# Controlled Iterative Cross-Coupling: On the Way to the Automation of Organic Synthesis**

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automation · catalysis · cross-coupling ·
iterative synthesis · palladium

*I*teration (lat. "iterare" = to repeat) is a powerful strategy employed in the biosynthesis of complex molecules, for example the synthesis of fatty acid polyketides from malonyl-CoA.[1] With nature as the role model, chemists have established iterative and automated syntheses for all three major classes of biopolymers (polypeptides,[2] oligonucleotides,[3] and most recently, oligosaccharides[4]). In these controlled iterative reactions,[5] di- and multifunctional building blocks are employed that contain only one reactive functional group ("ON"), while all other groups are unreactive ("OFF") thereby suppressing uncontrolled polymerization (Scheme 1). After the selective coupling of the reactive group, another, previously unreactive functional group is activated/deprotected ("ON") and the coupling sequence repeated, thus allowing the efficient formation of defined oligomers from readily available building blocks. This enables even nonexperts to synthesize complex molecules in a short time, and promotes the rapid investigation and application of these compounds in chemistry and biology. An ideal iterative coupling would meet the following criteria:

- many differently substituted building blocks are readily available and inexpensive;
- coupling and activation/deprotection step are high yielding, are tolerant of many different functional groups, and do not require nor produce toxic compounds;
- handling, separation, and purification are facile;
- the iterative coupling sequence is reliable and predictable, which are important aspects for applications in natural product synthesis and in industry;
- the sequence is suitable for solid phase synthesis and automation.
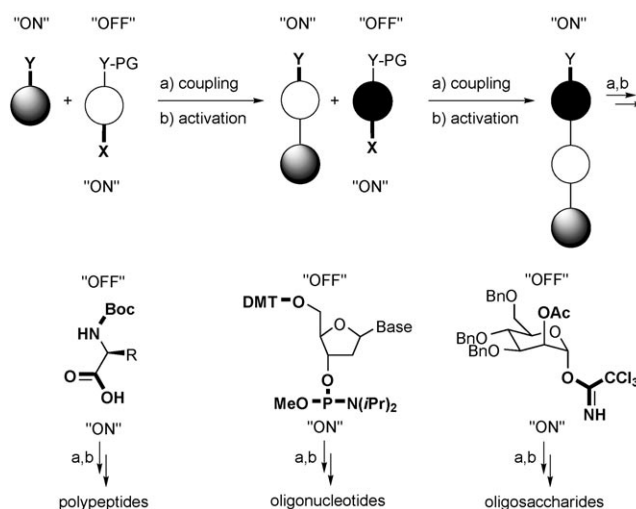


*Scheme 1.* General iterative coupling sequence and three typical building blocks bearing reactive ("ON") electrophilic and protected ("OFF") nucleophilic functional groups. Bn = benzyl; Boc = *tert*-butoxycarbonyl; DMT = dimethoxytrityl; PG = protecting group.

In recent years, transition-metal-catalyzed cross-coupling reactions have altered the way organic molecules are made and represent a reliable and general method for the formation of CC bonds.[6] The application of building blocks bearing two or more functional groups that are reactive under cross-coupling protocols seems to be attractive. However, lack of selectivity in such coupling reactions would result in mixtures of oligo- and polymers with different molecular weights.[7] Thus, efficient methods for the controlled metal-catalyzed iterative cross-coupling of di- or multifunctional building blocks are highly desirable and, recently, spectacular advances have been made.[8]

For a long time the iterative cross-coupling strategy has been limited to the synthesis of oligothiophenes and oligo(-phenylene ethynylene)s,[9] which are of great importance in materials chemistry. The required monomers can easily be activated or protected to allow selective coupling reactions (halogenations of thiophenes; silyl protection of terminal alkynes). A representative example by Tour and co-workers is shown in Scheme 2.[9e] Through an elegant iterative divergent/convergent approach, the molecular length is doubled with each iterative cycle, thus allowing the rapid and high yielding

