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C–C Coupling

The Liebeskind–Srogl C–C Cross-Coupling Reaction

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copper · cross-coupling · homogeneous catalysis · palladium · thioorganic compounds

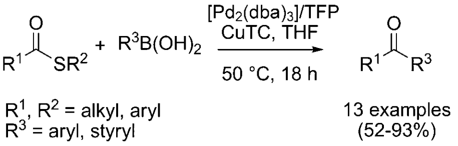
Although a plethora of highly selective and reliable methods for the construction of C–C bonds are known to organic chemists, there is growing interest in the development of new protocols that offer different or orthogonal reactivity to that of existing methods. In 2000, Liebeskind and Srogl described a mechanistically unprecedented transition-metal-catalyzed cross-coupling of thioesters with boronic acids to produce ketones under neutral conditions. This desulfitative cross-coupling process is catalytic in palladium(0), stoichiometric in copper(I), and applicable to a range of organosulfur derivatives and nucleophilic organometallic reagents. In this Minireview, we highlight recent applications of this intriguing cross-coupling reaction in modern organic synthesis, with an emphasis on cases in which traditional methods for C–C bond formation have failed.

1. Introduction

Transition-metal-catalyzed C–C cross-coupling reactions are among the most powerful and flexible transformations known to organic chemists and have revolutionized the art and practice of synthesis in the last two decades.[1] The generally mild reaction conditions, high functional-group tolerance, and broad availability of reagents have contributed to the growing success of these methods for C–C bond formation. Although most cross-coupling procedures involve the interaction of an electrophilic organohalide (or related substrate) with a nucleophilic organometallic reagent, the use of organosulfur compounds as electrophilic reaction partners has also been described.[2] In this context, a considerable variety of palladium- and nickel-catalyzed desulfitative C–C cross-coupling reactions of such substrates as sulfonyl chlorides, sulfoxides, and sulfones with organometallic reagents have been disclosed.[2]

As the oxidative addition of organosulfur compounds to low-valent transition-metal species is well established,[3] the key to catalytic turnover with organosulfur compounds is the activation of the very stable bond that is formed between the catalytically active metal (Pd, Ni, Pt) and the soft sulfur atom. The appropriate selection of a nucleophilic metallic reagent (for example, an organotin, organoboron, organosilicon, organozinc, or organomagnesium compound) for the following transmetalation step is of considerable significance. Among the plethora of cross-coupling procedures known today, protocols that involve boronic acids as coupling partners are becoming increasingly popular.[4] Most boronic acids are air- and moisture-stable and of relatively low toxicity, and nowadays many are commercially available. Therefore, cross-coupling chemistry with these reagents is highly attractive. The coupling of organosulfur compounds with boronic acids would be of particularly high synthetic value, as both reaction partners are readily available stable molecules of low toxicity. An essential step in this coupling process would be a transmetalation between the boronic acid and the metal thiolate intermediate, with concomitant replacement of the thiolate ligand. However, the low thiophilicity of boron in combination with the low nucleophilic reactivity of organoboron derivatives renders this transmetalation problematic.

In 2000, Liebeskind and Srogl disclosed a novel and mechanistically unprecedented palladium-catalyzed C–C cross-coupling protocol for the synthesis of ketones from thioesters and boronic acids under neutral conditions (Scheme 1).[5,6] A key feature of this method is the require-



Scheme 1. Palladium-catalyzed, copper(I)-mediated Liebeskind–Srogl ketone synthesis. CuTC = copper(I) thiophene-2-carboxylate, dba = dibenzylideneacetone, TFP = tris(2-furyl)phosphane.

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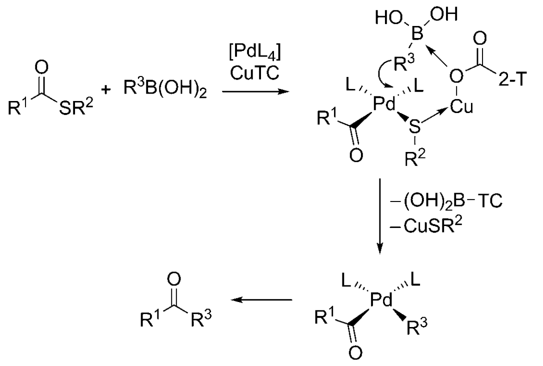
ment of a stoichiometric amount of a copper(I) carboxylate species, such as copper(I) thiophene-2-carboxylate (CuTC), as a thiophilic metal cofactor. Since the year 2000, the scope of this intriguing C–C bond-forming process has been extended considerably to enable successful cross-coupling reactions between a variety of organosulfur and organometallic reagents. We summarize herein the progress made in this rapidly growing field, with a focus on mechanistic aspects and synthetic applications of the Liebeskind–Srogl reaction.

2. Mechanistic Considerations

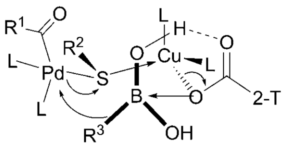
Palladium(0)-catalyzed, copper(I)-mediated desulfitative cross-coupling can be rationalized mechanistically in terms of a joint thiophilic/borophilic activation (selective interaction of the soft sulfur center with the soft copper center and of the carboxylate counterion with the boron center). When the copper(I) carboxylate was replaced with a copper(I) halide or CuCN, no coupling product was obtained.[5] The addition of a zinc(II) carboxylate was also ineffective, even though Zn^{II} salts function as activators of metal thiolates in nickel-catalyzed cross-coupling reactions of thioorganic compounds with organozinc reagents.[7]

The proposed reaction mechanism for the Cu^I-mediated, Pd^0-catalyzed coupling is shown in Scheme 2.[5,8] After oxidative addition of the thioester to the Pd^0 catalyst, the copper(I) carboxylate serves the dual role of polarizing the Pd–S bond through Cu^I coordination to the sulfur center and activating the trivalent boron compound simultaneously through coordination of the carboxylate to the boron center. A full equivalent of the Cu^I additive is required because of the need to scavenge the released thiolate as the reaction proceeds. Any readily available copper(I) carboxylate should be suitable for this coupling reaction. The choice of CuTC or, in subsequent studies, copper(I) 3-methylsalicylate (CuMeSal) or copper(I) diphenylphosphinate (CuDPP), all of which are now commercially available, was explained by Liebeskind and Srogl in terms of a combination of low cost and relative air stability.[5,7,8] To avoid any undesired oxidation of the Cu^I cofactor to a Cu^{II} species, the reaction generally has to be performed under an inert atmosphere.



