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Switchable Catalysis: Modular Synthesis of Functionalized Pyrimidinones via Selective Sulfide and Halide Cross-Coupling Chemistry

Carrie Kusturin,[†] Lanny S. Liebeskind,*[,‡] Hayat Rahman,[†] Kirby Sample,[†] Barbara Schweitzer,[†] Jiri Srogl,[‡] and William L. Neumann*[,†]

Pfizer Global Research and Development, St. Louis Laboratories, 800 North Lindbergh, St. Louis, Missouri, and Emory University, Department of Chemistry, 1515 Pierce Drive, Atlanta, Georgia 30322

wlneumann@mindspring.com

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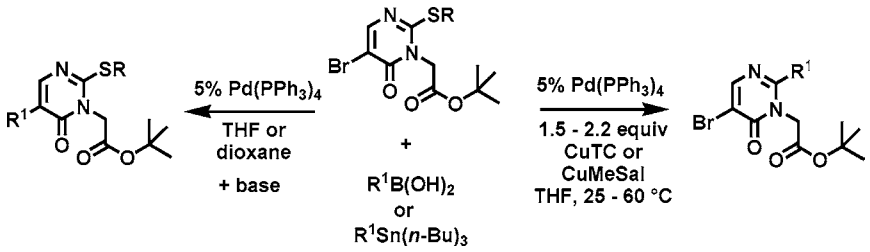
ABSTRACT



A general demonstration of orthogonal selectivity of the Liebeskind–Srogl cross-coupling protocol compared to the Suzuki–Miyaura and Stille variants is reported.

Heterocyclic structures have long been important to the pharmaceutical industry. In recent years, heterocycles have been successfully utilized as scaffold systems for lead discovery and prospecting for biological activities via the combinatorial and parallel medicinal chemistry formats.[1] As heterocycles can often be considered "condensed, conformationally constrained" derivatives of amino acids, they are ideal central platforms for the generation of peptide surrogates.[2] These systems can be designed to spatially display remnants of peptide secondary structure and side-chain functionality to enable the preferred ligand−receptor conformational ensemble in concordance with the strategic movement from peptides to peptidomimetics possessing the required pharmacokinetic characteristics.[3]

Herein, we report a modular synthesis of highly functionalized pyrimidinone heterocycles that has proven efficient for traditional analogue synthesis and may have application to parallel methodologies. This strategy can be envisioned as a combination of "graded functionality" and "orthogonal reactivity".[4] For selectivity, it relies upon the mechanistic differences between the Suzuki−Miyaura[5] and Stille[6] cross-coupling of halides compared to the Liebeskind−Srogl protocol for thioorganics.[7]

Pyrimidinone scaffold **4** was readily prepared from commercially available thiouracil **1** in three steps. Conversion

[†] Emory University.
[‡] Pfizer Global Research and Development.

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem Rev.* **2003**, *103*, 893. Villalgordo, J. M.; Heras, M.; Font, D. *J. Comb. Chem.* **2003**, *5*, 311. Krchnak, V.; Holladay, M. W. *Chem Rev.* **2002**, *102*, 61. Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195.
(2) Lewis, J. G.; Bartlett, P. A. *J. Comb. Chem.* **2003**, *5*, 278. Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441.
(3) Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541.
(4) Abell, C.; Oliver, S. F. *Curr. Opin. Chem. Biol.* **1999**, *3*, 299 and referenced cited therein.
(5) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213. Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457.
(6) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.