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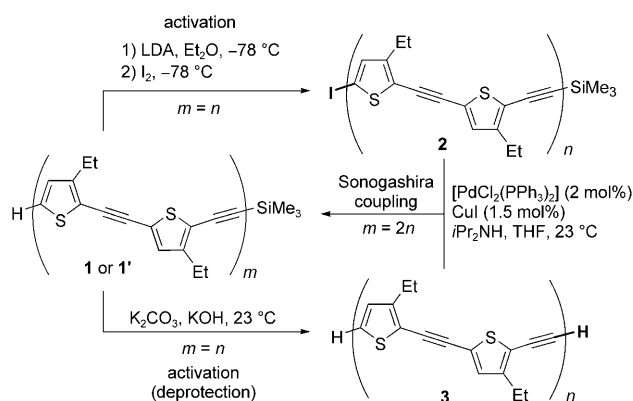
**Scheme 2.** Synthesis of oligo(thiophene ethynylene)s by iterative divergent/convergent Sonogashira coupling. LDA = lithium diisopropylamide; THF = tetrahydrofuran.

synthesis of a 100 Å long 16-mer ($m = 8$) in 15% overall yield in only three cycles. In detail, compound **1** ($2 \times$ "OFF") was split (divergent) into two parts, where one part was activated at the thiophene ring (**2**) and the other part was deprotected to yield the free terminal alkyne (**3**). In a Sonogashira coupling reaction, **2** and **3** were then selectively coupled (convergent) to the new dimeric product **1′**. Tour further extended this approach to solid-phase methods, thus making it suitable for automation.[9d]

An even more important, yet challenging objective is the synthesis of oligoarenes with benzene rings as monomers. The Suzuki–Miyaura coupling reaction is one of the most reliable and widely used reactions for the formation of CC bonds owing to its high efficiency, the low toxicity of boron compounds, as well as the high and predictable functional group compatibility.[10] Using a bifunctional building block in iterative Suzuki–Miyaura coupling reactions can proceed by two different strategies, the modulation of the reactivity of the electrophile (halide, triflate, etc.) or of the boron species. Employing the former method, Hamilton and co-workers made use of methoxyphenylboronic acids as precursors of the monomer units in the synthesis of substituted *para*-terphenyl derivatives (Scheme 3, $R^3 = Me$).[11] The methoxy group was converted into the activated triflate in two steps for the
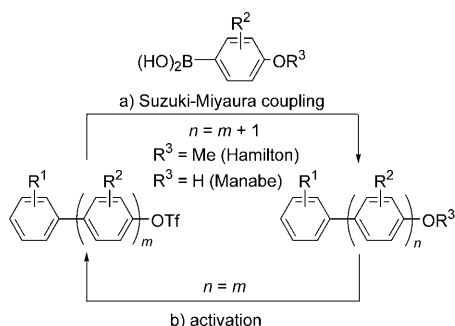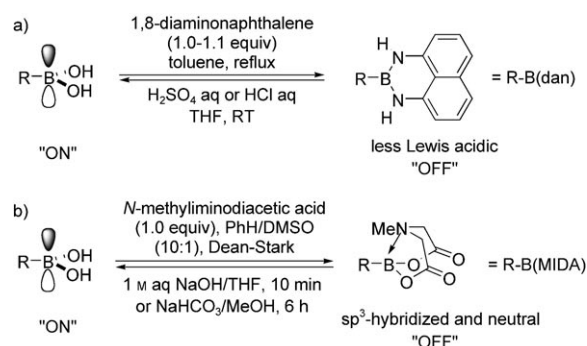
following Suzuki–Miyaura coupling. Recently, Manabe and co-workers developed a more efficient system using hydroxyphenylboronic acids (Scheme 3, $R^3 = H$) or pinacol boronates as precursors.[12] Intriguingly, the oligoarenes can be efficiently obtained by iteration of two nearly quantitative steps: the Suzuki–Miyaura coupling of hydroxyphenylboronic acid and the subsequent triflation of the hydroxy group. This method was successfully applied to the synthesis of oligoarene-type phosphine ligands, which showed excellent *ortho* selectivity in the Kumada coupling reaction of dihalophenols and dihaloanilines.[13]

