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# Stereoselective Double Functionalization of Geminated C(sp<sup>3</sup>)-Organodimetallic Linchpins

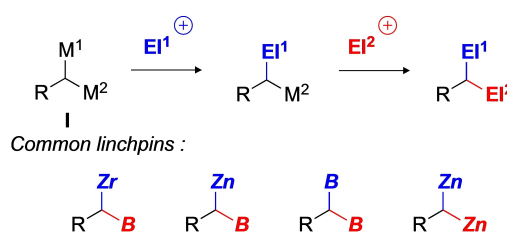
Federico Banchini,<sup>[a]</sup> Baptiste Leroux,<sup>[b]</sup> Erwan Le Gall,<sup>[b]</sup> Marc Presset,<sup>[b]</sup> Olivier Jackowski,<sup>\*[a]</sup> Fabrice Chemla,<sup>\*[a]</sup> and Alejandro Perez-Luna<sup>\*[a]</sup>

Geminated C(sp<sup>3</sup>)-organodimetallics can serve as dinucleophilic linchpins for the rapid assembly of complex molecular structures through two consecutive electrophilic substitution reactions with two different electrophiles. Implementation of these double functionalization sequences in a stereoselective manner to develop tools for asymmetric synthesis has attracted considerable interest from the synthetic community over the last decade. The focus has been put mostly on 1,1-bimetallic reagents containing boron, zinc or zirconium, and different

strategies have been applied for such a purpose, including the diastereoselective transformation of enantioenriched chiral reagents or the enantioselective conversion of achiral or racemic derivatives. Asymmetric catalysis is at stake in most of the approaches developed. In this review article, we highlight the key advances in the development of 1,1-bimetallic linchpins as tools for asymmetric synthesis, emphasizing the underlying general concepts.

## 1. Introduction

1,1-Bimetallic reagents (sp<sup>3</sup>-geminated organodimetallics) (I) have attracted pursued interest from the synthetic community since the pioneering studies of Wittig, Ziegler and West and Rochow in the 1940's.<sup>[1]</sup> Much of the initial synthetic focus was put on the use of 1,1-bimetalloethanes (I, R=H) to create carbon-carbon double bonds from carbonyl derivatives. The prospect to engage such dinucleophilic reagents in consecutive reactions with two different electrophiles was demonstrated next, paving the way for their use as linchpins that allow for the rapid and efficient assembly of molecular structures with a minimum of chemical steps (Scheme 1). In the case of geminated heterobimetallic reagents (I, M<sup>1</sup> ≠ M<sup>2</sup>), such possibility arises from the difference of reactivity of the two carbon-metal bonds. Seminal studies for this purpose include the work of Zweifel on *gem*-borosodio and *gem*-borolithio reagents,<sup>[2]</sup> Knochel on *gem*-borozincio compounds,<sup>[3]</sup> and Srebnik on *gem*-borozirconio derivatives.<sup>[4]</sup> Nevertheless, successive functionalization with two different electrophiles is also possible from geminated homobimetallics (I, M<sup>1</sup>=M<sup>2</sup>). This is related to the fact that these species are generally more reactive, notably towards transmetalation, than the



**Scheme 1.** 1,1-bimetallic reagents as linchpins through two consecutive electrophilic substitution reactions with two different electrophiles (Ei = electrophile).

(mono)organometallic intermediates arising from a first coupling. Normant, Knochel and Marek pioneered this approach with their studies on 1,1-biszincio reagents<sup>[5]</sup> prepared through Gaudemar's allylzincation of vinylmetals,<sup>[6]</sup> with a significant contribution of Matsubara.<sup>[7]</sup> Overall, the most popular 1,1-bimetallic reagents that have been used as linchpins in double sequential functionalization reactions are derivatives of boron, zinc or zirconium. Of note,  $\alpha$ -metalated organosilyl reagents represent a class of compounds that can also be related to this chemistry, given that the carbon-metal bond can be engaged selectively in electrophilic substitution reactions leaving intact the carbon-silicon bond which *holds potential* for further elaboration. In practice however, this second functionalization step is rarely implemented, if at all.

The possibility to perform stereoselectively the double functionalization reactions was established next, opening the way to the development of asymmetric variants.<sup>[8]</sup> This challenge became progressively an important endeavor in the field and is the focus of this *Concept* article. The main tactics developed so far to tackle this problem are depicted in Scheme 2 and can be classified in two general groups. A first group concerns the use of chiral non-racemic 1,1-bimetallic reagents; it includes derivatives for which the chirality is borne by the dimetalated carbon (**Ia**) or reagents with stereogenic

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centers on the carbon backbone (**1b**) that induce stereocontrol during electrophilic substitution reactions of prochiral *gem*-bimetallic units. For this first group, the stereoselective preparation of the requisite 1,1-bimetallic reagents has attracted most of the research efforts. The second group is the realm of asymmetric catalysis and concerns the use of achiral (**1c**) or racemic ((±)-**1d**) derivatives engaged in catalytic enantioselective desymmetrization or resolution reactions.

These approaches rely exclusively on catalyst-controlled transformations.



Federico Banchini, born in Livorno (Italy) in 1995, studied chemistry at the University of Pisa (Italy). He completed his master's degree (with honors) in 2020 under the supervision of Prof. Dr. Fabio Bellina, focusing on the direct C–H activation of azoles. Then, in 2021, he started his PhD at Sorbonne Université (Paris, France), in the ROCS team. His current doctoral research focuses on the development of novel asymmetric sequential cross-coupling reactions using prochiral C(sp<sup>3</sup>)-gem-dizinc reagents.



Baptiste Leroux, born in Vendôme (France) in 1997, studied chemistry at the engineering school of CPE in Lyon and the University Claude Bernard of Lyon. He completed his engineering degree alongside his master's degree in 2021, under the supervision of Professor Abderrahmane Amgoune, focusing on the Cross-Coupling with photoredox/Nickel Dual Catalysis. Then, in 2021, he started his PhD at ICMPE (Thiais, France) in the ECCO group. His current doctoral research focuses on the development of asymmetric multi-component reactions using prochiral C(sp<sup>3</sup>)-gem-dizinc reagents.



Prof. Dr. Erwan Le Gall received his PhD from the University of Rennes (France) in 1998. The thesis work was focused on  $\alpha$ -aminonitriles electrocatalysis and their application to the preparation of heterocyclic compounds. After a postdoctoral stay with Dr. Corinne Gosmini in the LECSO group, he was appointed Assistant Professor (2001) at Université Paris Est Créteil (UPEC). He obtained his habilitation degree in 2009 and was promoted Full Professor in 2014. His current research mainly focuses on the development of multi-component reactions involving preformed or in situ-generated organometallic reagents.