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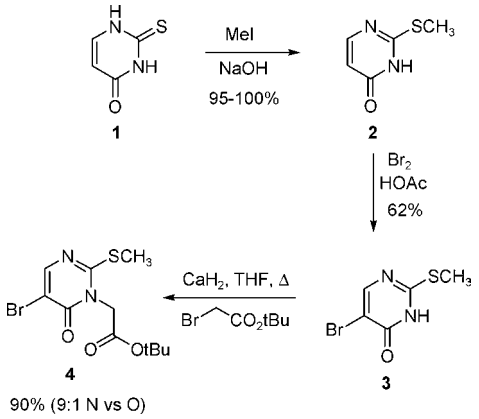
Scheme 1

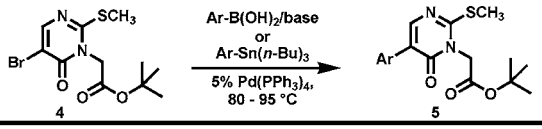


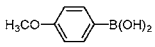
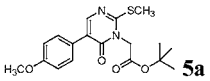
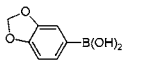
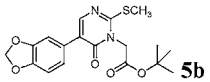
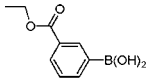
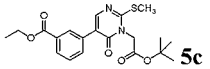
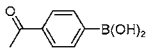
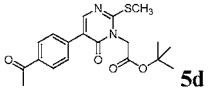
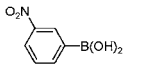
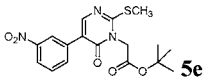
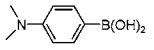
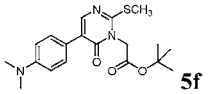
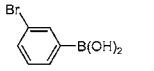
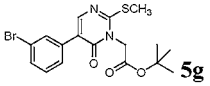
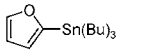
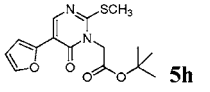
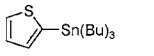
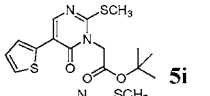
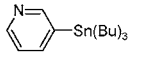
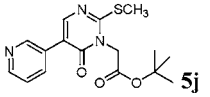
to thioether **2** by reaction with sodium hydroxide and methyl iodide followed by bromination afforded the known compound 5-bromo-2-methylthiouracil (**3**).[8] Synthesis of **4** was accomplished by regioselective N-alkylation with *tert*-butyl bromoacetate as described in Scheme 1. It is important to emphasize the simplicity of this rapid large scale assembly of a heterocyclic scaffold with three orthogonal points of reactivity.

Table 1 depicts the isolated and purified yields[9] of standard Suzuki−Miyaura and Stille couplings at the bromide position of **4**. In all cases, the principal product observed by analysis of the crude LCMS was formed via the desired bromide cross-coupling reaction. No lone cross-coupling at the thiomethyl center was detected, and only traces of double coupling products were observed. In some cases (entries 1 and 2), anhydrous conditions with Cs_2CO_3 afforded acceptable results. In reactions for which conversions were under 75% using Cs_2CO_3 as base (entries 3−7), aqueous carbonate conditions proved very effective for acceleration of the transmetalation step. The Stille variants (entries 8−10) were somewhat sluggish compared to the Suzuki cases and required higher temperatures and additional catalyst to proceed to completion. Still, under these more stringent conditions, good conversions and excellent selectivities were observed.

Table 2 depicts the isolated and purified yields[9] of selective cross-couplings at the thiomethyl position of **4** in the presence of the Suzuki- and Stille-active bromide. This unique selectivity is effected by the use of a Cu(I) carboxylate as a metal cofactor of higher thiophilicity than the Pd catalyst.[7] In addition to facilitating transmetalation from boron or tin

Table 1. Suzuki and Stille Couplings of Scaffold **4**



	boronic acid or stannane	base/ solvent/	product **5**	%
1		Cs_2CO_3/ Dioxane	 **5a**	77
2		Cs_2CO_3/ Dioxane	 **5b**	80
3[a]		Na_2CO_3 Dioxane-water	 **5c**	75
4[a]		K_2CO_3 Dioxane-water	 **5d**	72
5		Na_2CO_3 Dioxane-water	 **5e**	77
6		Na_2CO_3 Dioxane-water	 **5f**	79
7[a]		Na_2CO_3 Dioxane-water	 **5g**	68
8		None/ Dioxane	 **5h**	69
9[b,c]		None/ Dioxane	 **5i**	65
10[a,c]		None/ Dioxane	 **5j**	73