Another, more versatile strategy for iterative Suzuki–Miyaura cross-coupling reactions is to induce temporary inactivity of the boron species. This strategy can be realized either by borylation of a boron-free compound or by protection/deprotection of the boron species. Cheng and Snieckus used directed *ortho* metalation as a key step to introduce boronic acids into boron-free compounds in their iterative synthetic sequence to give oligoarenes.[14] Galda and Rehahn as well as Simpkins and co-workers adopted a similar Br–Li exchange reaction in the boronic acid formation step, thus allowing the assembly of oligoarenes with up to 15 *para*-connected benzene rings.[15] Finally, the research groups of Schlüter and Strongin reported the iterative divergent/convergent cross-coupling reactions by activating both ends of the bifunctional building blocks.[16] However, several additional transformation steps and sometimes strong bases like *n*BuLi are needed in these above-mentioned methods.

Recently, however, major breakthroughs have been made by the research groups of Suginome[17] and Burke,[18] who independently developed two different protection groups for boronic acids (Scheme 4), which allow efficient iterative Suzuki–Miyaura cross-coupling reactions. These masked boronyl groups are easily formed, stable under coupling conditions, and readily activated under mild, orthogonal conditions. By lowering the Lewis acidity of the boron atom, Suginome and co-workers demonstrated that 1,8-diaminonaphthalene is a good protection group in Suzuki–Miyaura coupling reactions by mesomeric interaction of the nitrogen atoms with the boron center (Scheme 4a). These masked haloaryl boronamides remained intact in palladium-catalyzed cross-coupling reactions of unmasked arylboronic acids, to afford the corresponding biaryls in high yields. Moreover, the



**Scheme 3.** Iterative Suzuki–Miyaura cross-coupling by activation of an HO- or MeO-group. Typical reaction conditions ($R^3 = H$): a) Pd(OAc)$_2$ (2 mol%), X-Phos (2.4 mol%), KF, THF/H$_2$O; b) Tf$_2$O, pyridine, CH$_2$Cl$_2$. Tf = trifluoromethanesulfonyl; X-Phos = 2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl.



**Scheme 4.** Transformation of boronic acids into unreactive boronamides (Suginome, a) and boronates (Burke, b) and reverse activation reaction.

masked boronic acids are stable and easily purified by recrystallization or column chromatography. The unmasking proceeds smoothly with diluted sulfuric acid or hydrochloric acid at room temperature. By iteration of the Suzuki–Miyaura coupling reaction and the unmasking process, oligoarenes like **4** can be synthesized in a highly selective manner (Scheme 5).
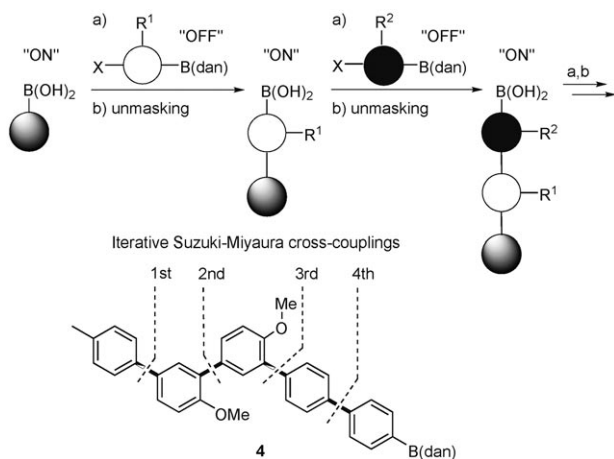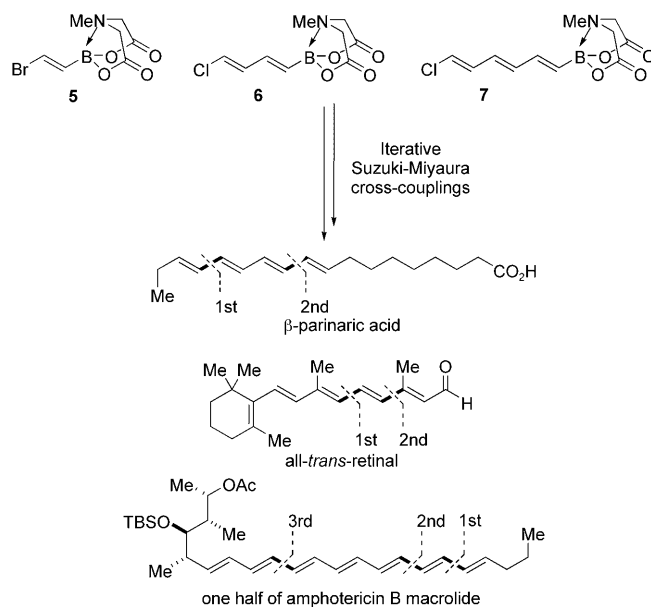


