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Palladium(0)-Catalyzed, Copper(I)-Mediated Coupling of Boronic Acids with Cyclic Thioamides. Selective Carbon−Carbon Bond Formation for the Functionalization of Heterocycles†

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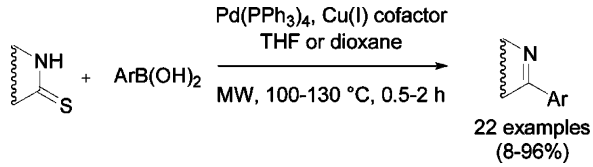

The palladium-catalyzed cross-coupling of cyclic thioamides with arylboronic acids in the presence of stoichiometric amounts of a copper(I) cofactor is described. The desulfitative carbon−carbon cross-coupling protocol is performed under neutral conditions and can be applied to a range of heterocyclic structures with embedded thioamide fragments. Successful carbon−carbon cross-coupling is independent of the ring size, aromaticity/nonaromaticity, the presence of additional heteroatoms, or other functional groups in the starting thioamide structure. Employing controlled microwave irradiation at 100 °C, most cross-couplings can be completed within 2 h and proceed in high yields. An advantage of using thioamides as starting materials is the fact that the system can be tuned to an alternative carbon−sulfur cross-coupling pathway by changing to stoichiometric copper(II) under oxidative conditions. Both types of thioamide cross-couplings are orthogonal to the traditional base-catalyzed Suzuki−Miyaura cross-coupling of aryl halides with boronic acids.

Introduction

Transition-metal-catalyzed cross-coupling procedures have revolutionized the art and practice of organic synthesis in the last two decades.[1] The in general mild reaction conditions, high functional group tolerance, and broad availability of starting materials have contributed to the growing success of many, for example, Pd-catalyzed carbon−carbon and carbon−heteroatom bond formation methods.[1−9] Apart from the well-known Suzuki−Miyaura biaryl cross coupling,[2] a growing number of related transition-metal-catalyzed carbon−carbon[1,3] and carbon−heteroatom coupling protocols[4] have been reported in the recent literature, underpinning the versatility and importance of transition metal-mediated reactions for organic synthesis. In many instances, these protocols have been employed in a drug discovery context for the scaffold decoration of biologically active molecules, in particular for the functionalization of heterocycles.[5−9] Numerous reports in the literature have described the generation of combinatorial libraries of heterocyclic core structures applying transition-metal-catalyzed cross-couplings of the Suzuki−Miyaura,[5] Buchwald−Hartwig,[6] Negishi,[7] Stille,[8] or Ullmann type.[9] In many cases controlled

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† Dedicated to Professor Miguel Yus on the occasion of his 60th birthday.

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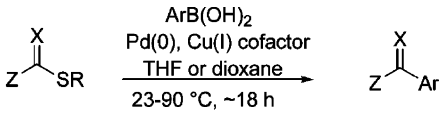
SCHEME 1. Liebeskind−Srogl Desulfitative Carbon−Carbon Cross-Coupling of Thioorganics with Boronic Acids



X = O, Z = C (thiol esters) R = alkyl, aryl
X = N, Z = C (heteroaromatics)
X = Z = N (isothioureas)

microwave dielectric heating has been employed to make these otherwise often slow processes more efficient.[5−10]

In addition to the plethora of transition-metal-catalyzed cross-coupling methods known today, Liebeskind and Srogl recently developed a novel carbon−carbon cross-coupling protocol, involving the Pd(0)-catalyzed, Cu(I)-mediated coupling of a variety of different thioorganics with boronic acids under neutral conditions (Scheme 1).[11−13] A key feature of these desulfitative carbon−carbon couplings[14] is the requirement of stoichiometric amounts of a Cu(I) carboxylate such as Cu(I)-thiophene-2-carboxylate (CuTC)[15] or Cu(I)-3-methylsalicylate as metal cofactor. Because of the higher thiophilicity of the soft Cu(I) metal, selective sulfide coupling under base-free Liebeskind−Srogl conditions can be performed even in the presence of a Suzuki-active bromide.[13] Despite the apparent attractiveness of these mild transition-metal-mediated protocols, there are surprisingly few applications of these desulfitative carbon−carbon cross-couplings for the functionalization of heterocyclic molecules.[16] Arguably, the large number of arylboronic acids that are commercially available and the easy accessibility of heterocycles with thioamide motifs makes this type of coupling chemistry highly attractive in the context of high throughput synthesis and scaffold decoration. In addition, boronic acids are air- and moisture-stable and of relatively low toxicity, and the boron-derived byproducts can easily be removed from the reaction mixture.[17]

In the context of our interest in the scaffold decoration of heterocycles, we have recently discovered that the Liebeskind−Srogl cross-coupling protocol can also be applied to cyclic thioureas and thioamides.[18,19] This novel transition-metal-catalyzed transformation, involving the desulfitative *carbon−carbon* coupling of a thioamide/thiourea containing a latent free thiol functionality (X = N, Z = N or C, R = H, Scheme 1) is

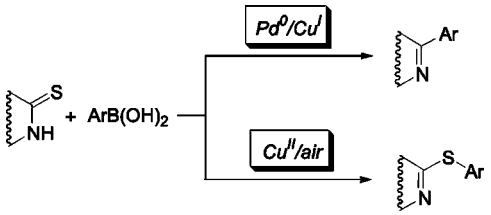


FIGURE 1. Carbon−carbon versus carbon−sulfur cross-coupling of thioamides with boronic acids.

highly unusual, since in this case the competing *carbon−sulfur* cross-coupling is typically the preferred pathway.[4,20−26]

Herein we describe the scope and limitations of this unusual carbon−carbon cross-coupling protocol in full detail[19] and present its application toward the rapid, microwave-assisted scaffold decoration of a variety of different heterocyclic core structures containing thioamide motifs. An unique advantage of using thioamides as starting materials for desulfitative carbon−carbon cross-coupling reactions with boronic acids is the fact that the presence of the latent thiol functionality also allows carbon−sulfur bond formation under suitable reaction conditions (Figure 1), which are also detailed in this publication.