Scheme 2. Proposed mechanism for the Liebeskind–Srogl reaction. 2-T = 2-thienyl, TC = thiophene-2-carboxylate, L = ligand.

Whereas the presence of a base is essential in the traditional Suzuki–Miyaura cross-coupling of boronic acids and organic halides,[9] an oxygen base was found to be deleterious to the Liebeskind–Srogl reaction.[10] This observation and the much greater reactivity of boronic acids relative to boronates led to the proposal of a hydrogen-bonded, ternary complex as the reactive intermediate (Scheme 3).[10] A low-energy reaction pathway via this ternary complex would most likely be sensitive to steric effects and would depend on the presence of hydrogen bonds from the boronic acid to the carboxylate counterion.[10]



Scheme 3. Proposed formation of a ternary complex in the Liebeskind–Srogl reaction.

The intermediacy of such a ternary complex was confirmed during the development of a Pd-catalyzed coupling of thioesters with aliphatic boron reagents.[10] In fact, alkyl boronic acids prove to be problematic in the traditional Suzuki cross-coupling and generally result in comparatively low product yields.[9] Similar low reactivity was observed in the Liebeskind–Srogl coupling of thioorganics. As in the case of the Suzuki transformation, this difficulty could be over-

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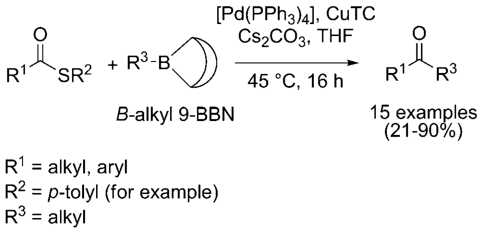
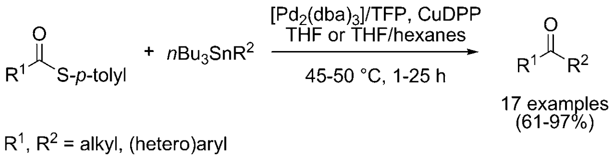
come by using, for example, a *B*-alkyl 9-BBN reagent (9-BBN = 9-borabicyclo[3.3.1]nonane).[10] Initially, *B*-alkyl 9-BBN reagents participated only sluggishly in the Liebeskind–Srogl coupling under nonbasic conditions. As observed with boronates, the greater steric demand of the *B*-alkyl 9-BBN reagents prevented dual activation by the copper(I) reagent and the formation of the ternary complex. Therefore, a base (Cs_2CO_3) was required to activate the boron reagent in this particular case. Under these modified conditions, aryl alkyl and dialkyl ketones with a variety of functional groups were synthesized in moderate to excellent yields (Scheme 4).[10]



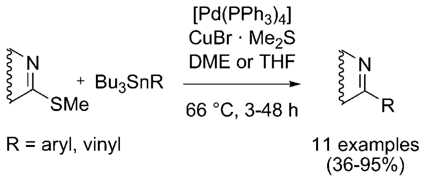
Scheme 4. Coupling of thioesters with aliphatic organoboron reagents.

Liebeskind and co-workers also developed an alternative approach to the synthesis of ketones through the coupling of thioesters with organostannane reagents (Scheme 5).[11] The reaction relies on the same base-free Pd^0-catalyzed, Cu^I-mediated methodology. The variant with tin reagents is particularly attractive in cases in which stannanes are more accessible than boronic acids. Furthermore, whereas various heteroaryl boronic acids with an α heteroatom, such as 2-pyridineboronic acid, are problematic substrates in cross-coupling reactions with thioorganic compounds, the corresponding organostannanes underwent efficient coupling.[11] The treatment of thioesters with tri-*n*-butylorganostannanes under the catalysis of $[Pd_2(dba)_3]$/TFP in the presence of one equivalent of CuDPP provided the desired ketones in 61–97 % yield (Scheme 5).



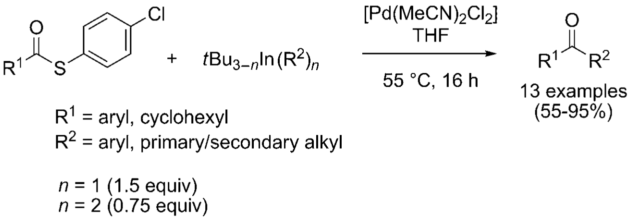
Scheme 5. Coupling of thioesters with organostannanes. CuDPP = copper(I) diphenylphosphinate.

In independent studies, Guillaumet and co-workers developed similar Pd-catalyzed cross-coupling reactions of vinyl and aryl stannanes with π-electron-deficient heteroaromatic compounds.[12] These reactions were carried out with methyl thioethers as the heteroaromatic substrate in the presence of copper(I) bromide–dimethyl sulfide complex ($CuBr{\cdot}Me_2S$; Scheme 6). The high yields observed for the isolated products suggest that the carboxylate counterion is not essential for the transmetalation from Sn to Pd (in contrast to the use of organoboron substrates; see Scheme 2) and that the cocatalytic Cu^I reagent acts as a simple activator of the Pd–S bond.



Scheme 6. Coupling of heteroaromatic thioethers with organostannanes in the presence of $CuBr{\cdot}Me_2S$. DME = 1,2-dimethoxyethane.