Dr. Marc Passet studied chemistry at the Université of Avignon, Ecole Normale Supérieure de Cachan and Aix-Marseille Université (PhD, Sup.: Dr Y. Coquerel and Prof. J. Rodriguez, 2010). Then, he held postdoctoral positions with Prof. G. A. Molander (University of Pennsylvania, USA), Dr F. Rombouts (Janssen, Belgium) and Prof. V. Gandon (Université Paris-Sud). In 2014, he moved to the Université Paris-Est Créteil where he was appointed Assistant Professor in 2015. His current research activities are focused on the development of new reactions and reagents.



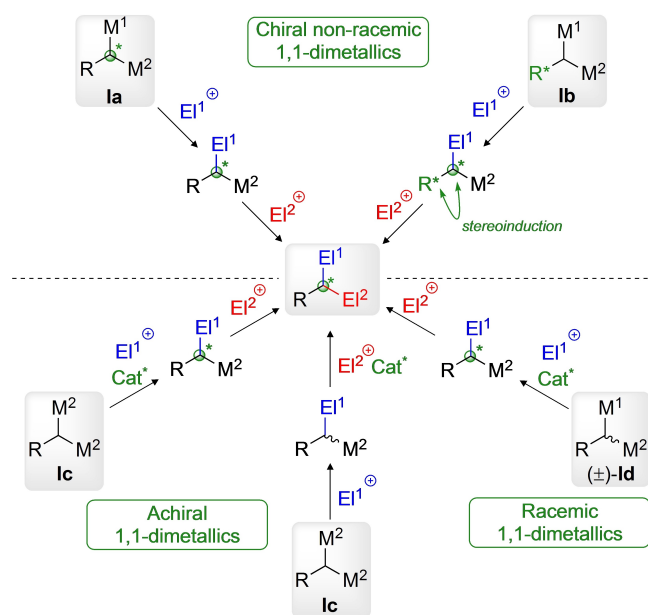
Dr. Olivier Jackowski was born in Ris-Orangis (France) in 1980. He began his career in carbohydrate chemistry, receiving his Ph.D. in 2008 from Université Nancy I, under the supervision of Dr Chapleur and, working then with Professor Décout (Grenoble). In 2009, he turned his researches to organometallics joining successively the groups of Prof. Alexakis (Geneva), Dr. Micouin (Paris) and Dr Virginie Vidal (Paris). In 2012, he was appointed as associate professor at Sorbonne Université. His research interests include the development of selective transformations as well as metal-catalyzed reactions, employing organometallic reagents for both.



Prof. Dr. Fabrice Chemla studied chemistry at the ESPCI – Paris (1986–1989) and obtained his PhD degree in 1992 under the supervision of Pr. Marc Julia (Ecole Normale Supérieure). After a postdoctoral stay with Pr. Reinhard W. Hoffmann (Marburg, 1992), he joined the Université Pierre et Marie Curie (now Sorbonne Université) as assistant professor. He obtained his habilitation degree in 2000 and was promoted as full professor in 2002 in Sorbonne Université. He develops research in the field of metal-mediated synthesis, with a focus on the design of new transformations involving main group organometallics species.



Dr. Alejandro Perez-Luna studied chemistry at the Ecole Nationale Supérieure de Chimie de Paris (Paris, 1997–2000) and then obtained a PhD degree with Laurent Micouin (Université Paris 5, 2003). After a postdoctoral stay with Peter Kündig (Geneva, 2004), he joined Université Pierre et Marie Curie (now Sorbonne Université) as a CNRS researcher. He obtained his habilitation degree in 2012 and was promoted Research Director in 2015. He develops research in the field of metal-mediated synthesis, with a focus on functionalized main-group organometallic reagents.

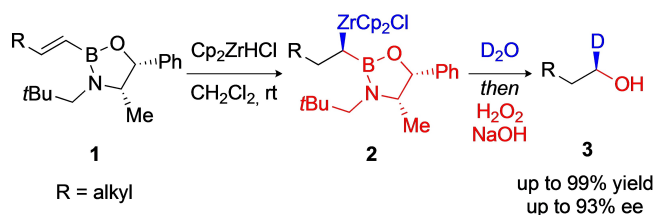


**Scheme 2.** General approaches for the stereoselective double electrophilic substitution of 1,1-bimetallic reagents.

## 2. Stereoselective Sequential Functionalization of Chiral Non-racemic 1,1-Bimetallic Reagents

The first forays in the field of stereoselective double functionalization of 1,1-bimetallic reagents were carried out by Srebnik as part of his studies on  $\alpha$ -boryl zirconocenes. Hydrozirconation of vinylboranes **1** having a chiral non-racemic pseudoephedrine-derived ligand, delivered 1,1-borylzirconioalkanes **2** with high levels of diastereoselectivity (Scheme 3).<sup>[9]</sup> The authors ascribed the selectivity of the reaction to diastereotopic face-discrimination during the hydrozirconation event, thus implying that intermediate **2** is configurationally stable. Regardless of this, stereoselective double functionalization of **2** was achieved through the selective cleavage of the (more reactive) carbon-zirconium bond by deuteration followed by oxidation of the carbon-boron bond. These two successive reactions proceed with retention of configuration at the carbon atom to afford alcohols **3** in high enantiomeric purity.