Results and Discussion

Reaction Optimization. As a starting point in our investigations, we examined the carbon−carbon cross-coupling of commercially available pyridine-2(1*H*)-thione (**1a**) and phenylboronic acid (Table 1, entry 1). The required Cu(I)-thiophene-2-carboxylate (CuTC) cofactor employed for this purpose was prepared according to the procedure described by Allred and Liebeskind in 1996.[27] All initial optimization studies were performed on a 0.18 mmol scale applying controlled single-mode microwave heating in sealed vessels.[10] The screening of the reaction conditions was performed tuning all the main

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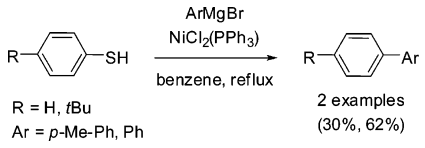


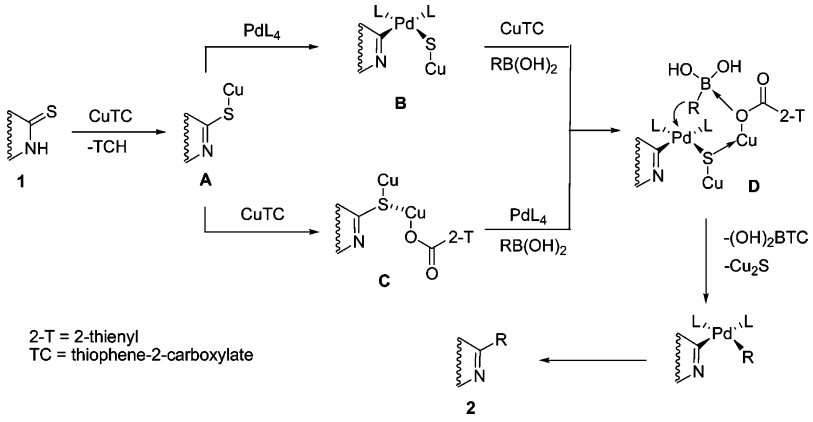
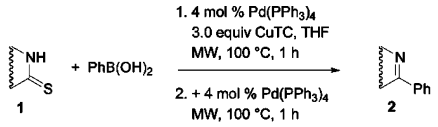


FIGURE 2. Proposed mechanism for the desulfitative thioamide−boronic acid cross-coupling.

TABLE 1. Carbon−Carbon Cross-Coupling of Cyclic Thioamides with Phenylboronic Acid



entry	substrate	1	yield of 2 (%)[b]	entry	substrate	1	yield of 2 (%)[b]
1		1a	90	5		1e	75
2		1b	83	6		1f	93
3		1c	96	7		1g	8
4		1d	67	8		1h	52

[a] For a general procedure, see the Experimental Section. [b] Isolated yields of pure product after column chromatography.

factors: solvent, molar ratio of reactants, percentage of catalyst and of the CuTC metal cofactor, catalytic systems (namely Pd(0) sources and ligands), reaction time, and temperature.

With respect to the solvent, our studies support earlier investigations by Liebeskind and co-workers[11−13] that the use of solvents with coordinating properties such as DMF or DMA is not suitable for these types of cross couplings. Ethereal solvents such as THF and dioxane proved to be the best solvents for this coupling protocol. In our hands, THF provided slightly higher product yields and therefore was used for all future studies. To avoid the undesired oxidation of the Cu(I) cofactor to the Cu(II) species, the use of dry and degassed solvent was necessary (CuTC is air-sensitive while in contact with solvent). For this reason, all reactions were performed under inert (argon) atmosphere.

Regarding the quantity of boronic acid coupling partner, we discovered that using 1.2 equiv of phenylboronic acid provided optimum results. While lower amounts of the boronic acid resulted in uncomplete conversions, the use of more than 1.2 equiv of the coupling partner produced substantial quantities of undesired biphenyl as a byproduct. For the required Cu(I) cofactor we experienced that 2−3 equiv of CuTC needed to be employed to achieve high conversion. This value appears to be somewhat higher than typically used in traditional Liebeskind−Srogl reactions (1.2−1.5 equiv)[11−13] but here can be rationalized based on the proposed reaction mechanism for thioamide−boronic acid couplings (see Figure 2). As far as the Pd(0) catalyst is concerned, most of the catalytic/ligand systems previously reported for Liebeskind−Srogl cross-couplings were evaluated. Screening of Pd sources such as $Pd_2(dba)_3$, $PdCl_2$-(dppf), $Pd(OAc)_2$, and $Pd(PPh_3)_4$ in combination with (when appropriate) additional ligands such as PPh_3 or tris(2-furyl)-phosphine (TFP) demonstrated that best results were typically observed employing $Pd(PPh_3)_4$ as a catalyst. Applying a 4 mol % quantity of commercially available $Pd(PPh_3)_4$ usually was sufficient to achieve good to excellent conversions within 1 h at 100 °C (see below). Reduced catalyst loadings (<3 mol %) led to significantly lower yields while higher amounts of the Pd catalyst did not improve the outcome significantly.

After considerable optimization applying automated sequential microwave synthesis,[28] the reaction temperature of choice was found to be 100 °C. Performing the thioamide−boronic acid cross-coupling in superheated THF at 100 °C (2−3 bar) typically provided the highest conversions after 1 h irradiation time. Higher reaction temperatures did not improve the efficiency of this transformation, while shorter reaction times led to incomplete conversions. Ultimately, the reaction proceeded most effectively heating 1 equiv of pyridine-2(1*H*)-thione (**1a**), 1.2 equiv of $PhB(OH)_2$, 3 equiv of CuTC, and 4 mol % of Pd-$(PPh_3)_4$ in THF at 100 °C for 1 h, delivering 71% of isolated 2-phenylpyridine **2a**. To further improve the product yield, an additional quantity of $Pd(PPh_3)_4$ (4 mol %) was added after the first heating cycle. The reaction mixture was subsequently heated at 100 °C for an additional 1 h. This two-step procedure consistently led to an improved 90% isolated product yield of coupling product **2a**. A similar experiment, irradiating a mixture containing 8 mol % of $Pd(PPh_3)_4$ for 2 h under otherwise identical reaction conditions, furnished a somewhat lower product yield (74%).

For product isolation, the crude reaction mixture was evaporated and subsequently washed with 25% aqueous ammonia to remove excess thiophene-2-carboxylic acid, boronic acid, and inorganic Cu species. The remaining material was subsequently purified by flash chromatography.

Diversity of Thioamide Fragments. With the optimized conditions in hand, we explored the scope and limitations of

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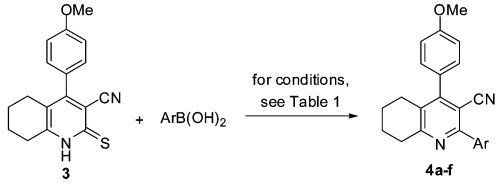
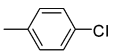
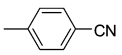
TABLE 2. Comparison of Microwave Heating and Conventional Heating for the Thioamide−Boronic Acid Cross-Coupling of Pyrimidine-2(1*H*)-thione and Phenylboronic Acid (Table 1, entry 2)[a]

entry	heating source	vessel	temp control	temp (°C)	time (h)	yield (%)[b]
1	MW	closed	IR	100	2	80
2	oil bath	closed	fiber-optic	100	2	81
3	oil bath	open[c]	thermometer	66	16	78
4	-	closed	thermometer	23	24	28

[a] Experiments were performed on a 0.54 mmol scale. For experimental details, see the Supporting Informations. [b] Isolated yields of pure product after column chromatography. [c] Reflux conditions.