Thus, thioesters are excellent cross-coupling partners for boronic acids and organostannanes under mild and nonbasic conditions. Our understanding of the principle behind the requirement for activation by Cu^I in the Liebeskind–Srogl reaction (Scheme 2 and Scheme 3) suggests that the Pd-catalyzed cross-coupling could proceed directly with sufficiently thiophilic organometallic cross-coupling partners in the absence of a stoichiometric Cu^I activator. On the basis of the principle of hard and soft acids and bases described by Pearson,[13] a genuine palladium-catalyzed, copper-free coupling of thioesters with thiophilic organoindium reagents was developed by the Liebeskind research group and reported in 2005.[14] Aryl as well as primary and secondary alkyl organoindium reagents were coupled with thioesters in the presence of $[Pd(MeCN)_2Cl_2]$ (5 mol %) in THF under nonbasic conditions to furnish the corresponding ketones in good yields (Scheme 7).

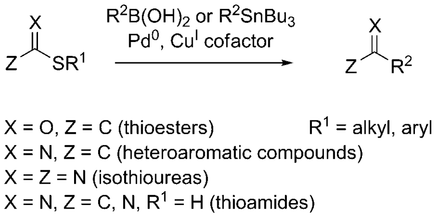


Scheme 7. Palladium-catalyzed coupling of thioesters with organoindium reagents.

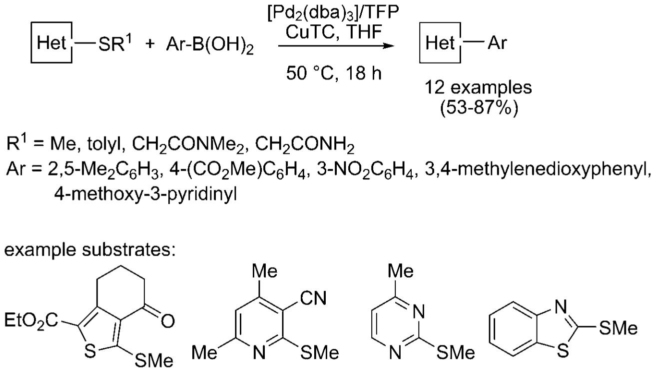
3. Scope and Limitations

The scope of these neutral Pd^0-catalyzed, Cu^I-mediated Liebeskind–Srogl C–C cross-coupling reactions, initially performed with a thioester as an organosulfur building block[5,10,11,14,15] and a boronic acid as the organometallic reagent (Scheme 1), was extended considerably over the following years. A variety of thioorganic reagents are now known to undergo selective C–C cross-coupling, not only with boronic acids, but also with other organometallic substrates, with remarkable reactivity and selectivity (Scheme 8).

In 2002, Liebeskind and Srogl demonstrated the efficient coupling of heteroaromatic thioethers with boronic acids under the standard conditions developed for thioester electrophiles (Scheme 9).[8] Generally, the cross-coupling reac-



Scheme 8. Substrate scope in the Liebeskind–Srogl reaction.

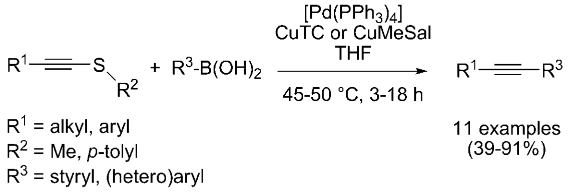


Scheme 9. Coupling of heteroaromatic thioethers with boronic acids.

tions proceeded smoothly within 18 h at 50 °C in THF. In some cases, for example, the treatment of 2-(methylthio)benzothiazole with 3-pyridineboronic acid, the reaction could be improved by the addition of $Zn(OAc)_2$. Presumably, $Zn(OAc)_2$ can bind to the basic 3-pyridinyl nitrogen atom to prevent deprotonation of the boronic acid. The same effect was observed in the coupling of other reagents containing a basic nitrogen atom.[8] Simple aryl thioethers showed limited reactivity toward C–C coupling under Liebeskind–Srogl conditions. Only those with electron-withdrawing substituents provided the desired coupling products in low yields.[8] The enhanced reactivity of heterocyclic thioethers can be rationalized in terms of the π-deficient heteroaromatic core, which incorporates an electronegative atom (N or S) in the α position to the sulfide group (Scheme 9).

The use of heterocyclic thioethers as substrates in C–C coupling reactions with aryl, heteroaryl, and alkenyl stannanes led to a variety of substituted heterocycles in good overall yields (see also Scheme 6).[16] Along the same line, the C–C coupling of thioethers has found application in the synthesis of protected aryl and heteroaryl amidines,[17] the functionalization of chiral oxazolines with organoborane and organostannane reagents,[18] the synthesis of diketopyrrolo[3,4-*c*]pyrrole fluorophores,[19] and the formation of differently substituted triazines[20] and tetrazines.[21]

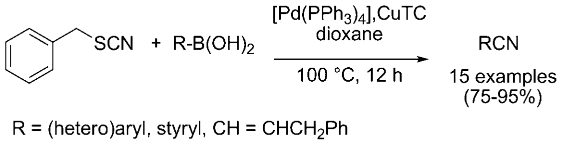
To complement the classical Sonogashira cross-coupling of terminal alkynes,[22] the Liebeskind–Srogl Pd^0/Cu^I-mediated reaction was adapted to the synthesis of unsymmetrical and symmetrical alkynes by the mild and nonbasic cross-coupling of thioalkynes with boronic acids (Scheme 10).[23] The occurrence of an oxidative addition of the C–S bond of



Scheme 10. Coupling of alkynyl thioethers with boronic acids to yield internal alkynes.

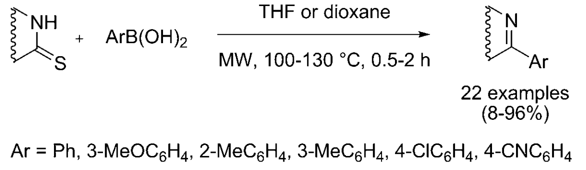
the thioalkyne to the Pd^0 center was confirmed by the isolation of an alkynyl palladium thiolate in 63 % yield when phenylethynyl *p*-tolyl sulfide was mixed with $[Pd(PPh_3)_4]$ in benzene at room temperature.

The growing family of desulfitative cross-coupling reactions between thioorganic and organometallic compounds also includes a novel method for the synthesis of nitriles, first reported by Zhang and Liebeskind in 2006.[24] A variety of aryl and alkenyl nitriles can be obtained in excellent yields through this unusual cyanation of boronic acids with thiocyanates (Scheme 11). However, neither boronate esters nor boroxines were effective substrates in this cyanative coupling.

