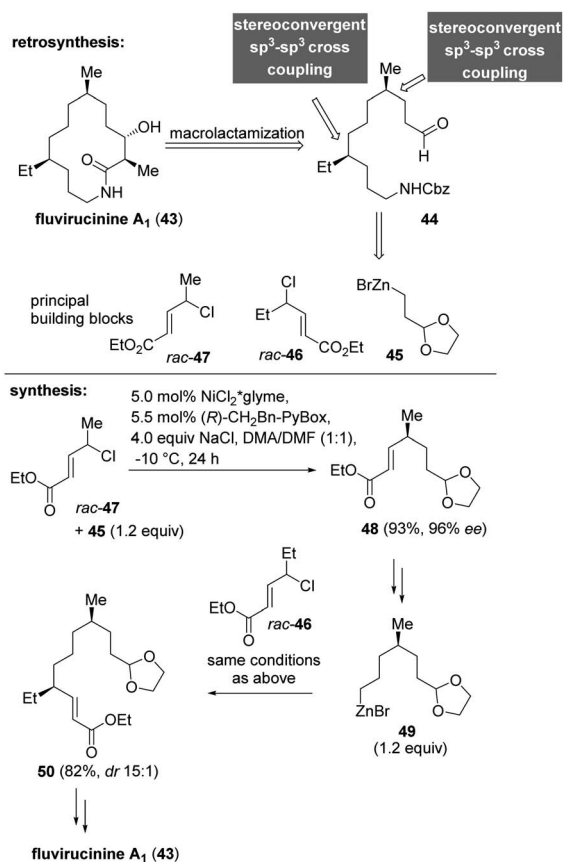
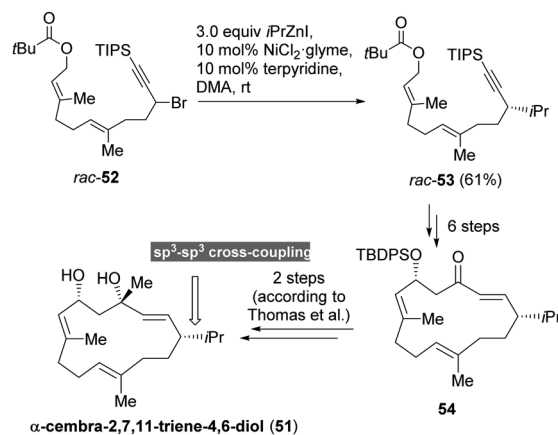
A more challenging application for this variant of the Negishi reaction was used in the synthesis of fluvirocinine A₁ (Scheme 11). The first total synthesis of fluvirucinine A₁ (43) was reported



Scheme 9 Negishi cross-coupling of non-activated secondary alkyl halides.

Scheme 10 Enantioselective Negishi coupling of two $\text{sp}^3\text{-sp}^3$ centres.

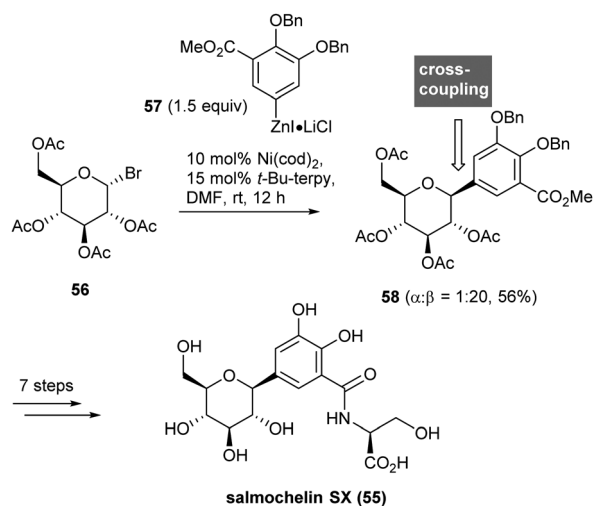
by Suh and co-workers in 1999. Aldehyde **44** was generated in 16 steps and Evans' chiral-auxiliary chemistry played a key role to access **44**.²² In contrast, their $\text{sp}^3\text{-sp}^3$ cross-coupling chemistry allowed Fu and Son to generate the same aldehyde **44** in only

