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Optimized Liebeskind–Srogl coupling reaction between dihydropyrimidines and tributyltin compounds

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ABSTRACT

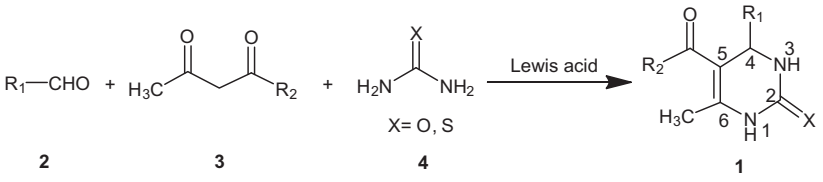
We developed an optimized Liebeskind–Srogl reaction in order to synthesize potentially biologically active 2-aryl-1,4-dihydropyrimidines. The pallado-catalyzed cross-coupling reaction between dihydropyrimidines and tributyltin derivatives appears particularly efficient (67–95% yields) when using CuBr·Me_2S as the copper cofactor.

Dihydropyrimidines (**1**), which were first produced by the Italian chemist Biginelli in 1893,[1] have a broad range of biological activities, such as anti-viral, anti-tumor, anti-bacterial, and anti-inflammatory activities.[2] In addition, they are also regarded as calcium channel blockers,[3] α-adrenergic antagonists,[4] mitotic kinesin Eg5 motor protein inhibitors,[5] as well as potent HIV gp-120-CD_4 inhibitors.[6]

During the past decade, the construction of dihydropyrimidine cores (**1**) by condensation of various aldehydes (**2**), 1,3-dicarbonyl compounds (**3**), and urea or thiourea (**4**) became one of the most efficient examples of multicomponent reactions (Scheme 1). Various Lewis acids were developed to catalyze this Biginelli condensation reaction under solvent-free[7] or microwave conditions[8] in good to excellent yields. Asymmetric syntheses of the chiral dihydropyrimidine ring at position 4 were also performed by Zhu and Gong with high ee values.[9] In contrast to these fruitful synthetic methods, there are only a few methods reported in the literature for further modifying this heterocyclic system.[10]

Recently, the 2-aryl-1,4-dihydropyrimidine heterocyclic scaffold was reported to display a range of interesting pharmacological properties. Compounds Bay 41-4109 (**5**, Fig. 1) and Bay 39-5493 (**6**, Fig. 1) showed highly potent anti-hepatitis B replication activity in vitro and in vivo.[11] Another compound (**7**, Fig. 1), the Rho-associated kinase isoform 1 (ROCK1) inhibitor, was reported as a potential therapeutic agent for cardiovascular diseases.[12] Synthetic routes to these 2-aryl-1,4-dihydropyrimidines are linear synthesis (and do not allow aryl diversity at the end of the synthesis) with low global yields (about 30%).[12]

In 2004, an unprecedented pallado-catalyzed cross-coupling reaction between dihydropyrimidine-2-thiones and boronic acids in the presence of CuTC (Scheme 2) under microwave irradiation was reported by Kappe.[13] This work was an important



2 3 4 1

Scheme 1. Three components Biginelli condensation.

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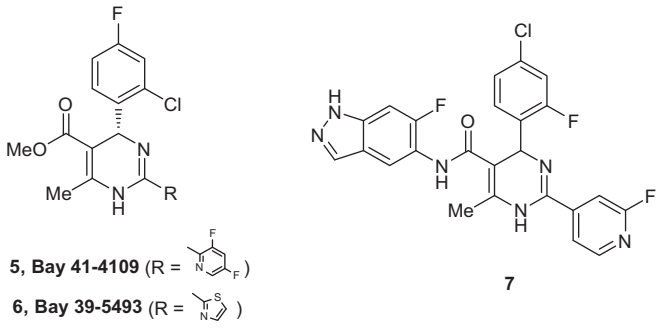
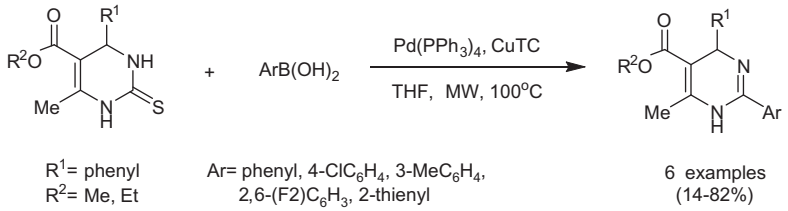


Figure 1. Examples of biologically active 2-aryl-1,4-dihydropyrimidines **5**, **6,** and **7**.