***Scheme 5.*** Iterative Suzuki–Miyaura cross-coupling using a boron-masking strategy by Suginome. Typical reaction conditions: a) [Pd-(P$t$Bu$_3$)$_2$] (2 mol%), CsF, dioxane/H$_2$O or THF; b) see Scheme 4a.

Burke and co-workers discovered that the trivalent *N*-methyliminodiacetic acid (MIDA) ligand deactivates and blocks the boron center by rehybridization to sp$^3$, while not providing an anionic boron "ate" complex that is electron-rich enough for transmetalation.[19] Consequently, the resulting boronates are inactive towards transmetalation under anhydrous cross-coupling conditions (Scheme 4b). The bifunctional halogen-containing MIDA boronates proved to be suitable precursors with excellent control of reactivity for palladium-catalyzed iterative Suzuki–Miyaura cross-coupling reactions, and was demonstrated in the total synthesis of ratanhine (Scheme 6). Remarkably, the MIDA-protected boronate esters are easily handled, indefinitely bench-top stable in air, and survive chromatographic methods.[18a] Still, deprotection is easily achieved at room temperature under mildly basic, aqueous conditions (Scheme 4).

Burke and co-workers further extended their method to create a series of alkenyl MIDA boronate building blocks,[18b–d] which are exceptionally useful, since the corresponding polyenyl boronic acids are very unstable and therefore difficult to employ in organic synthesis. In contrast, the MIDA boronates are tolerant of Heck, Stille, Suzuki–Miyaura, and Sonogashira coupling protocols, as well as oxidative, reductive, or strongly acidic conditions.[18c] The utility and flexibility of these building blocks was demonstrated by employing halogen-containing mono-, di-, and trienyl MIDA boronates **5**, **6**, and **7** in the modular synthesis of some polyene natural products such as β-parinaric acid, all-*trans*-retinal, and the polyene chain of amphotericin B, respectively (Scheme 7).[18b] Owing to the immense potential of this method for facile and time efficient synthesis, a large
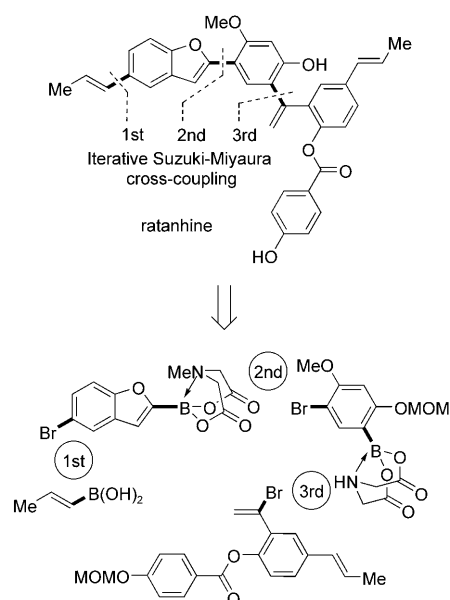


***Scheme 6.*** Iterative Suzuki–Miyaura cross-coupling using MIDA boronates by Burke. Typical coupling conditions: a) Pd$_2$dba$_3$, 2-(dicyclohexylphosphino)biphenyl, K$_2$CO$_3$, THF, 65°C; b) see Scheme 4b. MOM = methoxymethyl.