TABLE 3. Carbon−Carbon Cross-Coupling of Tetrahydroquinoline-2(1*H*)-thione 3 with Arylboronic Acids



entry	4	Ar =	yield (%)[a]	entry	4	Ar =	yield (%)[a]
1	**4a**		97	4	**4d**		93
2	**4b**		92	5	**4e**		77
3	**4c**		25	6	**4f**		76

[a] Isolated yields of pure product after column chromatography

this novel carbon−carbon cross-coupling reaction with a variety of simple cyclic thioamides. We were pleased to find that successful cross-coupling with phenylboronic acid was observed with aromatic and nonaromatic, six- and five-membered heterocycles containing thioamide fragments. As shown in Table 1, good to high product yields were achieved using our standard reaction conditions. The only exception proved to be 1,3-dihydroimidazole-2(1*H*)-thione (entry 7) where only 8% of the anticipated coupling product could be isolated. The success of the Pd(0)-catalyzed, Cu(I)-mediated carbon−carbon cross-coupling is apparently independent of the ring size, aromaticity/nonaromaticity, the presence of additional heteroatoms, or other functional groups (see also below).

At this point, the viability of the cross-coupling protocol was tested on a larger scale (0.54 mmol) using pyrimidine-2(1*H*)-thione **1b** as a starting material, applying different experimental setups and heating modes. At standard microwave conditions (100 °C, 2 h) an 80% yield of 2-phenylpyrimidine (**2b**) was obtained on a 0.54 mmol scale (Table 2, entry 1), comparing very favorably with the 83% yield isolated on a 0.18 mmol scale (Table 1, entry 2). Using our standard microwave dielectric heating conditions, the temperature is measured externally by an IR sensor (Initiator Eight, Biotage AB). To accurately monitor the internal reaction temperature, we have repeated this experiment using a different microwave reactor that allows monitoring of internal temperatures by more accurate fiber-optic probes (Discover, CEM Corp.).[29] Gratifyingly, the isolated product yields were identical (data not shown). To establish the absence of any nonthermal microwave effects, we have subsequently repeated the experiment using conventional oil bath heating at the exact same temperature using the identical sealed reaction vessel and fiberoptic temperature monitoring system.[29] Within experimental error, the results of the coupling performed in the preheated (100 °C) oil bath were the same as in the microwave run at the same temperature (Table 2, entries 1 and 2), therefore confirming the absence of any nonthermal microwave effects. In addition, we have also performed an experiment using classical reflux conditions at ∼66 °C. After 16 h under an inert atmosphere, 78% of the desired product was isolated (Table 2, entry 3). Shorter reaction times under reflux conditions led to incomplete conversions. Carbon−carbon cross coupling at room temperature is exceedingly slow and of little practical value. After 24 h at ∼23 °C a modest yield of 28% of **2b** could be isolated.

Having demonstrated that a variety of different simple cyclic thioamide scaffolds can be useful substrates for the Pd(0)-catalyzed, Cu(I)-mediated desulfitative carbon−carbon coupling with phenylboronic acid (Table 1), we next focused our attention on the use of more complex heterocylic cores containing additional functionalities and on the scope of the boronic acid diversity. In this context we have investigated the cross-coupling of 3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-2(1*H*)-thione (**3**)[30] with a range of arylboronic acids containing electron-donating or electron-withdrawing functional groups at the ortho, meta, and para positions. As depicted in Table 3, in most cases excellent yields of the anticipated 2-aryl-functionalized-tetrahydroquinoline cross-coupled products **4a**−**f** were obtained without further optimization of the reaction conditions. Only in the case of ortho-substituted arylboronic acid (entry 3) a moderate yield of 25% was experienced.

In a related example, we have employed our thioamide−boronic acid cross-coupling strategy for the generation of a small set of potentially biologically active 2-(hetero)aryl-1,4-dihydropyrimidines **6a**−**f**.[18] These heterocycles have been found to be highly potent nonnucleosidic inhibitors of hepatits B virus replication that have in vitro and in vivo antiviral activity.[31] The required functionalized cyclic thioureas of type **5** can be rapidly synthesized by microwave-assisted three-component condensation of the appropriate aromatic aldehydes, *β*-keto esters, and thiourea (Biginelli reaction).[18,28] Cross-coupling with boronic acids applying essentially the standard conditions described above provided the desired 2-aryl-1,4-dihydropyrimidines **6a**−**f**. While cross-coupling reactions of cyclic thioureas **5** with unsubstituted phenylboronic acid proceeded in excellent yields (Table 4, entries 1 and 2), coupling with substituted phenylboronic acids was more troublesome and in some cases required a higher catalyst loading (entries 3−5). Cross-coupling of heterocyclic boronic acids such as 2-thiophenylboronic acids was sluggish and furnished a mere 14% isolated product yield of the anticipated dihydropyrimidine derivative **6f** (entry 6).

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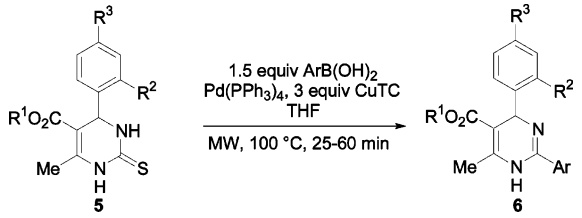
TABLE 4. Carbon−Carbon Cross-Coupling of Pyrimidine-2-thiones 5 with Arylboronic Acids

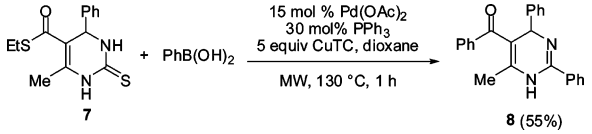


5 **6**

entry	**6**	Ar	R^1	R^2/R^3	$Pd(PPh_3)_4$	time (min)	yield (%)[a]
1	**6a**	Ph	Et	H/H	3 mol %	25	81
2	**6b**	Ph	Me	Cl/F	3 mol %	30	61
3	**6c**	4-ClPh	Me	Cl/F	3 mol %	25	71
4	**6d**	3-MePh	Me	Cl/F	5 mol %	30	82
5	**6e**	2,4-$(F)_2$Ph	Me	Cl/F	8 mol %	60	26
6	**6f**	2-thiophene	Me	Cl/F	6 mol %	50	14

[a] Isolated yields of pure product after column chromatography.