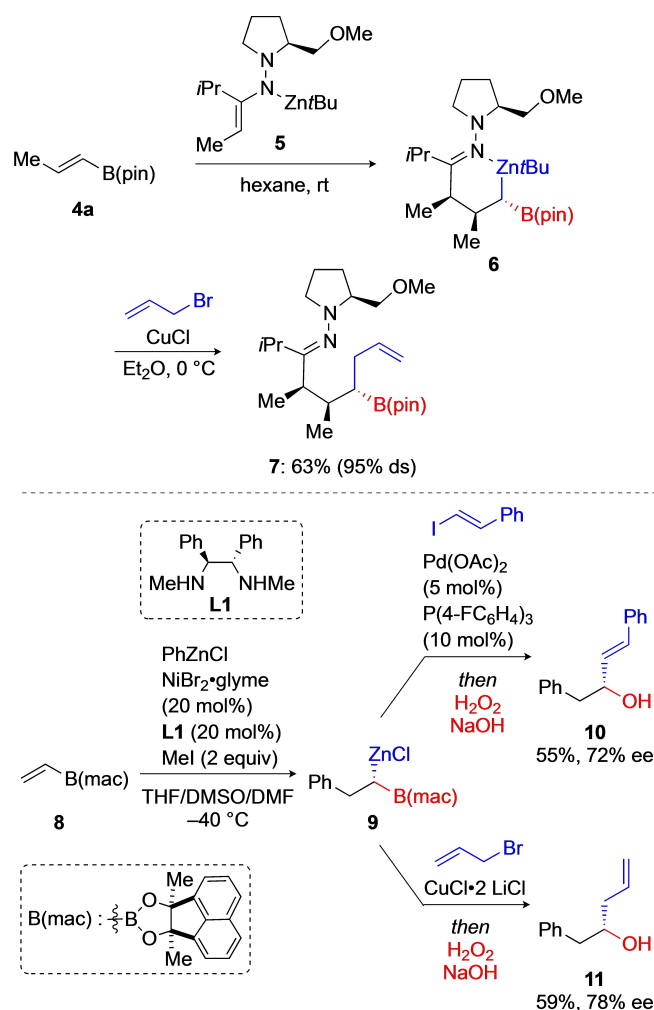
The Nakamura group later reported the stereoselective preparation of 1,1-borylzincioalkanes by carbozincation of vinylboranes with zincated hydrazones.<sup>[10]</sup> These 1,1-bimetallic intermediates are configurationally stable and can undergo



**Scheme 3.** Synthesis and double functionalization of chiral enantioenriched {Zr, B} 1,1-bimetallic reagents.

copper-mediated functionalization of the carbon-zinc bond with retention of configuration. The remaining boryl group can then serve as precursor to alcohols on oxidation. An asymmetric variant of the reaction was developed using enantiomerically enriched zincated hydrazone **5** (Scheme 4, top).<sup>[10]</sup> Carbozincation of vinylborane **4** to provide diastereo- and enantiomerically enriched 1,1-bimetallic intermediate **6** was followed by copper-mediated allylation to obtain product **7** with excellent stereoselectivity.

The scope of the use of chiral 1,1-borylzincioalkane linchpins was significantly increased more recently with the development by the Morken group of a general access to enantioenriched 1,1-borylzincioalkanes **9** through the enantioselective nickel-catalyzed carbozincation of vinylboronate **8** (Scheme 4, bottom).<sup>[11]</sup> Several possibilities for the double functionalization of intermediates such as **9** were developed through stereoretentive cross-coupling of the carbon-zinc bond, including copper-mediated allylation and palladium-catalyzed alkenylation, followed by stereoretentive oxidation of the resulting organoboranes. Overall, alcohols such as **10** or **11** were obtained from **8** in a three-step procedure with reason-

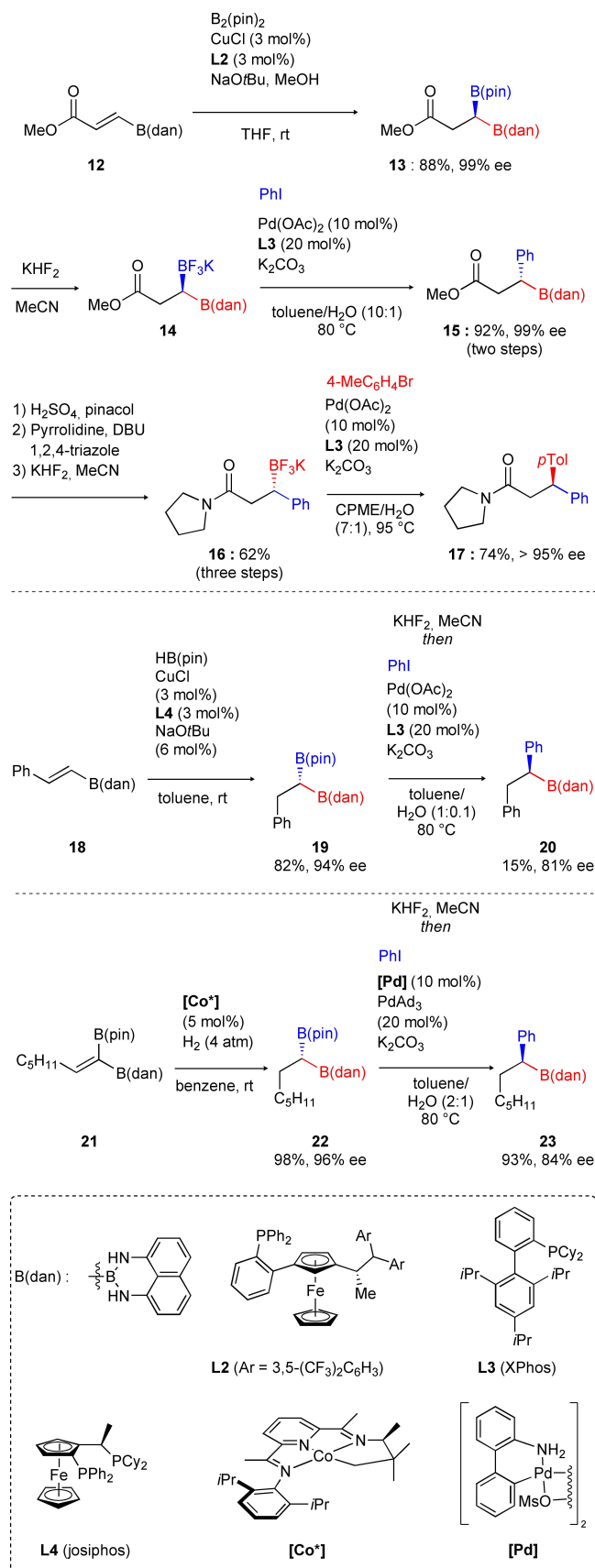


**Scheme 4.** Synthesis and double functionalization of chiral enantioenriched {Zn, B} 1,1-bimetallic reagents.

able yields and enantioselectivity. Of note, functionalization of the carbon-boron bonds other than oxidation were also combined with the first carbon-zinc cross-couplings. For instance, allylation-homologation or allylation-amination sequences were implemented in the context of applications in total synthesis.