[a] 10% catalyst. [b] 3%catalyst. [c] 105 °C.

to the −Pd−SMe bond,[7] the results reported herein suggest that interaction of the soft sulfur atom with the soft Cu(I) metal facilitates selective oxidative addition at the thiomethyl center through direct polarization of the C−S bond and/or through coordination of the adjacent pyrimidine nitrogen.[10] An elegant study reported by Jacobi, which supports this hypothesis, details the activation of a methylthioimidate C−S bond for oxidative addition to Pd(0) by Lewis acid coordination of the imidate nitrogen. The study also found that direct

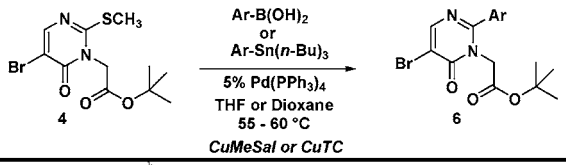
(7) (a) Heteroarylthioethers: Liebeskind, L. S.; Srogl, J. S. *Org. Lett.* **2002**, *4*, 979. Egi, M. Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801. Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803. For other thioorganic cross-couplings, see: Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3* (1), 91. Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3* (14), 2149. Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4* (6), 979. Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4* (6), 983. Liebeskind, L. S.; Srogl, J.; Savarin, C.; Polanco, C. *Pure Appl. Chem.* **2002**, *74* (1), 115. Egi, M.; Wittenberg, R.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2003**, in press.

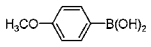
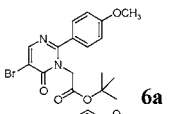
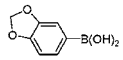
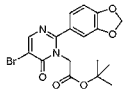
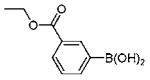
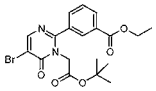
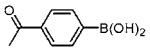
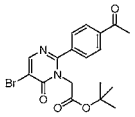
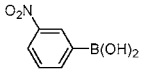
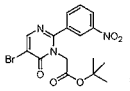
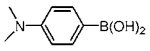
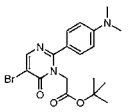
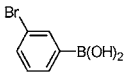
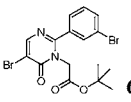
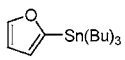
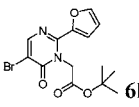
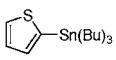
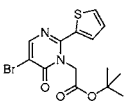
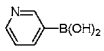
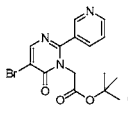
(8) Barrett, H. W.; Goodman, I. Dittmer, K. *J. Am. Chem. Soc.* **1948**, *70*, 1753.

(9) Unoptimized.

(10) An alternative explanation of the unique selectivity requires rapid and reversible oxidative addition to both the C−Br and C−SMe bonds followed by highly selective Cu(I) carboxylate activation of transmetalation at the C−Pd−SMe center under these nonbasic conditions.

Table 2. Liebeskind−Srogl Couplings of Scaffold **4**



	boronic acid[b] or stannane	Cu(I) carboxylate	Product **6**	%
1		CuTC (1.5 eq)	 **6a**	71
2		CuTC (1.5 eq)	 **6b**	74
3[a]		CuTC (1.5 eq)	 **6c**	69
4		CuTC (1.5 eq.)	 **6d**	66
5		CuTC (1.5 eq)	 **6e**	59
6		CuMeSal (2.2 eq)	 **6f**	77
7		CuTC (1.5 eq)	 **6g**	75
8[c]		CuMeSal (2.2 eq)	 **6h**	79
9[d]		CuMeSal (2.2 eq)	 **6i**	89[e]
10[d]		CuMeSal (2.2 eq)	 **6j**	47[e]