SCHEME 2. Liebeskind−Srogl-Type Bis-Couplings

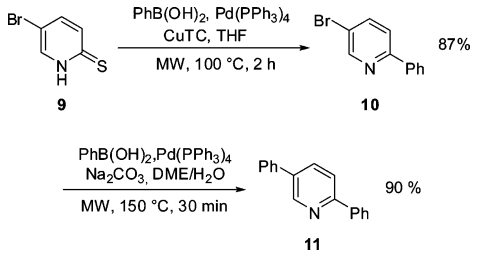


7 **8** (55%)

In the context of preparing combinatorial libraries of 5-aroyl-3,4-dihydropyrimidin-2-ones we have recently reported the efficient carbon−carbon cross-coupling of dihydropyrimidine-5-carboxylic acid thiol esters with boronic acids,[32] following the general strategy of a Liebeskind−Srogl ketone synthesis (Scheme 1, X = O, Z = C).[11] As shown in Scheme 2, it is possible to combine both carbon−carbon bond forming events in a one-pot reaction. Toward this end, a suitable 2-thioxotetrahydropyrimidine-5-carboxylic acid thiol ester containing two independent carbon−sulfur connections was synthesized via Biginelli multicomponent reaction and subsequently treated with an excess of phenylboronic acid using the Pd(0)-Cu(I) conditions. In the event, dihydropyrimidine **7** was treated with 4.0 equiv of phenylboronic acid, 15 mol % $Pd(OAc)_2$, 30 mol % PPh_3, and 5.0 equiv of CuTC in anhydrous dioxane. The corresponding bis-coupling product **8** was obtained in 55% isolated yield.

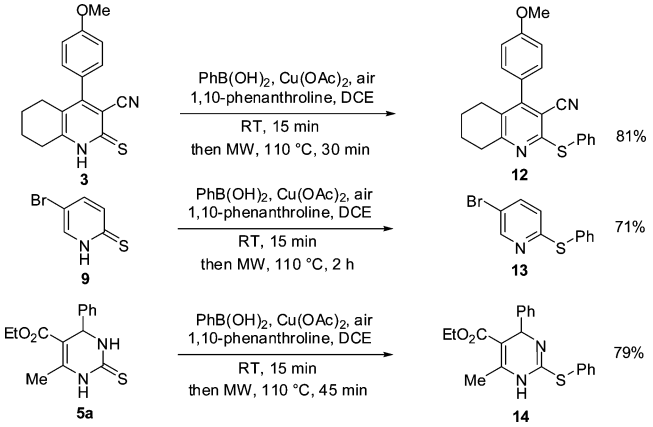
Mechanistic Considerations. The results presented so far demonstrate that thioamide fragments embedded in heterocyclic ring systems can be cross-coupled under comparatively mild and nonbasic conditions with a variety of boronic acids. Employing modified Liebeskind−Srogl Pd(0)-catalyzed, Cu(I)-mediated conditions, carbon−carbon cross-coupling with concomitant extrusion of sulfur occurs in moderate to good overall yields. This novel transformation tolerates a variety of functional groups on both the thioamide and boronic acid reaction partners. To confirm the anticipated[13] orthogonality of this neutral Liebeskind−Srogl-type coupling to the base-catalyzed Suzuki−Miyaura biaryl coupling,[2] we have selected 5-bromopyridine-2(1*H*)-thione **9** as a suitable model substrate (Scheme 3), since in addition to a thioamide fragment, this organosulfur compound also contains a Suzuki-active bromide. Using our optimized conditions for Pd-catalyzed desulfitative

SCHEME 3. Orthogonal Reactivity between Desulfitative Thioamide−Boronic Acid and Suzuki−Miyaura Biaryl Cross-Couplings in 5-Bromopyridine-2(1*H*)-thione



9 **10** **11**

SCHEME 4. Oxidative Carbon−Sulfur Coupling of Thioamides with Phenylboronic Acid



3 **12** **9** **13** **5a** **14**

carbon−carbon cross-coupling (Table 1), 5-bromopyridine-2(1*H*)-thione (**9**) was readily converted into 5-bromo-2-phenylpyridine (**10**) by treatment with phenylboronic acid in 87% yield (Scheme 3). There was no evidence for a competing Suzuki−Miyaura cross-coupling at the bromide position. For the Pd(0)/Cu(I) coupling pathway, this unique selectivity is ascribed to the use of CuTC as a metal cofactor of higher thiophilicity than the Pd catalyst and the neutral reaction conditions. On the other hand, the reaction of 5-bromo-2-phenylpyridine (**10**) with phenylboronic acid catalyzed by Pd-$(PPh_3)_4$ applying the Suzuki−Miyaura protocol using sodium carbonate as a base in DME/water provided the desired product **11** in 90% yield after purification by flash chromatography.

The mechanism of the desulfitative thioamide−boronic acid cross-coupling is related to the traditional Liebeskind−Srogl protocols,[11−13] in particular to the cross-coupling of N-heteroaromatic thioethers with boronic acids (Scheme 1).[12,13] This is made evident by the fact that the reaction requires both the Pd(0) catalyst and the specific Cu(I) carboxylate additive (CuTC) in stoichiometric quantity. Carbon−carbon coupling products were not obtained when CuTC was replaced with other Cu(I) salts such as CuBr or CuCl. The unique requirement of a Cu(I) carboxylate such as CuTC is accommodated by the intermediate **D** shown in Figure 2: the Cu(I) carboxylate simultaneously polarizes the Pd−S bond through Cu(I) coordination to S while activating the trivalent boron through coordination of the carboxylate to boron.[11−13]

In contrast to the cross-coupling of N-heteroaromatic thioethers with boronic acids[12,13] we noted that 2−3 equiv of the CuTC cofactor needed to be employed to achieve high conversions. We therefore propose the initial formation of a Cu(I)

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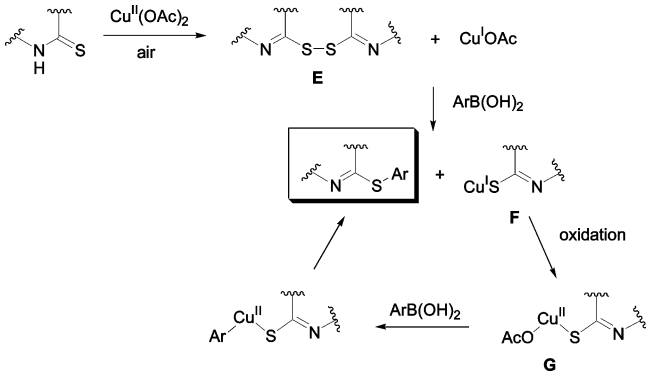

FIGURE 3. Proposed mechanism for the Cu-mediated carbon-sulfur cross-coupling of thioamides with boronic acid.

thiolate species of type **A**[33] which then can undergo either oxidative addition to the Pd(0) catalyst[34] (**B**) or further complexation with an additional equivalent of the CuTC cofactor (**C**). Both pathways will ultimately lead to the key intermediate **D**[11−13] which subsequently undergoes base-free transmetalation with extrusion of Cu_2S followed by reductive elimination to provide the carbon−carbon cross-coupled products.