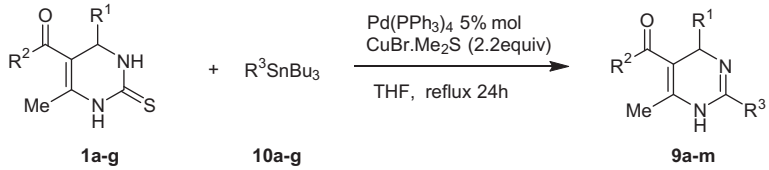
breakthrough for the Liebeskind–Srogl cross-coupling reaction[14] allowing the direct use of C=S function as electrophile. Dihydropyrimidine-2-thione derivatives provided 2-aryl-1,4-dihydropyrimidines in 14–82% yields. Despite this success, the low yields reported for a few aryl and heteroaryl boronic acids remained a challenge for this reaction.

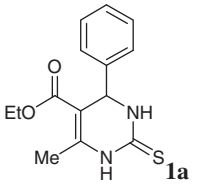
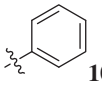
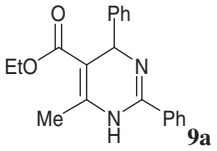
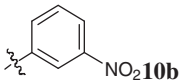
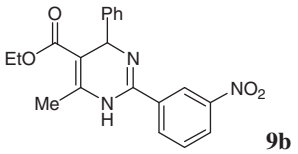
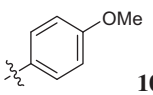
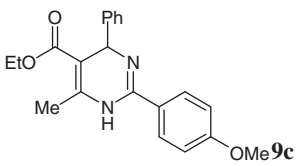
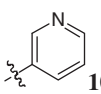
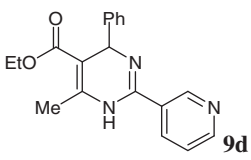
Since 2004, we have been engaged in the synthesis of dihydropyrimidines using anhydrous $ZnCl_2$ under solvent-free conditions.[15] Different substituted Biginelli products were provided by this simple method. We also reported the efficient copper bromide mediated pallado-catalyzed cross-coupling reaction of various heteroaromatic thioether derivatives with organostannanes.[16] This particular copper cofactor proved to be the successful strategy with



Scheme 2. Liebeskind–Srogl cross-coupling reaction between dihydropyrimidines and boronic acids.

Table 1
Coupling reaction between dihydropyrimidines and tributyltins



Entry	Dihydro-pyrimidines **1**[a]	Stannanes R^3SnBu_3	Products **9**	Yield (%)[b]
1	 **1a**	 **10a**	 **9a**	88
2	**1a**	 **10b**	 **9b**	92
3	**1a**	 **10c**	 **9c**	83
4	**1a**	 **10d**	 **9d**	78

(*continued on next page*)

Table 1 (*continued*)