Scheme 11 Formal synthesis of fluvirucine A₁ (**43**) via two catalytic stereoconvergent Negishi cross-coupling reactions.Scheme 12 Introduction of an iso-propyl group through nickel-catalysed $\text{sp}^3\text{-sp}^3$ cross-coupling.

eight steps. The key step of this synthesis was the stereoconvergent nickel-catalysed Negishi cross-coupling reaction starting from allylic chlorides to generate two tertiary stereogenic centres in excellent yields and ee.¹³

A second advanced application using this protocol can be found in Fu's formal synthesis of α -cembra-2,7,11-triene-4,6-diol **51** (Scheme 12). This diterpene has anti-tumor activity and was first synthesised by the groups of Marshall and Thomas.²³ Marshall introduced the *iso*-propyl group through [2,3]-Wittig ring contraction of a 17-membered propargylic ether. Thomas installed the *iso*-propyl group through asymmetric Sharpless epoxidation, followed by opening of the epoxide with an *iso*-propenyl magnesium bromide and reduction of the double bond.

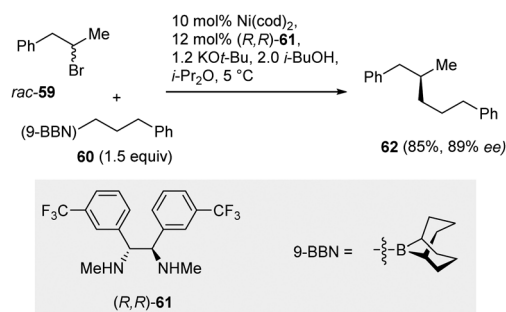
In contrast, in Fu and Smith's synthesis the introduction of the *iso*-propyl group was achieved through the cross-coupling of racemic propargylic bromide **52** and *i*-PrZnI as a key transformation to yield advanced intermediate **53**.²⁴ The benefit of this approach is the flexibility for introducing different alkyl groups.

Scheme 13 Key steps in total synthesis of salmochelin SX (**55**).

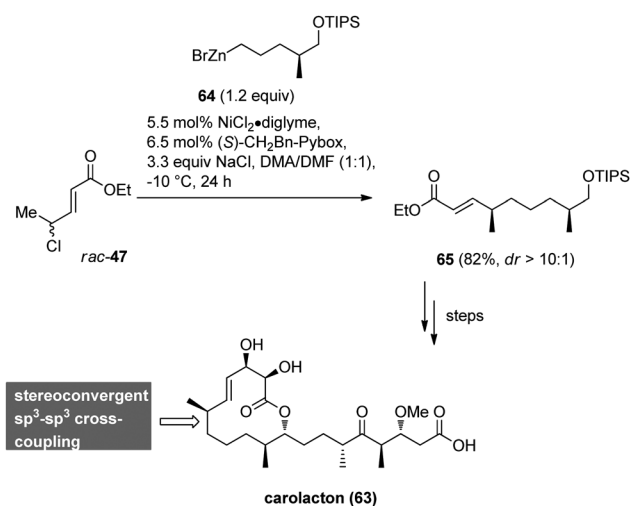
In 2008 Gagné and Gong reported the synthesis of fully oxygenated C-alkyl and C-aryl glycosides *via* nickel-catalysed Negishi cross-coupling reactions (Scheme 13). The methodology was successfully applied as a key step in the total synthesis of the C-glycoside salmochelin SX (55) using arylzinc species 57 and a glycosyl halide 56 as an electrophile.²⁵

sp^3 - sp^3 Cross-coupling chemistry can also be achieved by the nickel-catalysed Negishi reaction of non-activated alkyl halides, which is combined with the nickel-catalysed Suzuki cross-coupling. This strategy was exploited in the stereoconvergent coupling of racemic, homobenzylic halide *rac*-59 and the alkylborane 60 using Ni(cod)₂ in the presence of the chiral diamine ligand 61, which provided hydrocarbon 62 in 85% yield and 89% ee (Scheme 14).²⁶ This approach was extended to the stereoconvergent cross-coupling reaction of acylated halohydrins, β -halo arylamines and other heteroatom containing functional groups.²⁷