Carbon−Sulfur Cross-Coupling Reactions. As already mentioned, a distinct advantage of using thioamides with latent free thiol functionalities in the cross-coupling with boronic acids is the fact that by switching the catalytic system the reactivity can be tuned from *carbon−carbon* toward *carbon−sulfur* cross-coupling.[18] For transition-metal-catalyzed carbon−sulfur cross-coupling reactions a variety of different protocols are known.[4,20−25] These typically involve the Pd-catalyzed or Cu-mediated cross-coupling of aryl/alkyl thiols with aryl halides.[24,25] Recently, Guy and co-workers have described the carbon−sulfur cross-coupling of arylboronic acids and alkanethiols mediated by Cu(II) acetate and pyridine in anhydrous DMF.[22] The mechanistic rationalization presented by the authors is related to the proposed mechanism for Ullmann-type carbon−heteroatom cross-couplings of phenols or amines with arylboronic acids and was proposed to involve a Cu(II) intermediate.[35] This mechanistic hypothesis was later questioned by Liebeskind and co-workers,[23] suggesting a Cu(I) species and a disulfide as the key intermediates.

As far as the mechanism for carbon−sulfur cross-coupling is concerned, we suggest that for our cyclic thioamides, a mechanism that involves initial oxidation of the thioamide to a disulfide species promoted by the Cu(II) reagent is in operation. The optimum reaction conditions for the Pd-free, Cu-mediated carbon−sulfur cross-coupling were investigated using tetrahydroquinoline-2(1*H*)-thione **3** as starting material. Initially, the thioamide was allowed to react with phenylboronic acid, a stoichiometric quantity of Cu(II) acetate, and 2 equiv of 1,10-phenanthroline under an argon atmosphere.[21] Monitoring of the reaction mixture by HPLC established the formation of the corresponding disulfide as an intermediate.[23] Employing an independently synthesized sample of the disulfide, its smooth conversion to sulfide **12** (Scheme 4) under Cu(I) conditions using CuTC (1 equiv), $PhB(OH)_2$ (4 equiv), and 1,10-phenanthroline (2 equiv) in dichloroethane could be confirmed. However, full conversion of thioamide **3** to the corresponding carbon−sulfur cross-coupled product **12** was only possible in the presence of atmospheric oxygen.

With these results in hand, we have modified the protocol for carbon−sulfur cross-coupling to obtain complete conversion. Thus, a mixture of thioamide **3**, phenylboronic acid (4 equiv), Cu(II) acetate (1 equiv), and 1,10-phenanthroline (2 equiv) in dichloroethane was stirred under air for 15 min. During this time, full conversion to the disulfide was observed by HPLC. Subsequent microwave irradiation under sealed vessel conditions at 110 °C for 30 min (2−3 bar) delivered the desired sulfide **12** in 81% isolated yield after flash chromatography (Scheme 4). To demonstrate the flexibility of this method, the same protocol was applied successfully to 5-bromopyridine-2(1*H*)-thione **9** and tetrahydropyrimidine-5-carboxylate **5a**, providing the anticipated carbon−sulfur cross-coupled products in high yields (Scheme 4).

In a recent publication the synthesis of unsymmetrical sulfides via Cu-catalyzed coupling of disulfides with boronic acids was described by Taniguchi.[36] The author has proposed that the unreactive Cu(I) thiolate, formed as an undesired sideproduct (Figure 3), can be successfully transformed to the monosulfide in two catalytic cycles in the presence of oxygen. The reaction proceeds in very good isolated yields using catalytic quantities of a Cu(I) source. On the basis of all the above information, we propose the following mechanism for the Cu(II)-mediated cross-coupling of thioamides with boronic acids (Figure 3). Initially, the cyclic thioamide is oxidized to a disulfide species **E** promoted by the Cu(II) reagent in the presence of air. Subsequently, the Cu(I) reagent formed in the oxidation process catalyzes the coupling reaction of disulfide **E** with arylboronic acid to produce the desired aryl sulfide in addition to an equimolar amount of catalytically inactive Cu(I) thiolate **F**. We have confirmed by an independent experiment that the disulfide **E** undergoes efficient carbon−sulfur coupling reaction in the presence of a stoichiomentric amount of Cu(I)-thiophene-2-carboxylate (CuTC). Product yields higher than 50% are exclusively formed in the presence of air. As previously suggested by Taniguchi,[36] the Cu(I) thiolate can be oxidized to the Cu(II) species **G**, followed by the reaction with arylboronic acid to deliver desired aryl sulfide from the otherwise inactive Cu(I) thiolate **F**.

Conclusion

We have shown that thioamide fragments embedded in heterocyclic ring systems can be cross-coupled under comparatively mild and nonbasic conditions with a variety of boronic acids. Employing modified Liebeskind−Srogl Pd(0)-catalyzed, Cu(I)-mediated conditions, desulfitative carbon−carbon cross-coupling with concomitant extrusion of sulfur occurs in moderate to good overall yields. The carbon−carbon cross-coupling

(33) An equimolar mixture of thioamide **1c** and CuTC in dry and degassed THF rapidly forms an insoluble Cu-complex that after isolation can be used as a starting material for the reaction with phenylboronic acid in the presence of catalytic amounts of $Pd(PPh_3)_4$ to produce the desired carbon-carbon cross coupling product. For the formation and structures of various multinuclear Cu(I)-thioamide complexes, see: (a) Wycliff, C.; Bharathi, D. S.; Samuelson, A. G.; Nethaji, M. *Polyhedron* **1999**, *18*, 949. (b) Davies, S. C.; Durrant, M. C.; Hughes, D. L.; Leidenberger, K.; Stapper, C.; Richards, R. L. *J. Chem. Soc., Dalton Trans.* **1997**, 2409. (c) Raper, E. S. *Coord. Chem. Rev.* **1994**, *129*, 91.

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is independent of the ring size, aromaticity/nonaromaticity, the presence of additional heteroatoms, or other functional groups in the starting thioamide structure. By switching the catalytic system to stoichiometric Cu(II) under oxidative conditions, the reactivity can be tuned from carbon−carbon toward carbon−sulfur cross-coupling. We believe that both cross-coupling methods have great potential for the scaffold decoration of heterocycles containing thioamide motifs.

Experimental Section

General Procedure for the Carbon−Carbon Cross-Coupling of Thioamides with Phenylboronic Acid (Table 1). A dry microwave process vial was charged with the corresponding thioamide **1** (0.18 mmol), $PhB(OH)_2$ (26.3 mg, 0.22 mmol), CuTC (103 mg, 0.54 mmol), and $Pd(PPh_3)_4$ (8.3 mg, 0.007 mmol, 4 mol %). The reaction vessel was sealed and flushed with Ar. Through the septum was added anhydrous and degassed THF (1.8 mL). The mixture was subsequently heated in a microwave reactor at 100 °C for 60 min. After this period an additional amount of Pd catalyst (8.3 mg, 0.007 mmol, 4 mol %) was added and the reaction mixture was again heated at 100 °C for 1 h. After cooling, the solvent was evaporated and $CHCl_3$ (120 mL) was added. The crude reaction mixture was subsequently washed with 25% aqueous ammonia (3 × 40 mL). The aqueous ammonium layer was reextracted again with $CHCl_3$ (3 × 40 mL). The combined organic phase was dried over $MgSO_4$ and the residue after evaporation purified by flash chromatography.

