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Synthesis of Soai Type 2-Arylpyrimidine-5-carbaldehydes through Desulfurative Cross-Coupling with Arylboronic Acids

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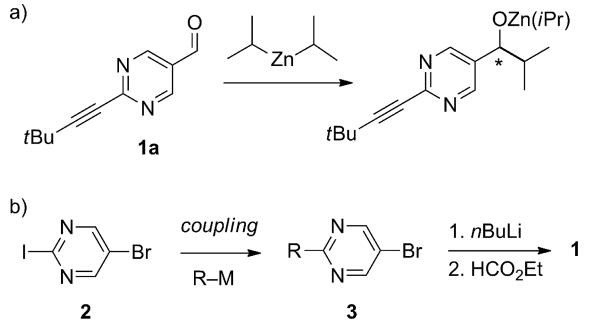
A two-step synthesis of 2-arylpyrimidine-5-carbaldehydes, which are of relevance as substrates for Soai's asymmetric autocatalysis, was realized by exploiting a hidden threefold symmetry in the target core structure. Condensation of Arnold's C_3-symmetric vinamidinium cation with *S*-methylisothiouronium sulfate provides 2-methylsulfanyl-pyrimidine-5-carbaldehyde; introduction of aryl groups at C-2 of the latter was accomplished by a Liebeskind–Srogl palladium-catalyzed desulfurative (de-methylsulfanylative) coupling with aryl boronic acids to obtain the target compounds **1** (14 examples, 60–95 % yield).

Introduction

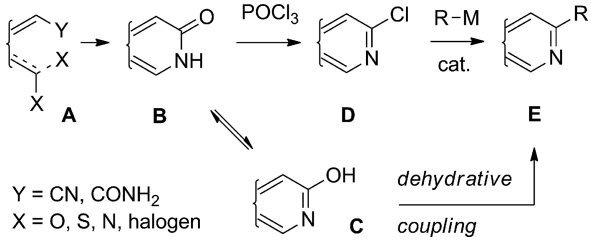
Pyrimidine-5-carbaldehydes **1** bearing unsaturated groups at C-2 have been introduced by Soai and co-workers as substrates for asymmetric autocatalytic additions of alkylzinc reagents, among which the reaction of the 2-*tert*-butylethynyl derivative **1a** with diisopropylzinc shows particularly strong asymmetric amplification (Scheme 1, a).[1,2] This reaction is an important tool to study processes of chirality transfer[2] and provides a remarkable example of absolute asymmetric synthesis.[3] Efficient synthetic approaches to **1** deserve interest because they will advance research in the field of asymmetric autocatalysis. Until recently, the important C-2-alkynylated aldehydes **1** were obtained in multistep syntheses through coupling of 5-bromo-2-iodopyrimidine (**2**) with alkynes, followed by bromine/lithium exchange and electrophilic formyl transfer (Scheme 1, b).[1,4]

The same sequence has provided access to 2-alkenyl-substituted targets through Stille coupling,[5] or to a 2-thiophenyl derivative through Negishi coupling.[6] A disadvantage of this approach is that the sequence **2**→**3**→**1** must be repeated each time a new group is attached at C-2, which limits both substance amounts and the number of derivatives available for screening studies in asymmetric autocatalysis. Although not fully satisfactory, this synthetic approach is rather typical for heterocyclic targets bearing carbon-substituents at ring-carbon atoms next to the imino-



Scheme 1. Soai-type C-2-substituted pyrimidine-5-carbaldehydes **1**: (a) As substrates in autocatalysis with asymmetric amplification. (b) General synthetic route to aldehydes **1** through cross-coupling and formylation from precursor **2**.

nitrogen: the condensation of various open-chain precursors **A** to lactam **B** or a tautomeric hydroxyimine **C** is followed by nucleophilic halogenation to provide an activated precursor **D** for cross-coupling to targets **E** (Scheme 2).[7]



Scheme 2. Standard route for the synthesis of heterocyclic targets that bear a carbon substituent at a ring-carbon next to an imino ring-nitrogen.

The recent introduction of formally "dehydrative" coupling reactions provides a short-cut from **B**/**C** directly to **E**.[8] The hydroxy moiety is not an actual leaving group in those couplings, which rely on activation of OH to a phos-

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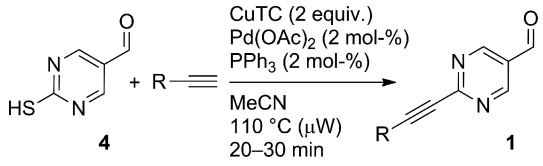
phonium or sulfonate leaving group in situ. Analogous palladium-catalyzed dehydrosulfurative couplings of heterocyclic mercapto or thiono substrates have been realized.[9–12] They require thiophilic copper(I) compounds such as copper(I) thiophene-2-carboxylate (CuTC) as activators and/or sulfur sequestering reagents and can be classified as Liebeskind–Srogl desulfurative couplings.[9a,13,14] We have recently shown that C-2-alkynylated pyrimidinecarbaldehydes **1** can be accessed in a single step by de-hydrosulfurative coupling of mercaptoaldehyde **4** with a range of alkynes (Scheme 3).[12a] In contrast to other dehydrosulfurative alkynylations,[12] the reaction proceeded under base-free conditions.