[a] 2% catalyst. [b] THF solvent/54 °C. [c] Dioxane solvent/54 °C. [d] Dioxane solvent/80 °C. [e] 10% catalyst.

coordination of the sulfur with Zn is also effective at promoting Pd(0) oxidative addition.[11] Thus, in the presence of CuTC or CuMeSal,[12] substrate **4** undergoes selective Pd-catalyzed thiomethyl cross-coupling with boronic acids and organostannanes in the presence of the bromide which participated in standard coupling reactions shown in Table 1.

By proceeding under nonbasic conditions, the Liebeskind−Srogl cross-coupling is distinguished from the Suzuki reaction, which requires a base or fluoride additive to activate transmetalation.[5] Furthermore, it is suggested by the accumulated results that the Cu(I) carboxylate not only activates the carbon−sulfur bond for oxidative addition, but also activates transmetalation by coordinative delivery of the carboxylate to the trivalent boron atom.[7a] For the boronic acid cases (entries 1−7), all reactions afforded very high conversions to the desired thiomethyl cross-coupling products (often >85% purities were observed by direct analysis of the crude LCMS traces). In all cases, less than 10% Suzuki coupling was detected, which was presumed to occur after the thiomethyl coupling reaction was complete.[13]

Remarkably, for the organostannane cases (entries 8−10), which generally do not require an additive for transmetalation, very high selectivity for thiomethyl cross-coupling was still observed. These results are a further testament to the ability of the Cu(I) carboxylate to *switch* on catalysis at the carbon−sulfur center. As was the case for the Suzuki−Miyaura and Stille reactions demonstrated in Table 1, a wide range of functionality is compatible with the Liebeskind−Srogl protocol as evident by the variety of substituted boronic acids and stannanes exemplified in Table 2. A particular noteworthy example is that of entry 7. Not only does cross-coupling occur selectively at the thiomethyl center but also generates a molecule with two differentially reactive bromides.

To fully illustrate the switchable selectivity and iterative nature of this carbon−carbon bond forming chemistry, the rapid assembly of compound **8** with three new points of diversity is presented in Scheme 2. In this sequence, product **6g** was selected for by employing the previously described Cu(I) cofactor to activate the carbon−sulfur bond. By substituting a base (Na_2CO_3) in place of the Cu(I) carboxylate, selective Suzuki−Miyaura coupling chemistry can now be *switched on* at the more reactive 5-bromopyrimidinone position. Thus, cross-coupling of **6g** with 4-acetylboronic acid afforded compound **7** in 78% yield. The sequence can also be reversed by conducting the Suzuki−Miyaura coupling first. As described in Table 1 (entry 4), 4-acetylphenylboronic acid was coupled selectively at the bromide position using basic conditions to afford compound **5d**. Intermediate **5d** was then converted to compound **7** by cross-coupling with 3-bromophenylboronic acid in the presence of CuMeSal.[14] Final Suzuki−Miyaura coupling with an olefinic boronic acid at the remaining 3-bromophenyl position afforded functionalized pyrimidinone example **8** in 91% yield.

In summary, the design and synthesis of an orthogonally functionalized pyrimidinone system **4** has been reported. Using this system, we have demonstrated the selective nature