***Scheme 7.*** Iterative Suzuki–Miyaura cross-coupling using different haloalkenyl MIDA boronates. TBS = *tert*-butyldimethylsilyl.

series of these MIDA boronate building blocks has already been made commercially available.[20] Finally, a recent report by Molander and Sandrock on the modulated reactivity of different boronyl species, namely a trifluoro borate and a borane, in palladium-catalyzed Suzuki–Miyaura coupling reactions should also prove useful for iterative couplings.[8,21] Most importantly, alkyl boranes (formed by hydroboration) and alkyl trifluoro borates were efficiently cross-coupled.

In a similar effort, Nakao, Hiyama and co-workers demonstrated the first iterative Hiyama coupling reaction of organo[2-(hydroxymethyl)phenyl]dimethylsilanes.[22] Owing to the unique activating effect of the proximal hydroxy group under basic conditions, the reactivity of the silyl group can be easily turned ON or turned OFF simply by protection or deprotection of the hydroxy group (Scheme 8). Noteworthy is
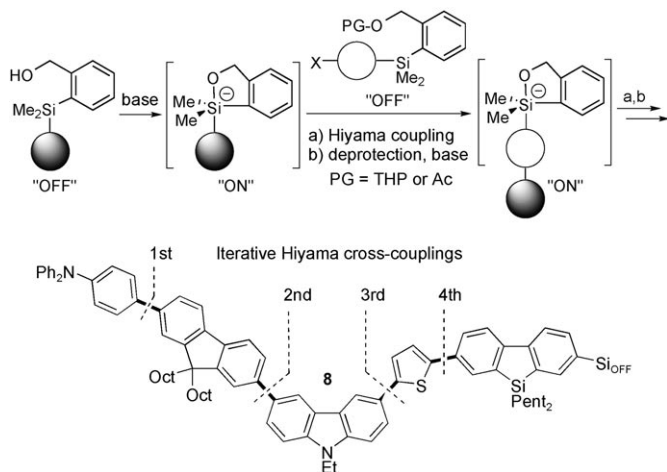


**Scheme 8.** Iterative Hiyama cross-coupling by Nakao and Hiyama. Typical reaction conditions: a) $[(\eta^3\text{-}C_3H_5)PdCl]$ (1 mol%), RuPhos (2 mol%), CuI (3 mol%), $K_2CO_3$, THF/DMF, 75 °C; b) PG = Ac: DIBAL-H, $CH_2Cl_2$, 78 °C or PG = THP: TsOH, MeOH/$CH_2Cl_2$, RT. DIBAL-H = diisobutylaluminium hydride; Oct = octyl; Pent = pentyl; RuPhos = 2-(dicyclohexylphosphino)-2',6'-diisopropoxybiphenyl; THP = tetrahydropyranyl; Ts = 4-toluenesulfonyl.

that both a THP and an acetyl group can be used as protection groups. Thus, the deprotection can proceed under acidic (for THP) or basic conditions (for acetyl), thus allowing adjustment of this method to the tolerance of different functional groups. With the repetitive deprotection/cross-coupling sequence, highly conjugated oligoarenylsilanes like **8** can be synthesized in a linear manner. Importantly, the silafluorene moiety can be tolerated with its CSi bonds remaining intact (the 4th iteration) under mild reaction conditions using $K_2CO_3$ as a base.

The methods described here meet many of the requirements for an ideal controlled iterative coupling (vide supra) and consequently, greatly facilitate the synthesis of complex oligoarenes and polyenes of defined size and structure. It is fair to predict that the number of commercially available building blocks and applications will dramatically increase in the near future. For example, efficient building blocks for the (asymmetric) coupling of alkyl groups would be particularly useful.[21,23] In addition, with the rapid development of catalytic CH bond activation reactions,[24] the iterative cross-coupling using CH activation as a key step will certainly be an emerging area.[5d] In analogy to peptide synthesis,[2] solid-phase synthesis technology is highly desirable for iterative cross-coupling reactions to facilitate handling and purification of the products. Although there are still many barriers to be overcome, the presented achievements constitute a major step towards the automation of organic synthesis.

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