Recent work has also been devoted to the preparation of enantiomerically enriched chiral 1,1-bisborooalkanes having different substitution patterns of the boron atoms (Scheme 5). The Hall group opened this research avenue with a report on the preparation of *gem*-bisboronate **13** in 99% ee by enantioselective copper-catalyzed boron conjugate addition to B(dan)-substituted acrylate **12** using B<sub>2</sub>(pin)<sub>2</sub> (Scheme 5, top).<sup>[12]</sup> The two different boron units could then be engaged in a sequence entailing two stereoselective Suzuki-Miyaura palladium-catalyzed arylation reactions. In general, secondary boronates are challenging substrates for such cross-coupling reactions. Nevertheless, it is well established that *gem*-bisboronates have better reactivity because the second boryl unit stabilizes the  $\alpha$ -boryl-Pd(II) intermediate that undergoes transmetalation.<sup>[13]</sup> Along these lines, it was found that the B(pin) unit of 1,1-bisboronate **13** could be cross-coupled readily, but only to afford products in racemic form, indicating that the reaction proceeded through a configurationally unstable intermediate that lost its stereochemical integrity. Thus, the pinacol boronic ester of **13** was converted into a trifluoroborate unit to provide 1,1-bisboronate **14** that proved competent, using Pd(OAc)<sub>2</sub>/L3 (XPhos) as catalytic system, to undergo cross-coupling reactions with aryl- and alkenyl halides while retaining its stereochemical integrity and leaving the B(dan) group intact. As shown with the formation of **15**, yields and ee obtained by this method were excellent and the cross-coupling occurred with inversion of configuration. Performing the second Suzuki-Miyaura cross-coupling from secondary boronate **15** proved highly challenging, and not only the B(dan) unit had to be converted to a trifluoroborate group, but also the ester moiety had to be changed into an amide function. Under these conditions, the corresponding "activated" secondary boronate **16** could be engaged in a stereospecific (invertive) arylation reaction using the same catalytic system as previously, to deliver **17** in 74% yield and >95% ee. The benefit obtained with the amide was ascribed to a more favorable coordination of the carbonyl oxygen to the boron atom of the catalytically active boronic acid intermediates derived from the trifluoroborate. This interaction, stronger in the case of the more Lewis basic amides than esters, was proposed to activate the carbon-boron bond towards boron-to-palladium transmetalation.

Following on the work of Hall, other strategies were designed to prepare enantiomerically enriched chiral 1,1-bisborooalkanes having one B(pin) and one B(dan) unit. On the one hand, the Yun group disclosed the asymmetric copper-catalyzed hydroboration of alkenyl B(dan) derivatives **18** to afford 1,1-bisborooalkanes **19** (Scheme 5, middle).<sup>[14]</sup> The strategy was further improved by Yu, Song and co-workers that developed a protocol wherein the requisite alkenyl B(dan) substrates for copper-catalyzed hydroboration with HB(dan) are formed in one pot through alkyne hydroboration with HB(dan)

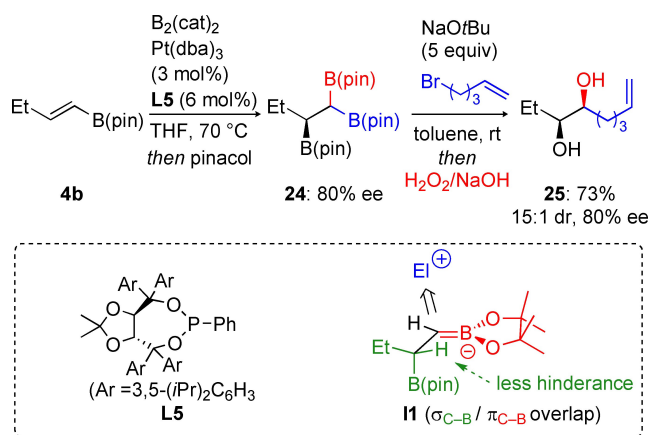


**Scheme 5.** Synthesis and double functionalization of chiral enantioenriched {B(pin), B(dan)} 1,1-bimetallic reagents.

(not shown in the scheme).<sup>[15]</sup> On the other hand, the Chirik group reported the asymmetric hydrogenation of 1,1-bisbor-oalkanes **21** yielding **22** in 96% ee (Scheme 5, bottom).<sup>[16]</sup> Interestingly, stereoinvertive Suzuki-Miyaura cross-coupling upon conversion to the corresponding trifluoroborates was considered for these mixed B(pin), B(dan) 1,1-bisboroalkanes (**19** and **22**) that don't have a pending carbonyl group. Here, not only efficient cross-coupling required more active catalysts, but non-negligible erosion of enantiomeric purity occurred. Moreover, the cross-coupling of the secondary B(dan) boronates prepared (**20** and **23**), which don't have pending activating groups, was not considered in any of the reports.

Another type of approach that has been exploited to use 1,1-bisboroalkanes as linchpins for stereoselective double functionalization reactions concerns derivatives having stereogenic centers on the carbon chain. Here, the chirality of the backbone exerts diastereocontrol during the first electrophilic substitution of the geminated prochiral boryl units to produce diastereo- and enantiomerically enriched secondary boronic esters poised for subsequent stereospecific functionalizations.

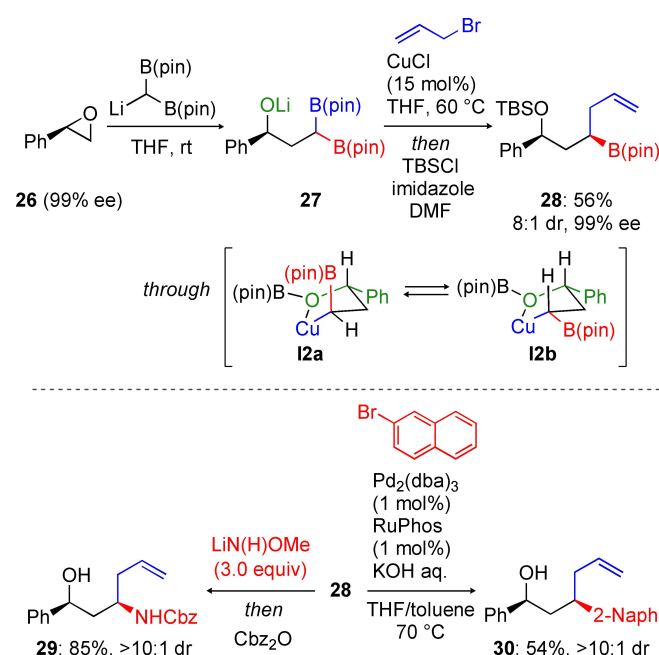
The Morken group was the first to investigate this approach and prepared enantioenriched (80% ee) 1,1,2-trisboronates such as **24** by platinum-catalyzed asymmetric diboration of alkenylboronic esters (i.e. **4b**) (Scheme 6).<sup>[17]</sup> Diastereoselective alkylation was achieved with high levels of selectivity on treatment of **24** with *t*BuONa in the presence of an alkyl bromide. The authors put forward a mechanistic scenario involving the formation of anionic intermediate **I1** following deboration of **24** on reaction with the alkoxide. Because the nucleophilicity of **I1** is enhanced by the hyperconjugation between the  $\pi$  carbon-boron bond and the adjacent carbon-boron  $\sigma$  bond, the most reactive conformations are those for which the  $\sigma$  carbon-bond and the  $\pi$  carbon-bond are perpendicular, and amongst these, the most favorable is the one (shown in Scheme 6) that avoids non-bonding interactions between the Et group and the boron unit of the reacting carbon. Following the alkylation step, stereoretentive oxidation of the remaining carbon-boron bonds was performed to produce enantioenriched diols. Product **25**, which was then