2-Phenylpyridine (2a). Purification by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:1:12) provided product **2a** (yield 90%) as a light yellow liquid. ^{1}H NMR (DMSO-d_6, 360 MHz): 8.67 (d, J = 4.5 Hz, 1H), 8.08 (d, J = 7.2 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.90−7.86 (m, 1H), 7.51−7.41 (m, 3H), 7.31−7.36 (m, 1H);[37] MS (pos. APCI): m/z 156.3.

2-Phenylpyrimidine (2b). Purification by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:1:12) provided product **2b** (yield 83%) as a light yellow semisolid,[38] ^{1}H NMR (DMSO-d_6, 360 MHz): 8.91 (d, J = 4.8 Hz, 2H), 8.41−8.38 (m, 2H), 7.54−7.52 (m, 3H), 7.45 (t, J = 4.8, 1H);[39] MS (pos. APCI): m/z 157.2.

2-Phenyl-1,4,5,6-tetrahydropyrimidine (2c). Purification by flash chromatography on basic alumina (MeOH/CH_2Cl_2/hexanes 1:3:6) provided product **2c** (yield 96%) as a light yellow solid, mp 84−86 °C, lit.[40] mp 83−85 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): 7.73−7.71 (m, 2H), 7.44−7.35 (m, 3H), 3.35 (t, J = 5.7 Hz, 4H), 1.71 (quin, J = 5.7 Hz, 2H),[41] MS (pos. APCI): m/z 161.4.

2-Phenylbenzimidazole (2d). Purification by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:1:2) provided product **2d** (yield 67%) as a white solid, mp 291−292 °C, lit.[42] mp 293−294 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): 12.91 (s, 1H), 8.18 (d, J = 7.5 Hz, 2H), 7.68−7.47 (m, 5H), 7.24−7.17 (m, 2H);[43] MS (pos. APCI): m/z 195.1.

2-Phenyl-4,5-*d*ihydro-3*H*-pyrrole (2e). Purification by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:1:1) provided product **2e** (yield 75%) as a semisolid, lit.[44] mp 44 °C. ^{1}H NMR (DMSO-d_6, 360 MHz): 7.83−7.81 (m, 2H), 7.45−7.43 (m, 3H), 3.94 (t, J = 7.3 Hz, 2H), 2.91 (t, J = 8.2, 2H), 1.98−1.89 (m, 2H);[45] MS (pos. APCI): m/z 146.2.

2-Phenyl-4,5-dihydroimidazole (2f). Purification by flash chromatography on basic alumina (acetone/$CHCl_3$ 1:5) provided product **2f** (yield 93%) as a light yellow solid, mp 92−94 °C, lit.[46] mp 96−98 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): 7.82−7.80 (m, 2H), 7.47−7.39 (m, 3H), 3.37 (br s, 4H);[47] MS (pos. APCI): m/z 147.0.

2-Phenyl-1*H*-imidazole (2g). Purification by flash chromatography on silica gel (ethyl acetate/hexanes 2:1) provided product **2g** (yield 8%) as a semisolid, lit.[48] mp 144−146 °C. ^{1}H NMR (DMSO-d_6, 360 MHz): 12.51 (s, 1H), 7.92 (d, J = 7.6 Hz, 2H), 7.43 (dd, J_1 = 7.6 Hz, J_2 = 7.3 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 7.24 (br s, 1H), 7.02 (br s, 1H);[49] MS (pos. APCI): m/z 144.9.

2,2,4-Trimethyl-5-phenyl-2*H*-imidazole (2h). Purification by flash chromatography on neutral alumina (ethyl acetate/hexanes 1:10) provided product **2h** (yield 52%) as a semisolid. ^{1}H NMR (DMSO-d_6, 360 MHz): 7.83−7.81 (m, 2H), 7.52−7.50 (m, 3H), 2.40 (s, 3H), 1.38 (s, 6H); MS (pos. APCI): m/z 187.4.

General Procedure for Carbon−Carbon Cross-Coupling of 3-Cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-2(1*H*)-thione (3) with Arylboronic Acids (Table 3). A dry microwave process vial was charged with 3-cyano-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-2(1*H*)-thione **3**[30] (30 mg, 0.10 mmol), the corresponding arylboronic acid (0.12 mmol), CuTC (58 mg, 0.30 mmol), and $Pd(PPh_3)_4$ (4.7 mg, 0.004 mmol, 4 mol %). The reaction vessel was sealed and flushed with Ar. Through the septum was added anhydrous and degassed THF (1 mL). The mixture was subsequently heated in a microwave reactor at 100 °C for 60 min. After this period an additional amount of Pd catalyst (4.7 mg, 0.004 mmol, 4 mol %) was added, and the reaction mixture was again heated at 100 °C for 1 h. After cooling, the solvent was evaporated and $CHCl_3$ (90 mL) was added. The crude reaction mixture was subsequently washed with 25% aqueous ammonia (3 × 30 mL). The aqueous ammonium layer was reextracted again with $CHCl_3$ (3 × 30 mL). The combined organic phase was dried over $MgSO_4$ and the residue after evaporation purified by flash chromatography.

4-(4-Methoxyphenyl)-2-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4a). Purification by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:3:6) provided product **4a** (yield 97%) as a light yellow solid, mp 139−142 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): 7.82−7.79 (m, 2H), 7.53−7.52 (m, 3H), 7.37 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H), 2.99 (t, J = 6.3 Hz, 2H), 2.50−2.46 (m, 2H), 1.88−1.81 (m, 2H), 1.72−1.65 (m, 2H); MS (pos. APCI): m/z 341.1.

4-(4-Methoxyphenyl)-2-(3-tolyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4b). Purification by flash chromatography on silica gel (CH_2Cl_2/hexanes 3:1) provided product **4b** (yield 92%) as a light yellow solid, mp 134−136 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): 7.60−7.58 (m, 2H), 7.41 (dd, J_1 = 8.3 Hz, J_2 = 7.7 Hz, 1H), 7.36 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H), 2.99 (t, J = 6.5 Hz, 2H), 2.48−2.46 (m, 2H), 2.39 (s, 3H), 1.86−1.83 (m, 2H), 1.70−1.67 (m, 2H); MS (pos. APCI): m/z 355.3.

4-(4-Methoxyphenyl)-2-(2-tolyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4c). Purification by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:3:10) provided product **4c** (yield 25%) as a light yellow solid, mp 138−140 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): 7.41−7.28 (m, 6H), 7.09 (d, J = 8.7 Hz, 2H), 3.83

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(s, 3H), 2.97 (t, J = 6.4 Hz, 2H), 2.54 (t, J = 6.4 Hz, 2H), 2.21 (s, 3H), 1.87−1.82 (m, 2H), 1.71−1.68 (m, 2H); MS (pos. APCI): *m*/*z* 355.1.