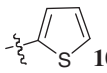
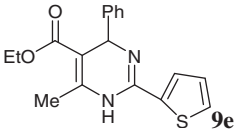
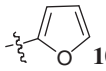
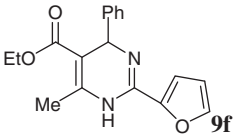
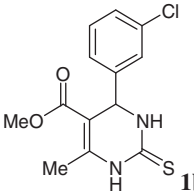
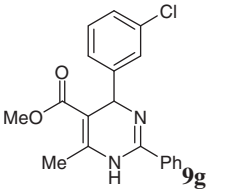
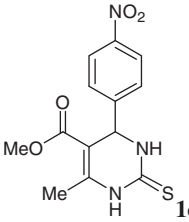
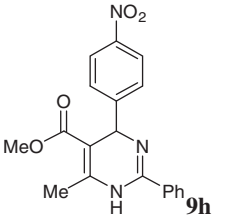
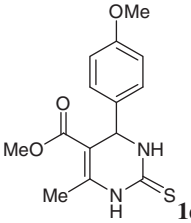
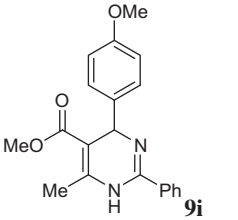
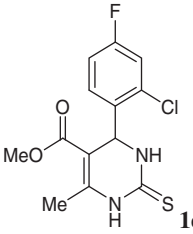
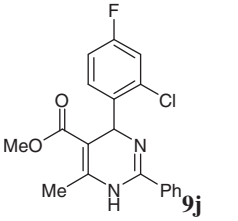
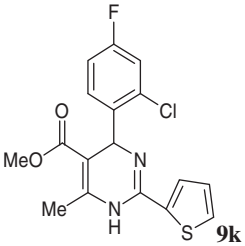
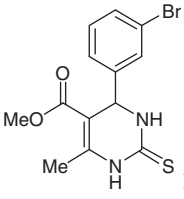
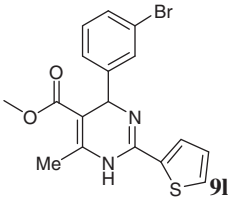
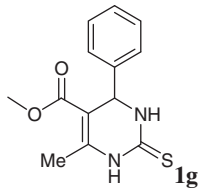
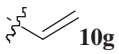
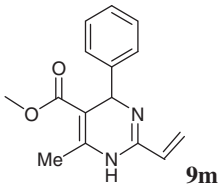
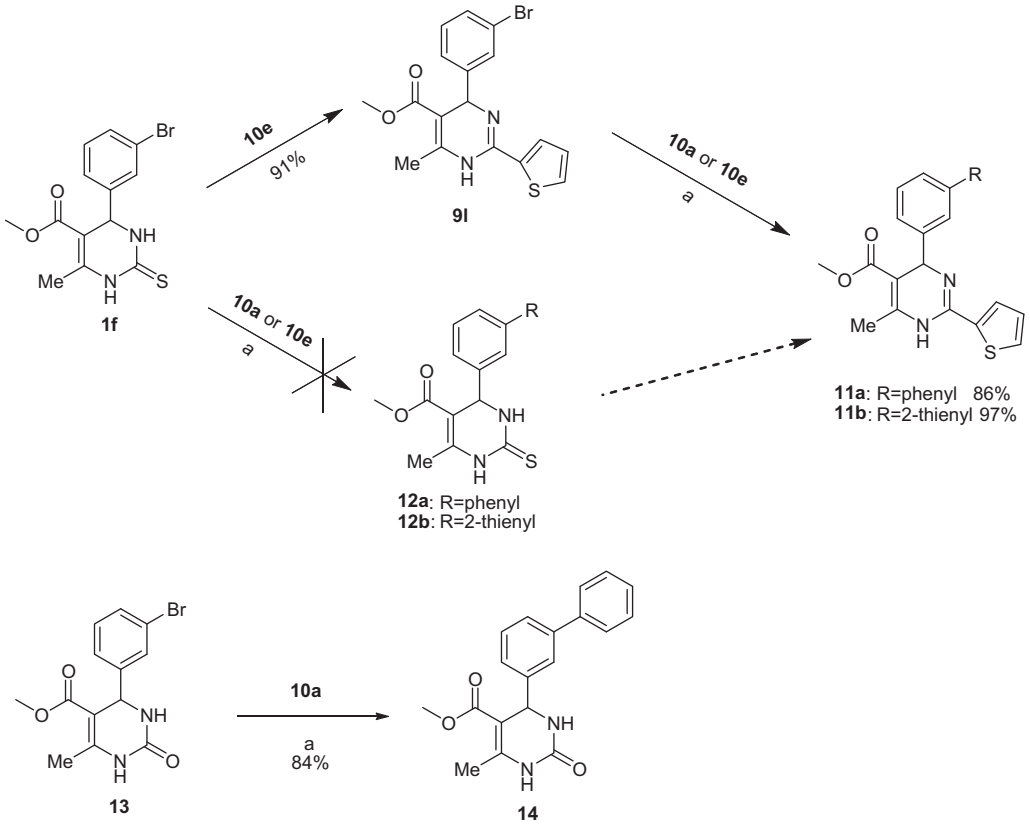
Entry	Dihydro-pyrimidines **1**[a]	Stannanes R^3SnBu_3	Products **9**	Yield (%)[b]
5	**1a**	 **10e**	 **9e**	95
6	**1a**	 **10f**	 **9f**	88
7	 **1b**	**10a**	 **9g**	89
8	 **1c**	**10a**	 **9h**	84
9	 **1d**	**10a**	 **9i**	67
10	 **1e**	**10a**	 **9j**	71
11	**1e**	**10e**	 **9k**	92
12	 **1f**	**10e**	 **9l**	91

Table 1 (*continued*)

Entry	Dihydro-pyrimidines **1**[a]	Stannanes R^3SnBu_3	Products **9**	Yield (%)[b]
13	 **1g**	 **10g**	 **9m**	–

[a] Refer to the Supplementary data.
[b] Isolated yield by column chromatography.