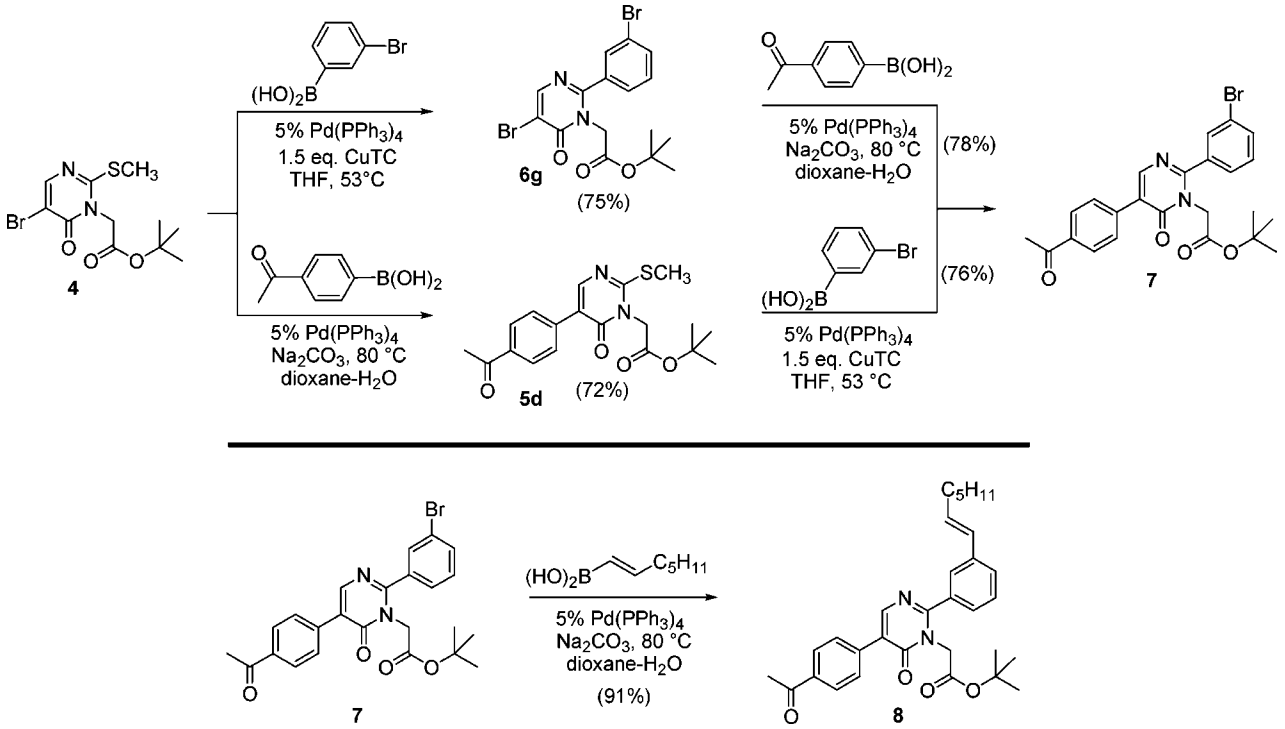
(11) Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2002**, *67*, 9304.

(12) CuTC = copper(I) thiophene-2-carboxylate. CuMeSal = copper(I) 3-methylsalicylate.

(13) There was no evidence of bromide cross-coupling products in these reactions in the absence of thiomethyl coupling. Only small amounts of double couplings could be detected as side products even though in most cases 1.5−2.0 equiv of boronic acid was used.

(14) This not only demonstrates the full selectivity of the coupling methods but provides chemical correlation of product **7** with regard to the differential reactivity of each bromide in **6g**.

Scheme 2



of the Liebeskind−Srogl thiomethyl cross-coupling protocol versus the Suzuki−Miyaura and Stille reactions. Due to the inherent mechanistic differences, coupling chemistry can be switched on and off between halide and thiomethyl positions by employing a base or a Cu(I) carboxylate cofactor as appropriate. As this chemistry can be used in an iterative fashion to rapidly build functionalized carbon frameworks around a heterocyclic core, it has great promise in the parallel synthesis format. Solid-phase synthesis applications of these systems will be reported in the future.

Acknowledgment. We thank Dr. Samuel Tremont for many helpful discussions and Drs. James Doom and David Masters-Moore of Pfizer—St. Louis for HRMS data.

Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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