2-(3-Methoxyphenyl)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4d). Purification by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:3:10) provided product **4d** (yield 93%) as a light yellow solid, mp 143−145 °C; ^{1}H NMR ($CDCl_3$, 360 MHz): 7.46−7.37 (m, 3H), 7.26−7.23 (m, 2H), 7.04−7.00 (m, 3H) 3.87 (s, 6H), 3.09 (t, J = 6.4 Hz, 2H), 2.54 (t, J = 6.4 Hz, 2H), 1.96−1.89 (m, 2H), 1.78−1.74 (m, 2H); MS (pos. APCI): *m*/*z* 371.3.

2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4e). Purification by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:3:13) provided product **4e** (yield 77%) as a offwhite solid, mp 197−199 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): 7.84 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H), 2.99 (t, J = 6.4 Hz, 2H), 2.54−2.47 (m, 2H), 1.86−1.81 (m, 2H), 1.70−1.65 (m, 2H); MS (pos. APCI): *m*/*z* 375.2.

2-(4-Cyanophenyl)-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4f). Purification by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:4:13) provided product **4f** (yield 76%) as a yellow solid, mp 198−201 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): 8.04−7.99 (m, 4H), 7.38 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 3.83 (s, 3H), 3.01 (t, J = 6.3 Hz, 2H), 2.53−2.50 (m, 2H), 1.87−1.84 (m, 2H), 1.72−1.68 (m, 2H); ^{13}C NMR (DMSO-d_6, 90 MHz): 161.9, 160.2, 156.2, 154.1, 142.5, 132.8, 131.2, 130.4, 130.3, 127.7, 118.6, 117.5, 114.6, 112.6, 106.1, 55.7, 33.5, 27.3, 22.3, 22.2; MS (pos. APCI): *m*/*z* 366.3.

General Procedure for Carbon−Carbon Cross-Coupling of Dihydropyrimidine (5) with Arylboronic Acids (Table 4). A dry microwave process vial was charged with the corresponding dihydropyrimidine (DHPM) **5** (0.25 mmol), the corresponding arylboronic acid (0.38 mmol), CuTC (143 mg, 0.75 mmol), and $Pd(PPh_3)_4$ (3−8 mol %). The reaction vessel was flushed with Ar and sealed. Through the septum anhydrous and degassed THF (5 mL) was added. The mixture was subsequently heated in a microwave reactor at 100 °C for 25−60 min. After cooling, the mixture was transferred to a round-bottom flask and adsorbed on silica gel. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes 1:3) to provide desired DHPMs **6** as semisolids. The analytical and spectroscopic data were in agreement with those previously reported.[18]

Ethyl 6-Methyl-2,4-diphenyl-1,4-dihydropyrimidine-5-carboxylate (6a). ^{1}H NMR ($CDCl_3$, 360 MHz): 7.67 (d, J = 7.5 Hz, 2H) 7.45−7.37 (m, 5H), 7.31−7.23 (m, 3H), 5.74 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H);[50] ^{13}C NMR ($CDCl_3$, 90 MHz): 145.0, 133.6, 131.2, 128.8, 128.5, 127.5, 127.1, 126.7, 59.9, 57.3, 29.7, 14.2.

Methyl 4-(2-Chloro-4-fluorophenyl)-6-methyl-2-phenyl-1,4-dihydropyrimidine-5-carboxylate (6b). ^{1}H NMR ($CDCl_3$, 360 MHz): 7.65 (d, J = 7.2 Hz, 2H), 7.46−7.37 (m, 3H), 7.32−7.28 (m, 1H), 7.16−7.13 (m, 1H), 6.94−6.89 (m, 1H), 6.08 (s, 1H), 3.62 (s, 3H), 2.55 (s, 3H); MS (pos. APCI): *m*/*z* 359, (neg. APCI): *m*/*z* 357.

Methyl 4-(2-Chloro-4-fluorophenyl)-2-(4-chlorophenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (6c). ^{1}H NMR ($CDCl_3$, 360 MHz): 7.62 (d, J = 7.1 Hz, 2H), 7.37 (d, J = 7.1 Hz, 2H), 7.32−7.27 (m, 1H), 7.18−7.15 (m, 1H), 6.97−6.92 (m, 1H), 6.08 (s, 1H), 3.64 (s, 3H), 2.56 (s, 3H); MS (pos. APCI): *m*/*z* 393.

Methyl 4-(2-Chloro-4-fluorophenyl)-6-methyl-2-(3-methylphenyl)-1,4-dihydropyrimidine-5-carboxylate (6d). ^{1}H NMR ($CDCl_3$, 360 MHz): 7.51 (m, 1H), 7.41−7.39 (m, 1H), 7.32−7.28 (m, 3H), 7.16−7.13 (m, 1H), 6.95−6.90 (m, 1H), 6.07 (s, 1H), 3.62 (s, 3H), 2.56 (s, 3H), 2.36 (s, 3H); MS (pos. APCI): *m*/*z* 373.

Methyl 4-(2-Chloro-4-fluorophenyl)-2-(2,6-difluorophenyl)-6-methyl-1,4-dihydropyrimidine-5-carboxylate (6e). ^{1}H NMR ($CDCl_3$, 360 MHz): 7.98 (m, 1H), 7.33−7.29 (m, 1H), 7.16−7.14 (m, 1H), 6.97−6.92 (m, 2H), 6.87−6.80 (m, 1H), 6.11 (s, 1H), 3.63 (s, 3H), 2.53 (s, 3H); MS (pos. APCI): *m*/*z* 394.

Methyl 4-(2-Chloro-4-fluorophenyl)-6-methyl-2-thien-2-yl-1,4-dihydropyrimidine-5-carboxylate (6f). ^{1}H NMR ($CDCl_3$, 360 MHz): 7.47−7.46 (m, 1H), 7.40−7.39 (m, 1H), 7.32−7.27 (m, 1H), 7.15−7.12 (m, 1H), 7.06−7.04 (m, 1H), 6.95−6.92 (m, 1H), 6.01 (s, 1H), 3.63 (s, 3H), 2.57 (s, 3H); MS (pos. APCI): *m*/*z* 365, (neg.APCL) *m*/*z* 363.