Scheme 3. Selectivity of Liebeskind–Srogl reaction and Stille coupling reaction. Conditions and Reagents: (a) $PdCl_2(PPh_3)_2$, PhMe, 100 °C, 48 h.

some specific substrates such as protecting-group-free 2-thiouracil derivatives.[17] Fortified by these experiments, we attempted to improve cross-coupling reactions between dihydropyrimidinethiones and organostannanes.

The first experiment was performed between dihydropyrimidine (**1a**) and phenyltributyltin (**10a**) using CuBr·Me_2S in refluxing THF in the presence of a catalytic amount of $Pd(PPh_3)_4$. To our delight, product **9a** (entry 1, Table 1) was isolated after column chromatography in 88% yield. MS analysis and $^1H/^{13}C$ NMR spectral data in $CDCl_3$ for compound **9a** were in accordance with the results reported in Kappe.[13] All the protons and carbons for compounds **9** were observed and carefully assigned in DMSO-d_6 by adding one drop of trifluoroacetic acid[18] or by using their HCl salts to fix the isomer (see S8). In the absence of $Pd(PPh_3)_4$ or CuBr·Me_2S product **9a** was not detected. These results encouraged us to explore the scope of this palladium-catalyzed cross-coupling reaction between dihydropyrimidines and tributyltin derivatives.

Using the previously reported experimental conditions,[17] we explored the possibility to extend this cross-coupling reaction to various organostannanes. The results are depicted in Table 1 (entries 2–6). Dihydropyrimidine (**1a**) was reacted with electron-poor (**10b**) or electron-rich aryltributylstannanes (**10c**) to provide the corresponding products **9b** and **9c** in good yields (entries 2 and 3). While some heteroarylstannanes were reported to cross-couple in low yields with CuTC,[13] interestingly, with CuBr·Me_2S, the desired products **9d** (78%), **9e** (95%), and **9f** (88%), were isolated in good to excellent yields (entries 4, 5, and 6).

Extension of this optimized Liebeskind–Srogl reaction to other dihydropyrimidines (**1b–f**) was also investigated and results are reported in Table 1 (entries 7–12). Various aryl groups on the

dihydropyrimidine core were well tolerated in these coupling reaction conditions and excellent yields of cross-coupled products were obtained with 2-(tributylstannyl)thiophene as well as tributylstannylbenzene. Unfortunately, no desired product **9m** was isolated for the reaction of dihydropyrimidine **1g** and vinyl tributyltin **10g**.

By-products resulting from the Stille cross-coupling reaction between bromoaryl–dihydropyrimidines **1f** and organostannanes were not observed and only the Liebeskind–Srogl adduct **9l** was isolated in good yield in accordance with the results of functionalized pyridinone reported by Liebeskind.[19] To better understand this selectivity between the Liebeskind–Srogl reaction and the Stille cross-coupling reaction, compound **9l** was then successfully converted into **11a** (yield: 86%) and **11b** (yield: 97%) by cross-coupling with **10a** and **10e** in the presence of $PdCl_2(PPh_3)_2$ in toluene. To our surprise, starting with the Stille cross-coupling reaction did not afford the expected cross-coupled product. As the presence of the thiocarbonyl function in **1f** was probably a contributing factor, we ran a test experiment with compound **13**[15] (the oxygenated analog of **1f**). The cross-coupled product **14** was isolated in an excellent yield showing that the present selectivity between the two cross-coupling reactions comes from the absence of reactivity of the thio derivatives under Stille conditions (Scheme 3).

In summary, we have developed an optimized Liebeskind–Srogl cross-coupling reaction to synthesize potentially biologically active 2-aryl-1,4-dihydropyrimidines in good to excellent yields with various heteroarylstannanes.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.067.

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