In 2012 Kirschning and Schmidt achieved the first total synthesis of carolacton (63), a potent biofilm inhibitor isolated from myxobacteria. One of the key steps of this total synthesis was the stereoconvergent sp^3 - sp^3 Negishi cross-coupling of racemic allylic chloride 47, which yielded ester 65 in 82% yield and high diastereoselectivity (*dr* = 10 : 1)(Scheme 15).²⁸



Scheme 14 Stereoconvergent cross-coupling of racemic secondary halides with alkylboranes.



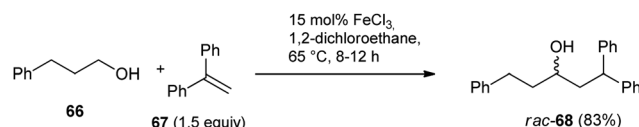
Scheme 15 Key step Negishi sp^3 - sp^3 cross-coupling in the total synthesis of carolactone 63.

Very recently, Fu and co-workers reported on the nickel-catalysed Suzuki cross-coupling reaction of unactivated tertiary alkyl halides with aryl boronic acids as nucleophiles. Tertiary alkyl halides show a low tendency to undergo oxidative addition, so such transformations are still rare.²⁹

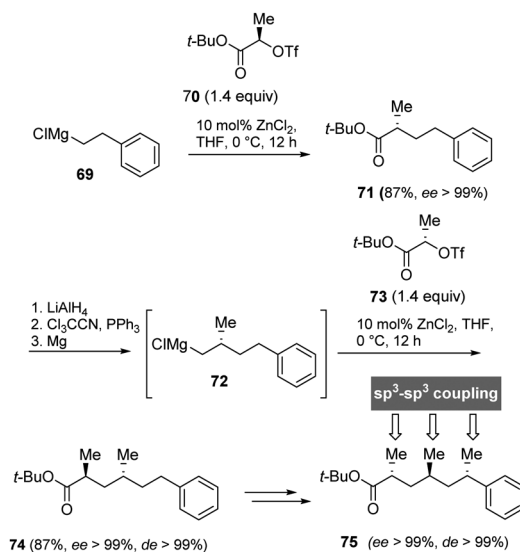
3.3 Other metals for sp^3 - sp^3 cross-couplings

Nickel and palladium are not the only metals that can be utilised in alkyl-alkyl cross-coupling reactions. The past decade has seen selected applications of iron-, zinc- and copper-complexes as catalysts for achieving sp^3 - sp^3 cross-couplings. The clear advantage of these metals are their low price as well as low toxicity. So far, the scope of these catalysts is still limited. Nevertheless, Tu and co-workers reported on the remarkable iron-catalysed cross-coupling of alkene 67 with alcohol 66 (Scheme 16).³⁰ The catalytic use of FeCl₃ in 1,2-dichloroethane provided carbinol 68 after sp^3 - sp^3 coupling, in yields in the range of 48% to 93%.³¹ The same group developed a related ruthenium-catalysed cross-coupling protocol starting from two alcohols which featured the *in situ* formation of the required alkene.³²