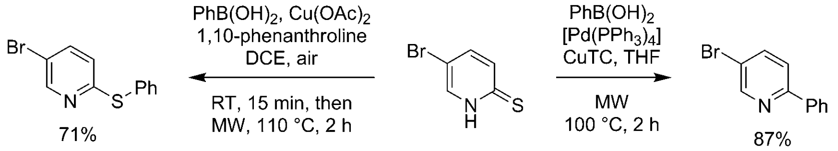


Scheme 11. Cyanation of boronic acids with thiocyanates for the synthesis of nitriles.

We recently developed a direct C–C cross-coupling of cyclic thioamides and thioureas with boronic acids under nonbasic Liebeskind–Srogl reaction conditions (Scheme 12).[25,26] The observed desulfitative coupling of thioamide fragments containing a latent free-thiol functionality may be considered highly unusual, as the competing C–S cross-coupling is typically the preferred pathway with such substrates.[27] Successful cross-coupling was observed for a variety of aromatic and non-aromatic five- and six-membered heterocycles containing a thioamide fragment. Under controlled microwave irradiation at 100 °C, most reactions were complete within 2 h and proceeded in high yields.[26] A larger amount (2–3 equiv) of the CuTC cofactor is needed for high conversion in these transformations than for the cross-



Scheme 12. Coupling of heterocyclic thioamide fragments with boronic acids. MW = microwave irradiation.

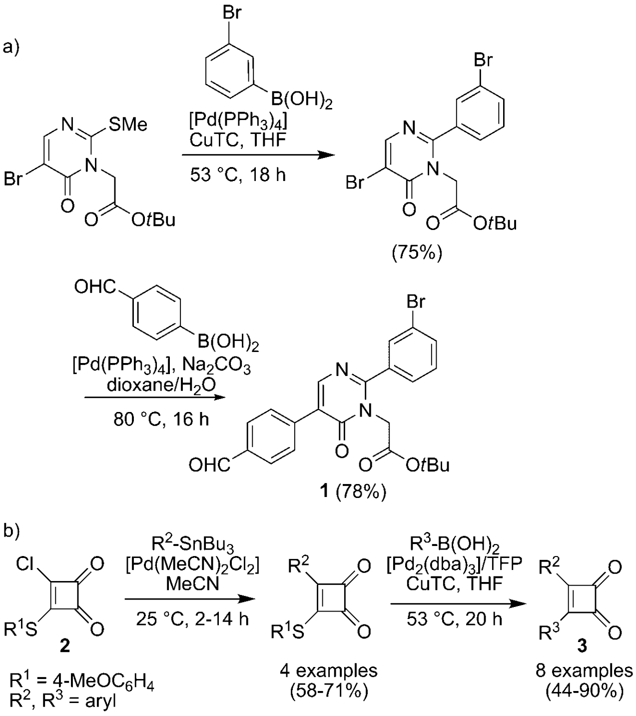


Scheme 13. Tunable cross-coupling reactivity of a brominated thioamide with phenylboronic acid.

coupling of N-heteroaromatic thioethers and thioesters with boronic acids (Scheme 1 and 9), possibly because of the initial formation of a copper(I) thiolate species from the thioamide fragment.

A distinct advantage of using thioamide substrates for reactions with boronic acids is that by exchanging the anaerobic Pd^0/Cu^I catalytic system for an aerobic Cu^{II} system, the reactivity can be tuned from C–C toward C–S cross-coupling (Scheme 13).[26] The direct C–C cross-coupling of cyclic thioureas with boronic acids has been employed for the generation of libraries of 2-aryl 1,4-dihydropyrimidines as potential nonnucleosidic inhibitors of hepatitis B virus replication[25] and for the synthesis of 2*H*-2-imidazolines.[28]

The Pd^0/Cu^I-mediated coupling discovered by Liebeskind and Srogl has several synthetic advantages, as the mild and nonbasic conditions are highly specific for thioorganic compounds. Thus, orthogonal reactivity may be observed with the Pd^0/Cu^I protocol with respect to traditional Pd^0-catalyzed Suzuki–Miyaura and Stille reactions.[29,30] The nonbasic conditions for the desulfitative coupling distinguish this process from the Suzuki reaction, which requires a base or fluoride additive to activate the boron compound for the transmetalation step.[9] Remarkably, even with organostannanes, which generally do not require an additive for transmetalation, very high selectivity for cross-coupling at a thio-substituted carbon center was observed.[30] These results are a clear demonstration of the ability of copper(I) carboxylates to switch on catalysis at the C–S center. The syntheses of the pyrimidinone **1** and bifunctionalized cyclobutenediones **3** are an impressive illustration of the selectivity of these C–C bond-forming reactions (Scheme 14; see also Scheme 13). Liebeskind and co-workers described the use of a pyrimidinone scaffold in a selective coupling mediated by palladium(0) and a copper(I) carboxylate between 3-bromobenzeneboronic acid and the C–SMe center of the heterocycle (Scheme 14a).[29] The copper(I) carboxylate was replaced with a base (Na$_2$CO$_3$) for the subsequent selective Suzuki–Miyaura coupling at the more reactive 5-bromo position to give the bis-substituted pyrimidinone **1** in 78 % yield. In the second example, Peña-Cabrera and Aguilar-Aguilar examined the synthesis of unsymmetrically substituted bisaryl cyclobutenediones (Scheme 14b). 4-(Arylthio)-3-chlorocyclobutene-1,2-diones **2** underwent Stille cross-coupling with a number of organostannanes exclusively at the C–Cl position in 58–71 % yield in the absence of a Cu^I source.[30] In a subsequent step, the cyclobutadienone ring was coupled with boronic acids or organostannanes at the thio-substituted carbon atom in the presence of a stoichiometric quantity of a copper(I) carboxylate to form the corresponding bisaryl cyclobutadienones **3** in moderate to excellent yields (44–90 %; Scheme 14b).[30,31]