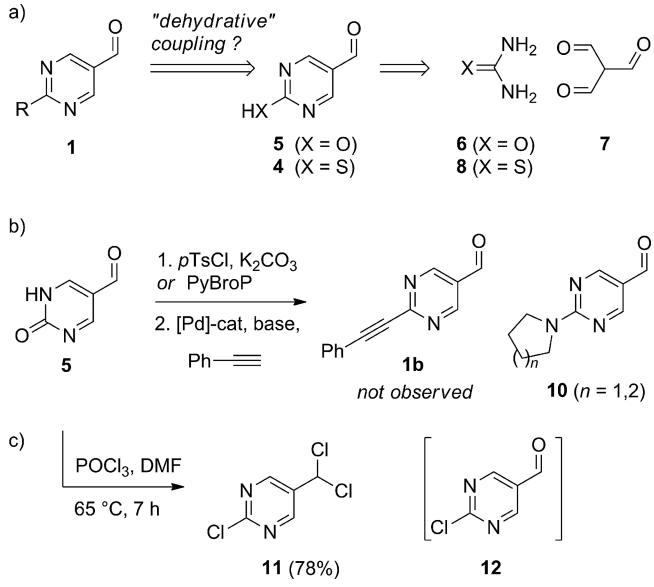


Scheme 3. Synthesis of Soai type aldehydes by dehydrosulfurative alkynylation of mercaptoaldehyde **4**.[12a]

In the present study, we wished to extend the synthetic methodology towards aldehydes **1** through one-step desulfurative couplings to other classes of organometallic nucleophiles. Boronic acids appeared to be the most promising for this purpose because of their low toxicity and ready availability, their expected compatibility with formyl groups, and because of the interest of C-2-arylated targets **1** as potential substrates for asymmetric autocatalysis.[2] Although syntheses of 2-aryl-substituted pyrimidine-5-carbaldehydes have been reported, they take the aryl group through one or several intermediates.[15,16] Here, we evaluate the synthetic approaches towards those targets, and describe an efficient, new, one-step synthesis through desulfurative Liebeskind–Srogl boronic acid coupling from a readily available thioether precursor.

Results and Discussion

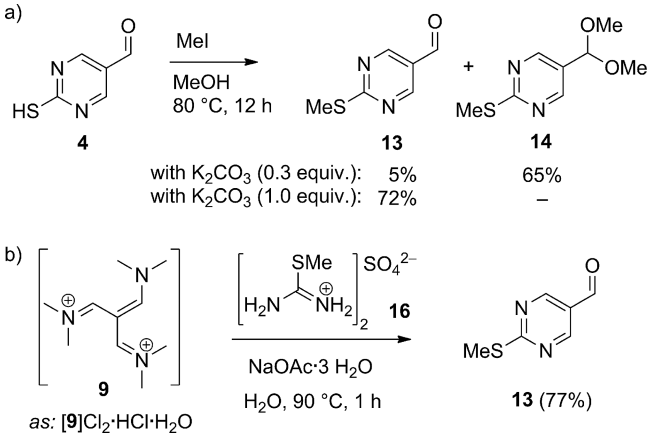
At the outset of the project we wanted to realize a short, general and (atom-)economic synthesis of Soai type aldehydes **1** by profiting from two innovative elements, namely: (1) the use of dehydrative coupling methodology on hydroxyaldehyde **5** as substrate, and (2) by taking advantage of a hidden threefold symmetry in **5**, which is revealed by its disconnection to urea (**6**) and triformylmethane **7** (Scheme 4, a). We have previously shown that **5** and **4** are obtained by condensing Arnold's vinamidinium cation **9**[17] (see below) – a synthetic equivalent of **7**[18] – with urea (**6**) or thiourea (**8**), respectively.[12a] Attempts to perform dehydrative couplings of **5** with alkynes through in situ activation by either the *p*TsCl/base[8c,8e] or the phosphonium salt protocol[8a,8b,8d] were unproductive (Scheme 4, b). Defined heterocyclic products were not usually isolated from such experiments, and 1,4-diphenylbutadiyne was the major product in attempted alkynylations with phenylacetylene. Starting with the more activated mercaptoaldehyde **4** and either PyBrOP[19] as coupling reagent or piperidine as base, 2-amino aldehydes **10** were detected by GC–MS analysis, in which the amine unit is derived from the coupling reagent or the base, respectively. The failure to realize in situ activation led us to investigate the activation of **5** with $POCl_3$/*N*,*N*-dimethylformamide in a separate step, which resulted in the formation of trichloride **11** rather than the expected aldehyde **12** (Scheme 4, c). The latter compound was only detected in trace amounts (by GC–MS analysis) during the reaction, which might imply that the most nucleophilic center of **5** is at the carbonyl oxygen rather than the hydroxyl group, and this may explain the failure to activate the latter position in situ. Consequently, the substrate for activation in situ was changed from **5** to **4** with its more nucleophilic mercapto group.[12a]