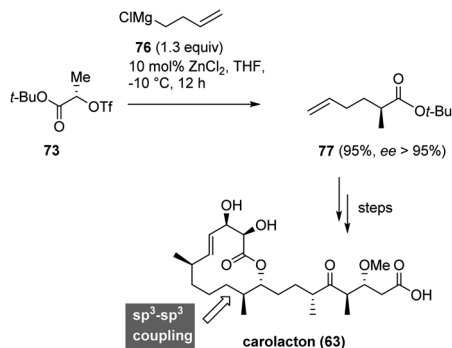
Nakamura and co-workers also provided insight into iron-catalysed alkyl-alkyl cross-coupling chemistry based on the Suzuki-Miyaura reaction. Alkylboronic acids and non-activated alkyl halides were coupled in high yields using a catalyst combination consisting of an iron salt and a bisphosphine



Scheme 16 Iron-catalysed cross-coupling generating a sp^3 - sp^3 bond.



Scheme 17 ZnCl₂ mediated sp^3 - sp^3 cross-coupling as a general method for the synthesis of (oligo)deoxypropionates.



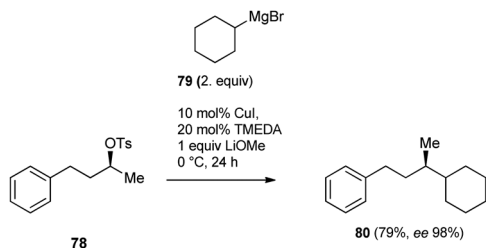
Scheme 18 ZnCl_2 mediated sp^3 - sp^3 cross-coupling in the total synthesis of carolacton (63).

ligand that contains a large bite angle. Mechanistically, the transmetalation step is the critical step as it requires a combination of a carbanionic activator such as *i*-PrMgCl and a Lewis acidic metal salt.³³

Breit and co-workers reported on the general synthesis of (oligo)deoxypropionates that are common motifs in a large number of biologically relevant polyketide natural products. The method is based on an enantiospecific zinc-catalysed cross-coupling reaction of lactic acid *t*-butylestertriflates **70/73** with different Grignard reagents (*e.g.*, **69** and **72**) to yield branched esters **71** and **74**, respectively. This transformation can be interpreted as a nucleophilic substitution ($\text{S}_{\text{N}}2$) (Scheme 17). This key step was used in an iterative fashion, *e.g.*, in the synthesis of all four possible diastereomers of the trideoxypropionate **75**.³⁴

Our group exploited this protocol in the total synthesis of carolacton (**63**) (see also Scheme 15).²⁸ The southwestern part of carolactone **77** was prepared from lactic triflate **73** after substitution with homoallyl Grignard reagent **76** (Scheme 18).

Related to this protocol is the copper-mediated cross-coupling reaction of non-activated secondary alkyl halides and tosylates **78** with secondary alkyl Grignard reagents **79** (Scheme 19) to yield product **80**. The reaction most likely proceeds through a $\text{S}_{\text{N}}2$ mechanism with inversion of configuration and therefore provides a general approach for the stereocontrolled formation of C–C bonds from chiral alcohols.³⁵ The copper-catalysed cross-coupling with tertiary alkyl Grignard reactants has also been reported.³⁶



Scheme 19 Copper mediated cross-coupling of secondary tosylates with aliphatic Grignard reagents.

4 Conclusion

The coupling of two different alkyl groups is probably one of the most useful C–C bond forming processes in the portfolio of synthetic chemists. However, so far the alkyl–alkyl cross-coupling reaction is not well advanced. Still, it is established that for this transformation palladium and nickel catalysts are applicable even in the total synthesis of complex natural products. Importantly, Organ *et al.* studied sp^3 - sp^3 Negishi cross-coupling reactions using palladium catalysts that contain NHC ligands.⁶ Mechanistically they provided evidence that not only the steric bulk of the NHC ligands but also the generation of high order zincates are crucial for the success of this C–C bond forming reaction. These promising results may pave the way for the routine application of alkyl–alkyl cross-coupling reactions in natural product synthesis in the future.

5 Acknowledgements

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6 Notes and references

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