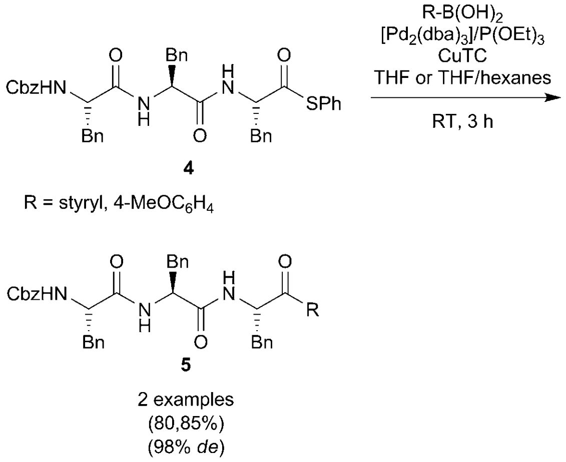


Scheme 14. Orthogonal reactivity: a) Liebeskind–Srogl and Suzuki–Miyaura coupling; b) Stille and Liebeskind–Srogl coupling.

4. Application in Organic Synthesis

4.1. Peptide Synthesis

An ongoing challenge in peptide chemistry is the development of new synthetic pathways for the formation of enantiomerically pure N-protected α-amino ketones and peptidyl ketones. Recently, Liebeskind and co-workers introduced the first procedure for the synthesis of pH-sensitive peptidyl ketones from mono-, di-, and tripeptidyl thioesters and boronic acids.[32] The N-protected peptidyl ketones were prepared in good to excellent yield with high enantiomeric purity by Pd^0-catalyzed, Cu^I-mediated cross-coupling with aryl, π-electron-rich heteroaryl, or alkenyl boronic acids under slightly modified Liebeskind–Srogl conditions. The choice of catalytic system proved critical for these transformations, as a facile metal-catalyzed decarbonylation–β-hydride elimination sequence can occur as a side reaction.[32] The use of a small weakly donating P(OEt)$_3$ ligand provided the ideal coupling conditions for *N*-Cbz- and *N*-Boc-protected α-amino thioesters. The poorly basic small P(OEt)$_3$ ligand fills the coordination sites at the Pd center without attenuation of the electrophilicity of the catalyst and thus increases the rate of transmetalation and retards the decarbonylation side reaction. Thus, the highly enantiomerically pure *N*-Cbz-protected peptidyl ketones **5** were synthesized from the peptidyl thioester **4** and a boronic acid (1.5–3 equiv) by using [$Pd_2(dba)_3$] (2.5 mol%) and $P(OEt)_3$ (20 mol%) as the catalyst system in the presence of CuTC (1.2 equiv) in THF or in a mixture of THF and hexanes at room temperature (Scheme 15).[32] Importantly, the presence of unprotected sensitive polar functional groups and variations in the electronic nature of the boronic acid were possible under these conditions. In this mild and versatile cross-coupling process, the configuration of stereogenic centers was preserved completely.

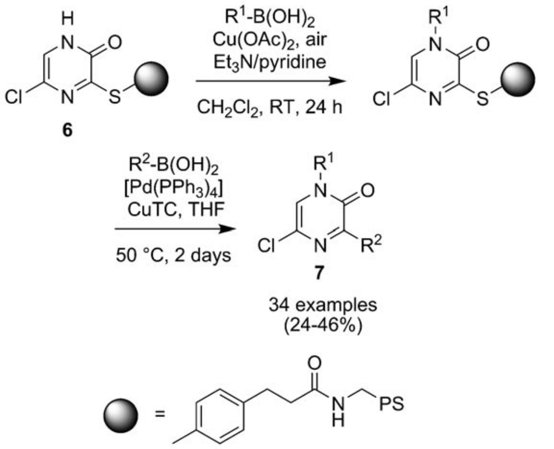


Scheme 15. Synthesis of enantiomerically pure peptidyl ketones **5**. Bn = benzyl, Cbz = carbobenzyloxy.

4.2. Solid-Phase Organic Synthesis

Solid-phase organic synthesis is a widely used strategy for library generation. In general, considerable attention has to be paid to the linker systems employed.[33] Sulfide-based linkers are stable under diverse sets of reaction conditions and are typically activated by oxidation to a sulfone before the final cleavage step (safety-catch linker).[33] The desired library compounds are then cleaved from the support by substitution with nucleophiles, such as amines or alcohols. Alternatively, in some cases, the target compounds can be released directly from a sulfide linker upon treatment with a strongly nucleophilic amine.[34] Both methods lead to the formation of a carbon–heteroatom bond in the final product.

Van der Eycken and co-workers recently reported a new reaction based on the Liebeskind–Srogl C–C cross-coupling procedure for cleavage from the solid phase.[35] In this transition-metal-catalyzed orthogonal solid-phase procedure, a Chan–Lam N-arylation[36] of a resin-bound pyrazinone of type **6** with a boronic acid in the presence of a Cu^{II} source was followed by a Pd^0/Cu^I-mediated Liebeskind–Srogl reaction, again with a boronic acid, to cleave the pyrazinone heterocycle from the sulfide linker (Scheme 16). Optimum results were observed for the cleavage step when the resin-bound pyrazinones were treated with an excess of the aryl boronic acid (2 equiv), [$Pd(PPh_3)_4$] (6 mol%), and CuTC (3 equiv) in THF at 50 °C for 2 days. The desired 2(1*H*)-pyrazinones **7** were obtained in high purity (Scheme 16). The synthesis of pyrazinones **7** by an analogous solution-phase procedure was described by the same research group.[37]

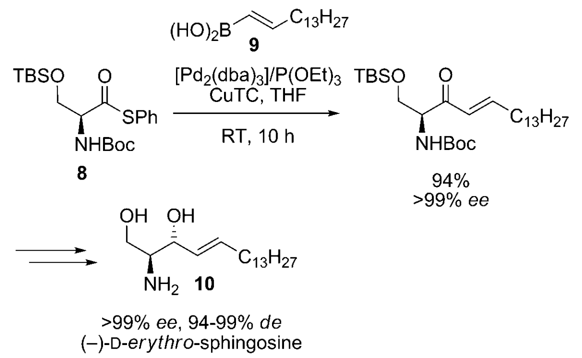


Scheme 16. Solid-phase synthesis of pyrazinones with the Liebeskind–Srogl reaction as a cleavage method. PS = polystyrene resin.