**Scheme 6.** Synthesis and double functionalization of chiral enantioenriched 1,1,2-trisboronates.

advanced to natural product *exo*-brevicommin, was obtained from **24** in 73% yield, 15:1 dr and 80% ee.

In a second system, Meek and co-workers formed chiral 1,1-bisboroalkanes like **27** by ring opening of chiral epoxides following reaction with lithiated 1,1-diborylmethane (Scheme 7).<sup>[18]</sup> Copper-catalyzed allylation of these intermediates was achieved, in the same pot, with excellent levels of diastereoselectivity, delivering enantioenriched boronic esters like **28** that could be further transformed by stereoretentive oxidation or amination to produce alcohols or amines (i.e. **29**). Stereoselective Suzuki-Miyaura cross-coupling of these intermediates is also feasible, as illustrated with the formation of **30**. It is likely that the pending alcohol facilitates the reaction and it is noteworthy that the cross-coupling proceeds with inversion of configuration at the reacting carbon center. Mechanistic studies to determine the origin of the stereoinduction in the first step demonstrated that coordination of the pending alkoxide to the boron atom of one of the B(pin) groups of the prochiral *gem*-diboryl motif was scarcely diastereoselective and the rate for the copper-mediated electrophilic substitution was similar for both diastereomeric cyclic boron "ate" intermediates. Hence, the high levels of stereoinduction were rather attributed to the reaction of the  $\alpha$ -boryl copper intermediates **I2a** and **I2b**, but it was not established if it was related to a diastereoconvergent transmetalation from the cyclic boron "ate" complexes or to dynamic kinetic resolution during the electrophilic substitution event.



**Scheme 7.** Synthesis and double functionalization of chiral enantioenriched {B(pin), B(pin)} 1,1-bimetallic reagents.

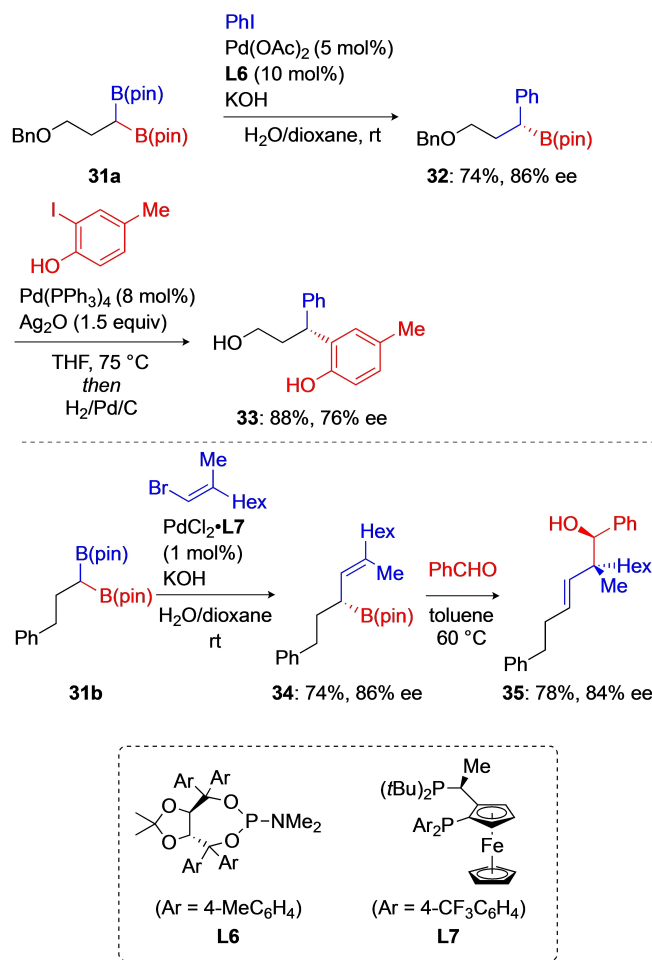
### 3. Enantioselective Sequential Functionalization of Achiral 1,1-Bimetallic Reagents

The advent of a large array of methods to prepare prochiral symmetric geminated diboryl species from readily available precursors has driven the focus of considerable current research to their use in asymmetric transformations. Owing to the configurational stability of organoboron reagents, most of the implemented approaches to achieve enantioselective double functionalization rely on a first enantiotopic group-selective cross-coupling reaction. These reactions proceed usually through the catalytic generation of a chiral  $\alpha$ -boryl organometallic upon boron-to-metal transmetalation. For most cases however, it is difficult to establish whether these intermediates are configurationally stable or not and thus the origin of enantioselectivity that may arise either from stereoselective transmetalation or dynamic kinetic resolution processes.

Morcken opened this research direction in 2014 with the achievement of the enantioselective desymmetrization of achiral 1,1-bisboronates **31** having geminated prochiral B(pin) units upon palladium-catalyzed Suzuki-Miyaura cross-coupling with aryl iodides or aryl bromides (in the presence of sodium iodide) (Scheme 8, top).<sup>[19]</sup> The catalytic system employed relied on the use of Pd(OAc)<sub>2</sub> and phosphoramidite ligand **L6**. Mechanistic investigations strongly suggested that the transmetalation step is the stereoselectivity determining one. Secondary organoboron intermediates (i.e. **32**) were obtained in consistently high enantioselectivity for either primary alkyl- or secondary alkyl-substituted bis(boronates), with little variation according to the nature of the arylhalide partner. As demonstrated with the formation of compound **33** from **32**, a second stereoselective cross-coupling of the remaining B(pin) unit was possible in the presence of silver oxide using Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst. The cross-coupling proceeded with retention of the carbon configuration, but a slight loss of stereochemical integrity was observed.