Procedure for the Bis-Carbon−Carbon Cross-Coupling of *S*-Ethyl 6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbothioate (7) with Phenylboronic Acid. A dry microwave process vial was charged with DHPM **7**[32] (43.9 mg, 0.15 mmol), phenylboronic acid (73.2 mg, 0.6 mmol), CuTC (143 mg, 0.75 mmol), $Pd(OAc)_2$ (5.05 mg, 0.023 mmol, 15 mol %), and PPh_3 (11.8 mg, 0.045 mmol, 30 mol %). The reaction vessel was sealed and flushed with Ar. Through the septum of the microwave vessel was added anhydrous and degassed dioxane (1 mL). The mixture was subsequently heated in a microwave reactor at 130 °C for 1 h. After cooling to ambient temperature, the solvent was evaporated and the crude mixture diluted with ethyl acetate (50 mL) and extracted with 10% aqueous ammonia (3 × 15 mL). The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/hexanes 5:1) to provide 29.1 mg (55%) of 5-benzoyl-6-methyl-2,4-diphenyl-1,4-dihydropyrimidine **8** as a yellow oil, ^{1}H NMR (DMSO-d_6, 360 MHz): 7.91 (d, J = 7.3, 2H), 7.56−7.44 (m, 8H), 7.32−7.20 (m, 5H), 5.70 (s, 1H), 1.84 (s, 3H); MS (pos. APCI): *m*/*z* 353.4.

5-Bromo-2-phenylpyridine (10) (Scheme 3). Following the general procedure for the carbon−carbon cross-coupling of thioamides with phenylboronic acid (see above) and purification by flash chromatography on silica gel (THF/hexanes 1:10), product **10** was obtained in 87% yield as a light yellow solid, mp 72−75 °C, lit.[51] mp 74−76 °C. ^{1}H NMR (DMSO-d_6, 360 MHz): 8.78 (d, J = 2.3 Hz, 1H), 8.12 (dd, J_1 = 8.5 Hz, J_2 = 2.3 Hz, 1H), 8.08−8.06 (m, 2H), 7.95 (d, J = 8.5 Hz, 1H), 7.52−7.43 (m, 3H);[52] MS (pos. APCI): *m*/*z* 233.9.

2,5-Diphenylpyridine 11 (Scheme 3). A microwave process vial was charged with a stir bar. To the vessel were added 5-bromo-2-phenylpyridine **10** (15 mg, 0.06 mmol), $PhB(OH)_2$ (11.7 mg, 0.10 mmol), $Pd(PPh_3)_4$ (7.4 mg, 0.006 mmol, 10 mol %), and 1,2-dimethoxyethane (0.75 mL). To the reaction mixture was added a solution of Na_2CO_3 (10.2 mg, 0.10 mmol) in H_2O (0.25 mL). The reaction vessel was sealed and irradiated at 150 °C for 30 min. After cooling, the mixture was transferred to a round-bottom flask, and adsorbed on silica gel. The residue was purified by flash chromatography on silica gel (ethyl acetate/CH_2Cl_2/hexanes 1:3:20) to provide 12.5 mg (90%) of 2,5-diphenylpyridine **11** as a white solid, mp 170−172 °C, lit.[53] mp 174−175 °C. ^{1}H NMR (DMSO-d_6, 360 MHz): 8.99 (d, J = 2.4 Hz, 1H), 8.17 (dd, J_1 = 8.3 Hz, J_2 = 2.4 Hz, 1H), 8.16−8.13 (m, 2H), 8.05 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 7.4 Hz, 2H), 7.54−7.41 (m, 6H);[54] MS (pos. APCI): *m*/*z* 232.4.

General Procedure for Carbon−Sulfur Cross-Coupling of Thioamides (3, 9, 5a) with Phenylboronic Acid (Scheme 4). A microwave process vial was charged with 0.16 mmol of the corresponding thioamide, $PhB(OH)_2$ (77 mg, 0.63 mmol), $Cu(OAc)_2$ (28.7 mg, 0.16 mmol), 1,10-phenanthroline (56.9 mg, 0.32 mmol), and 1,2-dichlorethane (1.5 mL). The reaction mixture was stirred under air for 15 min. After that time the reaction vessel was sealed and irradiated at 110 °C for 30−120 min. After cooling, the mixture

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was transferred to a round-bottom flask and was adsorbed on silica gel. The residue was purified by flash chromatography on silica gel to provide the corresponding products.

4-(4-Methoxyphenyl)-2-phenylsulfanyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (12). Reaction time 30 min; purification by flash chromatography on silica gel (ethyl acetate/hexanes 1:6) provided 48.3 mg (81%) of **12** as a yellow solid, mp 167−170 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): 7.56−7.53 (m, 2H), 7.46−7.45 (m, 3H), 7.31 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 3.82 (s, 3H), 2.68 (t, J = 6.1 Hz, 2H), 2.38 (t, J = 6.1 Hz, 2H), 1.75−1.70 (m, 2H), 1.61−1.58 (m, 2H), ^{13}C NMR (DMSO-d_6, 90 MHz): 162.1, 160.2, 157.2, 154.2, 134.6, 130.2, 129.8, 129.6, 129.5, 129.0, 127.4, 116.0, 114.6, 105.9, 55.7, 33.5, 26.9, 22.3, 22.1; MS (pos. APCI): *m*/*z* 373.2.

5-Bromo-2-(phenylthio)pyridine (13). Reaction time 120 min; purification by flash chromatography on silica gel (CH_2Cl_2/hexanes 1:1) provided 31.1 mg (71%) of **13** as a semisolid; ^{1}H NMR (DMSO-d_6, 360 MHz): 8.53 (d, J = 2.5 Hz, 1H), 7.88 (dd, J_1 = 8.6 Hz, J_2 = 2.5 Hz, 1H), 7.60−7.57 (m, 2H), 7.51−7.49 (m, 3H), 6.91 (d, J = 8.6 Hz, 1H);[55] MS (pos. APCI): *m*/*z* 267.9.

Ethyl 6-Methyl-4-phenylsulfanyl-1,4-dihydropyrimidine-5-carboxylate (14). Reaction time 45 min; purification by flash chromatography on silica gel (ethyl acetate/hexanes 1:3) provided 44.5 mg (79%) of **14** as a ca. 2:1 mixture of 1,4- and 3,4-dihydropyrimidine tautomers;[18] **A**: ^{1}H NMR ($CDCl_3$, 360 MHz): 9.77 (s, 1H), 7.40−7.13 (m, 10 H), 5.40 (s, 1H), 4.00 (q, J = 7.5 Hz, 2H), 3.32 (s, 3H), 2.23 (t, J = 7.5 Hz, 3H); ^{13}C NMR (DMSO-d_6, 90 MHz): 166.4, 150.0, 146.5, 145.2, 134.6−126.6 (phenyls), 98.9, 59.2, 53.4, 17.8, 14.5; **B**: ^{1}H NMR ($CDCl_3$, 360 MHz): 8.80 (s, 1H), 7.40−7.13 (m, 10H), 5.26 (s, 1H), 3.99 (q, J = 7.5 Hz, 2H), 3.32 (s, 3H), 1.11 (t, J = 7.5 Hz, 3H), ^{13}C NMR (DMSO-d_6, 90 MHz): 166.3, 159.7, 155.8, 144.4, 134.6−126.6 (phenyls), 104.0, 60.1, 59.2, 23.1, 14.5; MS (pos. APCI): *m*/*z* 353, (neg. APCL) *m*/*z* 351.

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Supporting Information Available: General experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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