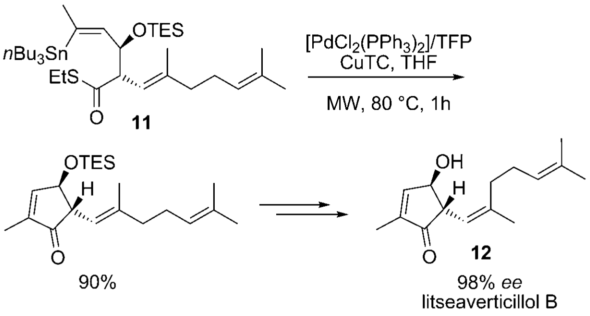
4.3. Natural Product Synthesis

Applications of the desulfitative Pd^0-catalyzed, Cu^I-mediated Liebeskind–Srogl reaction in total synthesis typically take advantage of the wide generality and functional-group tolerance of this procedure.[38–40] Yang and Liebeskind, for example, elaborated a six-step total synthesis of highly enantiomerically pure (−)-D-*erythro*-sphingosine (**10**) from *N*-Boc-L-serine by using a thioester/boronic acid cross-coupling for the critical bond-forming step (Scheme 17).[38] Treatment of the *N*-Boc- and *O*-TBS-protected serine thiophenyl ester **8** with (*E*)-1-pentadecenylboronic acid (**9**) in the presence of a Pd^0 catalyst and a copper(I) carboxylate delivered (−)-D-*erythro*-sphingosine (**10**) in high yield (94%) with high enantiomeric purity (> 99% *ee*). No *E*/*Z* isomerization of the α,β-unsaturated ketone was observed during the course of the reaction and workup procedure. The extension of the synthesis to different functionalized serine thioesters showed a high tolerance of the method for phosphate and glycoside functional groups.[38]

The first intramolecular version of the Pd^0/Cu^I-mediated coupling was described by Morita and Kuwahara.[39] In their six-step enantioselective total synthesis of the 1*R*,5*S* stereoisomer of litseaverticillol B (**12**),they used a microwave-promoted cyclization of the stannylated thioester **11** as the crucial C–C bond-forming step (Scheme 18).



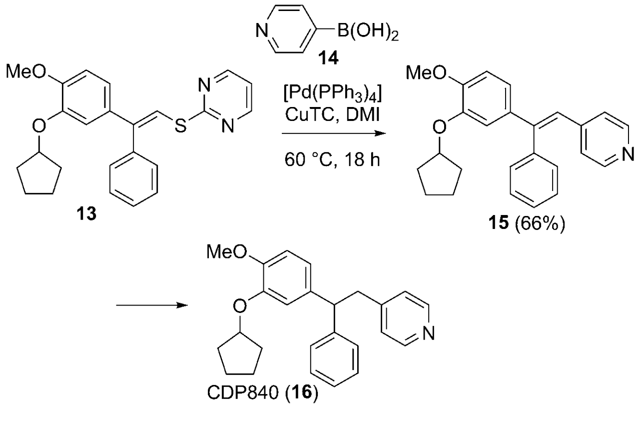
Scheme 17. Total synthesis of (−)-D-*erythro*-sphingosine (**10**). Pd^0/Cu^I-mediated coupling of thioester **8** with the alkenyl boronic acid **9**. TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.



Scheme 18. Total synthesis of litseaverticillol B. Pd^0/Cu^I-mediated intramolecular coupling of the stannylated thioester **11**. TES = triethylsilyl.

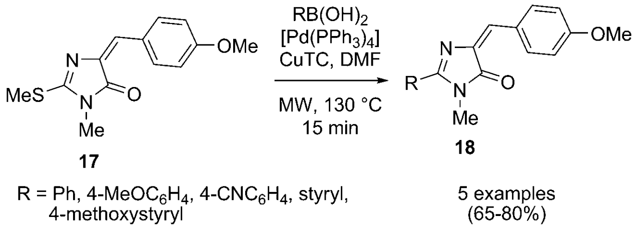
4.4. Scaffold Decoration of Heterocycles

Itami, Yoshida, and co-workers examined an unusual type of Liebeskind–Srogl coupling in the synthesis of CDP840 (**16**), a potential therapeutic agent for asthma.[40] After a stereoselective double Mizoroki–Heck reaction and formation of the desired β,β-diarylated vinyl sulfide **13**, the installation of the 4-pyridyl group in a vicinal position to the aryl substituents on the alkene was a critical step (Scheme 19). A desulfitative coupling of the alkenyl 2-pyrimidyl sulfide **13** with 4-pyridineboronic acid (**14**) was carried out in the presence of [Pd(PPh$_3$)$_4$] and CuTC to give **15**. Both the alkenyl and the pyrimidyl group on the sulfur atom can be transferred to form a coupling product, and pyrimidyl-group transfer proved to be faster than the transfer of the alkenyl group. The outcome of the Liebeskind–Srogl reaction was found to depend critically on the nature of the aryl substituent on the sulfur atom. Best results for alkenyl-group transfer to form **15** were observed with the 2-pyrimidyl-substituted alkenyl sulfide **13**.



Scheme 19. Total synthesis of CDP840. Pd^0/Cu^I-mediated coupling of alkenyl sulfide **13** with boronic acid **14**. DMI = 1,3-dimethyl-2-imidazolidinone.