The same strategy was next implemented with alkenyl bromides as electrophiles for the first cross-coupling (Scheme 8, bottom).<sup>[20]</sup> Here, the enantiotopic group selective desymmetrization was achieved with PdCl<sub>2</sub> pre-catalyst and Josiphos-type ligand **L7**, producing secondary allylboronates **34** in high yields and enantiomeric purity. The allylic nature of the intermediates offered additional opportunities for subsequent (stereospecific) elaboration of the remaining carbon-B(pin) bond, including regioselective ( $\alpha$  or  $\gamma$ ) oxidations, or, as for the formation of **35**, condensation with benzaldehyde through S<sub>E</sub>2' electrophilic substitution reactions. These second steps are achieved in the absence of a transition-metal catalyst and full retention of stereochemical integrity was noted.

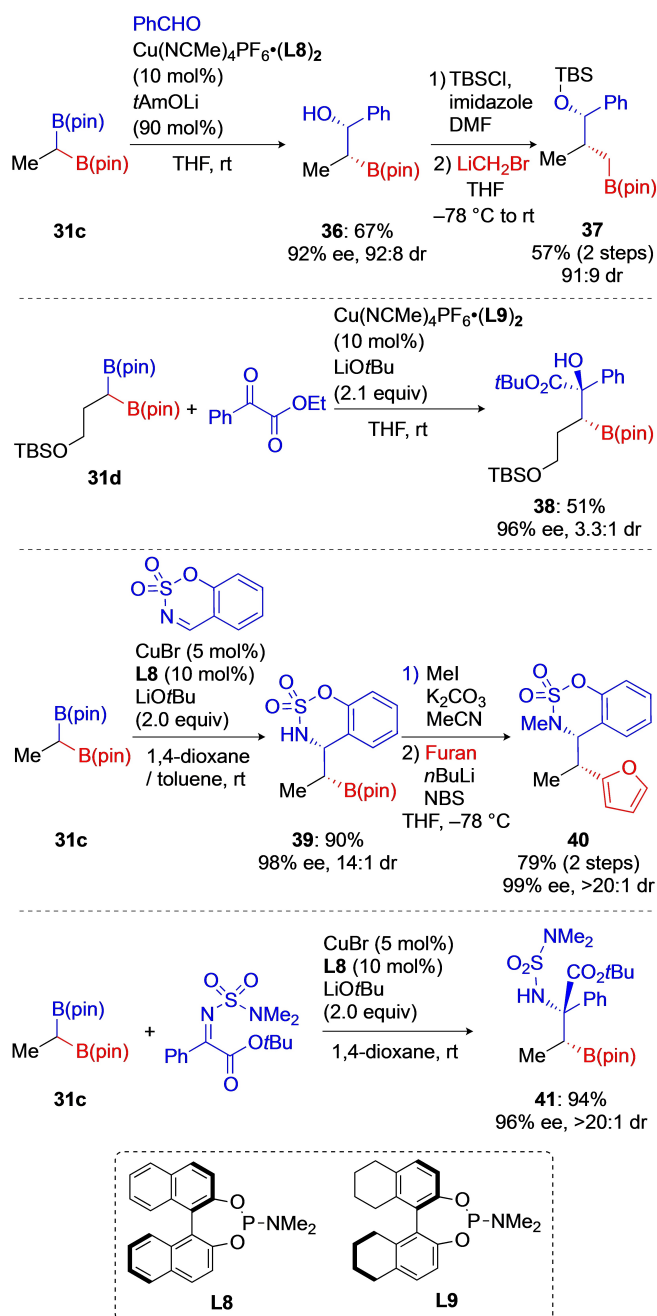
Following on the successful development of asymmetric palladium catalysis in the field, copper-catalysis was developed. The Meek laboratory considered the 1,2-addition of 1,1-bisboronates **31 c** to aryl aldehydes (Scheme 9, top).<sup>[21]</sup> In the presence of the chiral non-racemic copper complex Cu(NCMe)<sub>4</sub>PF<sub>6</sub>•(**L8**)<sub>2</sub>, *syn*-1,2-hydroxyboronates such as **36** were obtained with



**Scheme 8.** Enantioselective desymmetrization of achiral {B(pin), B(pin)} 1,1-bimetallic reagents by Suzuki-Miyaura cross-coupling.

excellent levels of diastereocontrol and enantioselectivity (up to 96% ee). Mechanistic investigations evidenced that the reaction involves the intermediate formation with high stereopurity of a chiral  $\alpha$ -boryl alkylcopper complex ((Cu, B(pin)) 1,1-bimetallic). Stereoretentive elaboration of the second carbon-B(pin) moiety was achieved through conversion into alcohols or amines under typical conditions or through homologation, as shown with the conversion of **36** to **37**. The protocol for addition was extended to other carbonyl acceptors. Alkenyl aldehydes were well-suited, but diastereoselectivity (though not enantioselectivity) was only satisfactory for substituted vinyl aldehydes. By contrast,  $\alpha$ -keto esters gave very good results and 1,1-bisboronates other than 1,1-bisboronethane could be used.<sup>[22]</sup> As shown with the transformation of **31 d** into **38**, these reactions produce quaternary stereogenic centers in very high ee (96%) and good dr (3.3:1) (Scheme 9, middle). Of note, another catalytic protocol relying on silver acetate was also developed to prepare *anti*-1,2-hydroxyboronates by similar deborylative 1,2-additions to aryl, alkenyl and alkyl aldehydes, albeit as racemates.<sup>[23]</sup>

The Cho group extended further Meek's protocol to encompass 1,2-additions of 1,1-bisboronates **31** to C=N bonds. Cyclic aldimines performed very well, leading to *syn*-1,2-amino-



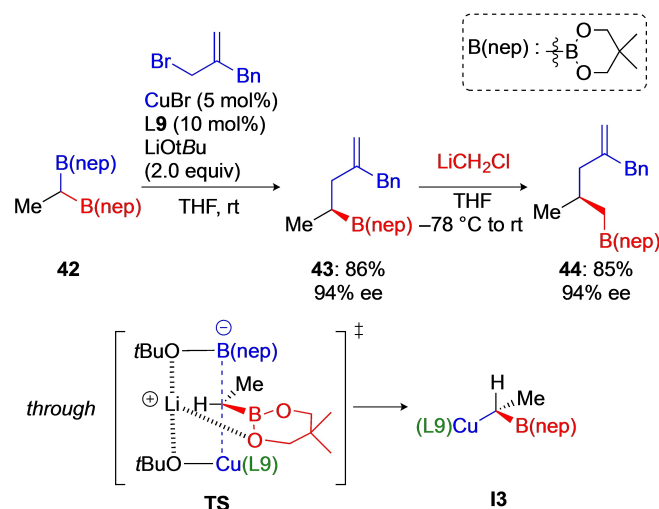
**Scheme 9.** Enantioselective desymmetrization of achiral {B(pin), B(pin)} 1,1-bimetallic reagents by copper-catalyzed addition to carbonyl or imine derivatives.