Scheme 4. Retrosynthetic strategy and initial reactivity studies. (a) Retrosynthetic analysis of Soai type aldehydes **1**. (b) Attempted dehydrative couplings. (c) Threefold nucleophilic chlorination of **4**.

Extending the successful alkynylation of **4** (Scheme 3) to dehydrosulfurative couplings with boronic acids looked like a promising strategy, considering that similar dehydrosulfurative arylations of heterocyclic thiono substrates have been described by Kappe and others.[10,11] However, reactions of mercapto aldehyde **4** with phenylboronic acids under typical conditions for such couplings[20] were not effective (< 20% yield of **1b**). Our attention therefore shifted to Liebeskind–Srogl de-alkylsulfanylative couplings of arylboronic acids,[13] which suggested the use of methylthio-aldehyde **13**[16] as a potential substrate. We first obtained the latter by alkylating **4** with methyl iodide, in the presence of a molar equivalent of potassium carbonate (Scheme 5, a).

When a limiting amount of base was used in the alkylation, dimethyl acetal **14** became the major reaction product, presumably as a result of hydriodic acid catalyzed acetalization of intermediary **13** (Scheme 5, a).[21] Later, we developed a second and overall more efficient route to **13** by modifying the reported condensation of vinamidinium cation **9** with *S*-methylisothiouronium sulfate (**16**) (Scheme 5,



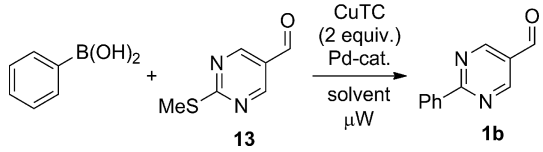
Scheme 5. Syntheses of 2-(methylsulfanyl)pyrimidine-5-carbaldehyde (**13**): (a) By methylation of mercaptoaldehyde **4**. (b) By condensation of vinamidinium cation **9** with *S*-methylisothiouronium sulfate (**16**).

b).[16] Instead of obtaining the tetrafluoroborate,[15b,18] hexafluorophosphate,[22] or perchlorate salts[17b] of **9**, we directly applied crude acidic chloride [**9**]Cl_2·HCl·H_2O as starting material.[12a,23] Condensation with **16** in hot ethanol gave mixtures of **13** (17–31%) and its diethyl acetal **17** (23–35%), with the composition depending on the mixing ratio and reaction time.[24] In aqueous solution (90 °C, 2 h), a yield of only 29% of **13** resulted at a **9**/**16** ratio of 1:0.75,[25] but addition of sodium acetate as buffer increased the yield of **13** to ≥ 75%, although the conditions also gave rise to some 2-(dimethylamino)-pyrimidine-5-carbaldehyde (**18**) as contaminant, more so at extended reaction times. Performing the reaction over a short time in hot, buffered aqueous solution gave optimal results (Scheme 5, b).

The development of reaction conditions for the desulfurative coupling of **13** with phenyl boronic acid as test substrate began with a base-free protocol, using $Pd(PPh_3)_4$ as catalyst and 2 equiv. of CuTC as activator.[13] To simplify the optimization process, we performed the reaction in a microwave reactor[26] at a fixed heating interval of 30 min. Under those conditions, product yield was optimized against reaction temperature rather than reaction time, which can speed up the discovery process. The conversion of **13** and the yield of **1b** were analyzed in the crude reaction mixture by qNMR with an internal standard. Satisfactory conversions and yields were immediately obtained in tetrahydrofuran (THF) as solvent by gradually increasing the temperature, with the best result at 90 °C (Table 1, entries 1–4).