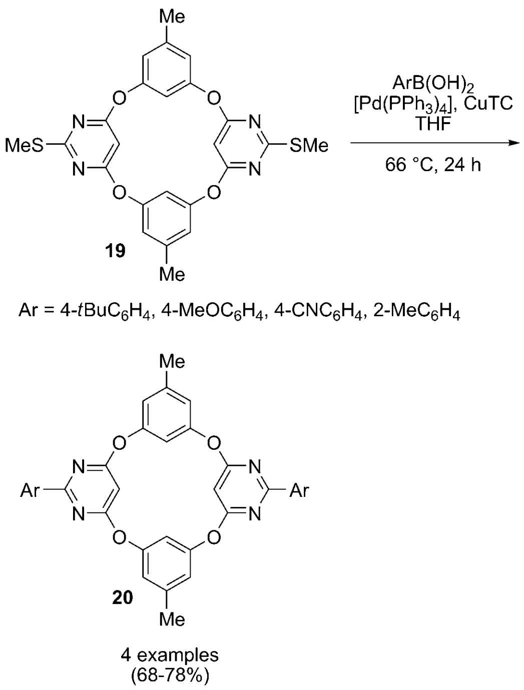
A large number of the recently described applications of the Liebeskind–Srogl reaction deal with the scaffold decoration of heterocyclic molecules containing appropriate thioorganic structural units. The Liebeskind–Srogl reaction has particular merit and often provides superior results in cases in which traditional transition-metal-catalyzed reactions can not be employed, or an orthogonal reactivity with respect to other methods is required. Limitations of classical decoration methods are often a consequence of the structure of the substrates; for example, the substrates may be difficult to prepare or may show low stability or low reactivity. The synthesis of 2-aryl imidazolinones **18** by the Liebeskind–Srogl coupling of the 2-methylthioimidazolone **17** with aryl and alkenyl boronic acids is a representative example:[41] As 2-chloro- or 2-(trifluoromethylsulfonyloxy)imidazolinones can not be used as substrates in a traditional cross-coupling reaction owing to their inherent instability, the Liebeskind–Srogl coupling of the completely stable 2-methylthioimidazolone **17** was chosen as an alternative method (Scheme 20).



Scheme 20. Functionalization of imidazolinones. DMF = *N*,*N*-dimethylformamide.

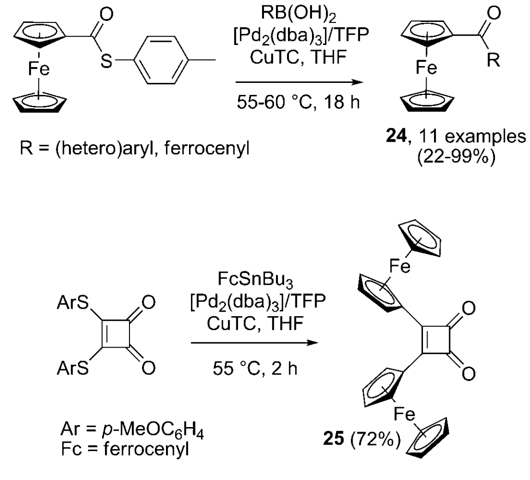
Similarly, Dehaen and co-workers described the synthesis of novel and diversely functionalized oxacalix[2]arene[2]pyrimidines **20** from the bis(methylthio)-substituted oxacalix[4]arene **19** (Scheme 21).[42] Several different aryl groups were introduced onto the pyrimidine units in Liebeskind–Srogl reactions in good yields (68–78 %). The one-step postmacrocyclization arylation procedure proved to be more efficient than the assembly of the target macrocycles from the corresponding aryl-substituted dihalopyrimidine components.[42]

As the strong thiophilic character of the Cu^I reagent is responsible for the selective reactivity of thioorganic compounds under Liebeskind–Srogl conditions, intriguing orthogonal reactivity may be observed with different nucleophilic coupling partners when an appropriate second electrophilic center (usually an organohalide) is present in the sulfide



Scheme 21. Functionalization of oxacalix[4]arenes.

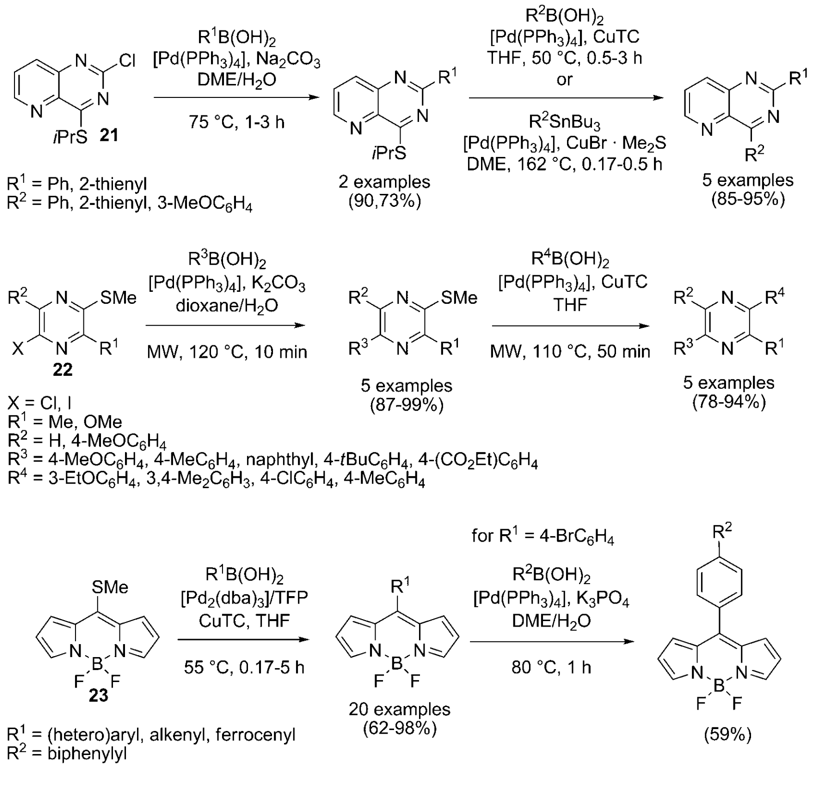
substrate. Orthogonal reactivity of this type was used to advantage in the functionalization of pyrido[3,2-*d*]pyrimidines **21**,[43] pyrazines **22**,[44] and bodipy (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) dyes **23**[45] with multiple reaction centers (Scheme 22). Liebeskind–Srogl cross-coupling reactions were also applied successfully in the synthesis of ferrocene derivatives, namely, in the preparation of mono- and bis-substituted aryl ferrocenyl ketones of the type **24**[46] and the "squarylferrocene" **25**[47] (Scheme 23).