boronates such as 39 in very high diastereoselectivity and > 95% ee (Scheme 9, bottom).<sup>[24]</sup> Acyclic arylaldimines were also amenable to diastereo- and enantioselective 1,2-addition. For *N*-tosyl-protected substrates,<sup>[24]</sup> the diastereoselectivity of the process was modest, but this problem was solved conveniently using *N,N*-dimethyl sulfamoyl-protected aldimines.<sup>[25]</sup> Later, it was demonstrated that cyclic ketimines and  $\alpha$ -imino esters also performed very well, providing  $\beta$ -aminoboronate esters such as 41 bearing adjacent quaternary stereocenters with very high diastereo- and enantioselectivity.<sup>[26]</sup> As previously for the  $\beta$ -

hydroxyboronate esters, elaboration of the remaining carbon-B(pin) bond was possible through typical boron chemistry, including stereoretentive conversion into alcohols, amines or homologation. The transformation of 39 into 40 introducing a furyl group illustrates further the potential for functionalization of these intermediates using 1,2-borate rearrangement chemistry.

Enantioselective desymmetrization of 1,1-bisborooalkanes was next achieved by the Cho group through copper-catalyzed allylic substitution reactions (Scheme 10). Using as catalytic system CuBr (5 mol%) and phosphoramidite ligand L9 (10 mol%) in the presence of tBuOLi, allylation of {B(nep), B(nep)} 1,1-bimetallic reagents such as 42 by reaction with allyl bromides delivers secondary homoallylic boronates 43 in high yields and excellent ee. The carbon-boron bond of the B(nep) boronates could be functionalized similarly as that of B(pin) boronates, as shown for example with the stereoretentive homologation implemented to convert 43 into 44. It is worthy-of-mention that 1,1-bisborooalkanes having B(pin) units also participated readily in the desymmetrization reactions but with slightly lower levels of enantioselectivity than the B(nep) congeners.<sup>[27]</sup>

Extensive experimental and theoretical mechanistic investigations carried out as part of this work led to important insights about the way copper promotes enantiotopic group selectivity. It was proposed that the boron-to-copper transmetalation step occurs in a stereoinvertive manner through the open transition state TS (Scheme 10) to deliver with high stereoselectivity chiral  $\alpha$ -boryl alkyl copper intermediate I3, which then engages in the allylation reaction (which can be both S<sub>E</sub>2- or S<sub>E</sub>2'-like) with retention of configuration at the carbon bearing the carbon-copper bond. Given that the copper-catalytic system of these reactions is very similar to those used for the desymmetrization upon 1,2-additions discussed previously, one can infer that the same mechanistic picture operates for the latter.



**Scheme 10.** Enantioselective desymmetrization of achiral {B(nep), B(nep)} 1,1-bimetallic reagents by copper-catalyzed allylation.

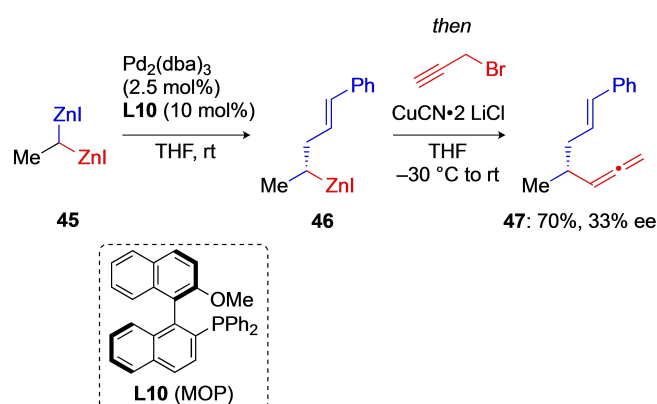


The other family of achiral 1,1-bimetallic reagents that have served as linchpins for double enantioselective catalytic cross-coupling reactions is that of 1,1-biszincioalkanes. One fundamental difference between the chemistry of dizinc and diboryl linchpins is that the successive functionalizations are performed in one pot, without isolation of the (mono)organometallic intermediate. Another asset of the zinc chemistry is that cross-coupling reactions of secondary organozinc reagents are often easier and larger-in-scope than those of secondary organoboronates, and thereby the possibilities for double cross-coupling are, in principle, wider.

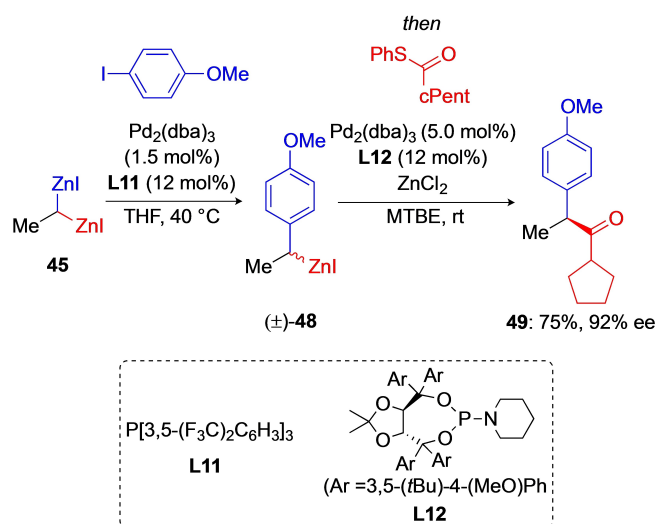
In seminal, work, Matsubara considered the enantiotopic group-selective cross-coupling reaction of 1,1-biszincioethane (45) under palladium catalysis (Scheme 11).<sup>[28]</sup> The resulting chiral secondary organozinc reagent 46 was then trapped *in-situ* by copper-mediated propargylic substitution to deliver product 47, in 70% yield but low 33% ee. The scenario put forward by the authors to rationalize this result relies on the configurational stability of intermediate 46, that then undergoes stereospecific copper-catalyzed cross-coupling. Hence, the low overall enantiomeric excess obtained was ascribed to a low enantiotopic discrimination of the prochiral carbon-zinc bonds of 45. Note however that the possibility to have a loss of enantiopurity by racemization of the secondary copper intermediate was not excluded experimentally.