Scheme 23. Synthesis of ferrocene derivatives.

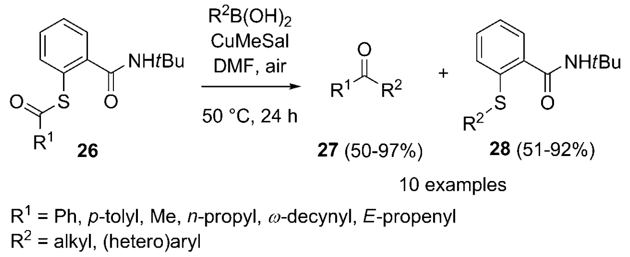
5. Related Cross-Coupling Protocols

A disadvantage of the Liebeskind–Srogl protocol is the requirement of a stoichiometric amount of a Cu^I cofactor in



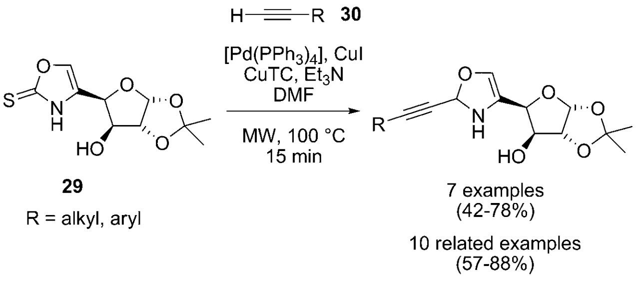
Scheme 22. Functionalization of pyrido[3,2-*d*]pyrimidines **21**, pyrazines **22**, and bodipy dyes **23**.

combination with an inert atmosphere to prevent oxidation of the cofactor to a Cu^{II} species. Clearly, a coupling process involving only a catalytic amount of the copper cofactor would constitute a major improvement in this transformation. Recently, Villalobos, Srogl, and Liebeskind reported a copper-catalyzed, palladium-free coupling of thioesters with boronic acids under aerobic conditions (Scheme 24).[48] Investigations into the scope of this reaction revealed that only specific thioesters of the type **26** with appropriately positioned ligating groups participated in efficient copper-catalyzed coupling reactions to form the desired ketone products **27**. Successful C–C coupling was observed for different *S*-acyl thiosalicylamides **26** with boronic acids (2.5 equiv) in the presence of CuMeSal (5 mol%) in DMF at 50 °C in air. In all cases, the formation of the S-arylated by-product **28** in a roughly 1:1 ratio with the desired ketone product **27** was observed. According to the mechanism proposed by the authors to rationalize these results, the Cu^{I}-coordinated thioester is oxidized initially to a $Cu^{II/III}$ intermediate, which is reduced in situ by excess boronic acid to return the active Cu^{I} species.[48]



Scheme 24. Copper-catalyzed aerobic cross-coupling of thioesters with boronic acids.

An additional recent variation of the classic Liebeskind–Srogl coupling method was elaborated by Tatibouët and co-workers, who developed a Sonogashira/Liebeskind-type Cu^{I}-catalyzed desulfitative coupling (Scheme 25).[49] The coupling of 1,3-oxazoline-2-thiones **29** with a variety of terminal alkynes **30** proceeded smoothly with catalytic amounts of $[Pd(PPh_3)_4]$, CuI, and CuTC in the presence of Et_3N in DMF. A cooperative effect of the two different Cu^{I} species, CuI and CuTC, plays an important role in the proposed mechanism. Catalytically active alkynyl copper is involved in the regeneration of CuTC and formation of CuSH, which then acts as a source of Cu^{I} for the generation of further alkynyl copper species. Successful coupling was also observed for 1,3-oxazoline-2-thiones incorporated in a variety of structures.[49]



Scheme 25. Pd/Cu-catalyzed desulfitative cross-coupling of oxazolinethiones.

6. Summary and Outlook

In the past few years, the Liebeskind–Srogl cross-coupling reaction, which is complementary to the many other procedures for transition-metal-catalyzed cross-coupling that have been developed since the 1980s, has emerged as a very valuable C–C bond-forming method.[1] Initially described in 2000 for the synthesis of ketones from thioesters and boronic acids, this transformation is clearly an important addition to previously existing methods for ketone synthesis from carboxylic acids and their derivatives.[50] Some of these methods for ketone synthesis require highly nucleophilic (strongly basic) organomagnesium and organolithium reagents and are therefore unsuitable for the synthesis of more complex multifunctional ketones, when a high degree of chemoselectivity is required. Alternative mild methods for ketone synthesis include the palladium-catalyzed coupling developed by Fukuyama and co-workers between thioesters and organozinc reagents[51] and related transition-metal-catalyzed transformations of boronic acids, such as palladium-catalyzed cross-coupling with carboxylic acids,[52,53] esters,[54] acid chlorides,[55,56] or anhydrides,[55–57] as well as the $[Ru_3(CO)_{12}]$-catalyzed cross-coupling of esters[58] with organoboron compounds.

The Liebeskind–Srogl method was subsequently extended successfully to a variety of other thioorganic reagents. The ever-increasing scope and potential of this mechanistically unique base-free cross-coupling method has already led to a number of interesting applications in heterocyclic/medicinal chemistry, peptide and solid-phase synthesis, and the total synthesis of natural products. In many cases, the use of stable organosulfur building blocks in combination with the neutral reaction conditions has shown distinct advantages over more established C–C cross-coupling methods, such as the Suzuki reaction. Although the requirement of a stoichiometric amount of a Cu^{I} cofactor is a serious limitation, especially on a large scale, recent developments (Scheme 24)[48] provide hope that procedures for the C–C coupling of organosulfur electrophiles in the presence of only a catalytic quantity of a copper reagent may be developed in the future. Thus, it is very likely that in a few years Liebeskind–Srogl-type cross-coupling reactions will be implemented as standard methods for C–C bond formation.

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