To overcome these two possible problems, our group considered an alternative approach based on the intermediate formation of a configurationally labile organozinc intermediate engaged in a second cross-coupling for which enantioselection is achieved by dynamic kinetic resolution. In such a situation, it is no longer necessary to achieve the desymmetrization of the starting achiral 1,1-bimetallic reagent enantioselectively and configurational instability becomes a requirement instead of a draw back.

Implementation of this prospect was achieved in an enantioselective double cross-coupling reaction sequence involving aryl iodides and then thioesters (Scheme 12).<sup>[29]</sup> As illustrated with the formation of 49, first, mono-arylation of 45 was achieved using  $[Pd_2(dba)_3/L11]$  as catalytic system. Then,



**Scheme 11.** Enantioselective desymmetrization of achiral {Zn, Zn} 1,1-bimetallic reagent 45 by one-pot Pd-catalyzed allylation – Cu-catalyzed propargylation.



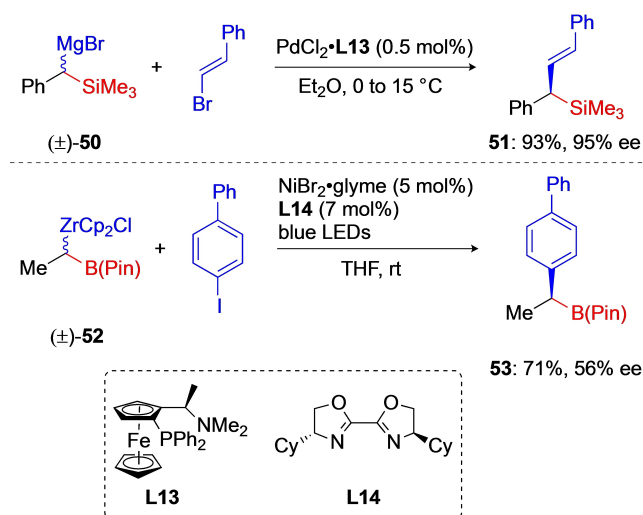
**Scheme 12.** Enantioselective desymmetrization of achiral {Zn, Zn} 1,1-bimetallic reagents by one-pot Pd-catalyzed arylation – Pd-catalyzed acylation.

enantioconvergent Pd-catalyzed Fukuyama cross-coupling of  $(\pm)$ -48 was achieved, in the same pot, using  $Pd_2(dba)_3/L12$  as catalytic system. It is noteworthy that the main challenge for this approach is that stereodifferentiation during the second step is achieved despite the presence of the achiral ligand required for the first catalytic system. The procedure was found applicable with various aryl iodides, with little impact of their electronic character, and thioesters, even though the less bulkier primary thioesters afforded lower ee. Beyond 45, other 1,1-biszincioalkanes with primary alkyl chains were also amenable to the enantioselective cross-coupling despite a decrease of yield and ee with the increase of the size of the alkyl chain.

## 4. Enantioselective Sequential Functionalization of Racemic 1,1-Bimetallic Reagents

A last possibility that has been considered to achieve enantioselective functionalization of hetero-1,1-bimetallic reagents is based on the implementation of stereoconvergent cross-coupling reactions. By doing so, the selectivity does not rely on the stereochemical purity of the starting reagent, with the obvious advantage being that it can be engaged in racemic form. Stereoconvergence might become possible either because of the absence of configurational stability of one or more reaction intermediates (including the starting reagent) or because one or more intermediates lose their stereochemical integrity (i.e. radical derivatives).

The palladium-catalyzed alkenylation of  $\alpha$ -silyl Grignard reagent  $(\pm)$ -50 reported by Kumada represents an example of the first situation (Scheme 13).<sup>[30]</sup> Using the josiphos-type ligand **L13**, cross-coupling with 1-bromostyrene delivered secondary chiral organosilane 51 in 93% yield and 95% ee. No attempt to



**Scheme 13.** Enantioconvergent cross-coupling reactions of racemic {Mg, Si} and {Zr, B} 1,1-bimetallic reagents.

functionalize further the remaining carbon-silicon bond was however reported. Along the second approach, the arylation of  $\alpha$ -boryl zirconocenes such as ( $\pm$ )-52 under nickel-catalysis and photoirradiation was considered by Qi and co-workers.<sup>[31]</sup> As illustrated with the formation of 53, the cross-coupling reactions occurred in good yields but only modest enantioselectivity.

## 5. Summary and Outlook

The last decade has witnessed a tremendous impulse in the development of  $sp^3$ -geminated organodimetallics as tools for asymmetric synthesis. Through the sequential double functionalization of each carbon-metal bond, such reagents serve as linchpins for the rapid chemo- and stereoselective assembly of complex molecular structures with a minimum of chemical steps, which is a key endeavor of modern synthetic chemistry. Different strategies have been applied for such a purpose, including the diastereoselective transformation of enantioenriched chiral reagents or the enantioselective conversion of achiral or racemic derivatives. In the vast majority of cases, the desymmetrization systems are designed so that the first electrophilic substitution delivers an enantioenriched configurationally stable (mono)organometallic intermediate with the capacity to undergo subsequent stereospecific transformations. The potential of the alternative approach relying on non-configurationally stable (mono)organometallic intermediates has been uncovered very recently and will certainly be the focus of further research.

The field has been so far dominated by  $\alpha$ -metalated organoboronate linchpins, which offer many advantages, including chemical and stereochemical stability of the bimetallic and mono-organoboron derivatives and ready availability of a large array of linchpins. The power of this chemistry has already been exploited for various synthetic applications. The other side of the coin is that secondary organoboronates are rather feeble

partners for cross-coupling reactions what tends to limit the scope of the second functionalization step, which in addition is rarely performed in one-pot procedures. Solutions here might come from  $\alpha$ -boryl silicon<sup>[32,33]</sup> or germanium<sup>[34]</sup> linchpins, for which the stereoselective cross-coupling chemistry of the secondary organosilanes and organogermanes needs to be developed. *gem*-Dizinc linchpins could also offer further options, but the challenge here remains to develop truly broad and efficient access to the starting linchpins. In a longer time-scale, the highly challenging objective to construct tetrasubstituted stereogenic carbon centres through double functionalization of appropriate 1,1-bimetallic reagents, which remains a totally unexplored field, might also stimulate future research efforts.

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## Conflict of Interests

The authors declare no conflict of interest.

**Keywords:** bimetallics · cross-coupling · enantioselectivity · boron · zinc

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