Reactions in other polar solvents such as dioxane or *N*,*N*-dimethylformamide (DMF) were also suitable, without offering a major advantage (Table 1, entries 5 and 6). The reaction also occurred with $Pd(OAc)_2$ as sole catalyst precursor (entry 7). This allowed a study of the effects of added ligands by combining the pre-catalyst with several phosphanes (entries 8–10); however, none of the resulting systems was superior to the tetrakis(triphenylphosphane)palladium catalyst under comparable conditions (entry 5). Given that conversions were still incomplete and the yields were confined to the 60% range, we gradually increased the quantity of boronic acid and achieved an optimal result when using a twofold excess of that reagent (entries 11–13). The remaining problem appeared to be the limited stability of the catalyst. However, increasing the catalyst loading while lowering the reaction temperature did not increase the yield or conversion further (entry 14). The conversion and yield could however be raised by performing the reaction in two consecutive heating intervals of 30 min at 90 °C with

Table 1. Screening of reaction parameters in the desulfurative arylation of **13** with phenyl boronic acid.

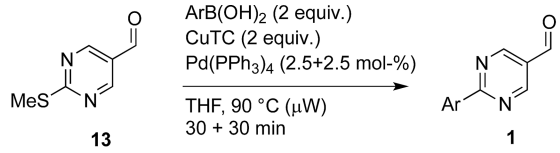


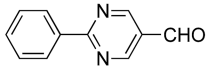
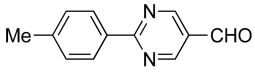
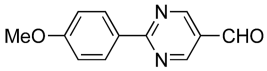
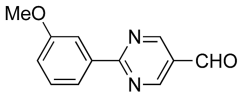
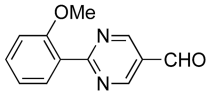
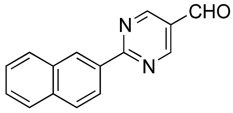
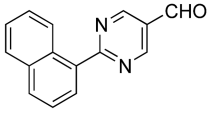
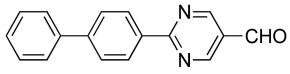
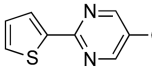
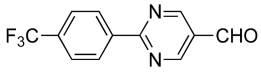
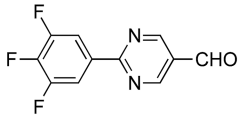
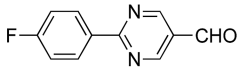
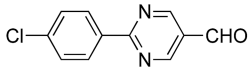
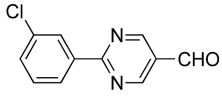
Entry	Catalyst ([mol-%])	$PhB(OH)_2$ [equiv.]	Solvent[b]	Temp. [°C]	Time [min]	Conv. [%][a]	Yield [%][a]
1	$Pd(PPh_3)_4$ (2)	1.25	THF	70	30	58	45
2	$Pd(PPh_3)_4$ (2)	1.25	THF	90	30	85	69
3	$Pd(PPh_3)_4$ (2)	1.25	THF	110	30	88	62
4	$Pd(PPh_3)_4$ (2)	1.25	THF	130	30	85	62
5	$Pd(PPh_3)_4$ (2)	1.25	dioxane	110	30	82	61
6	$Pd(PPh_3)_4$ (2)	1.25	DMF	110	30	86	67
7	$Pd(OAc)_2$ (2)	1.25	dioxane	110	30	76	51
8	$Pd(OAc)_2$ (2) + P(*o*Tol)$_3$ (2)	1.25	dioxane	110	30	62	39
9	$Pd(OAc)_2$ (2) + SPhos (2)	1.25	dioxane	110	30	81	52
10	$Pd(OAc)_2$ (2) + *t*BuXPhos (2)	1.25	dioxane	110	30	72	60
11	$Pd(PPh_3)_4$ (2)	1.75	THF	110	30	93	76
12	$Pd(PPh_3)_4$ (2)	2.00	THF	110	30	96	80
13	$Pd(PPh_3)_4$ (2)	2.20	THF	110	30	97	78
14	$Pd(PPh_3)_4$ (5)	2.00	THF	90	60	97	78
15	$Pd(PPh_3)_4$ (2.5 + 2.5)	2.00	THF	90	30 + 30	100	86

[a] Conversion and yield determined by qNMR against internal standard. [b] DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran.

renewed addition of catalyst after the first heating phase (entry 15).[26] Further experiments showed that neither variation of the relative amount of CuTC nor addition of a base were beneficial.[24] The optimized conditions fall within the known range of parameters of other desulfurative Liebeskind–Srogl couplings,[13,14] but each class of thioalkyl substrates requires a specific set of parameters to obtain the best results. The optimized protocol was applied to the coupling of thioether **13** with a variety of boronic acids on a preparative scale (Table 2). The desired arylated aldehydes **1** were usually returned in good to excellent yields without further optimization.

Table 2. Substrate range of the desulfurative boronic acid coupling.[a]



Entry	Product		Yield [%][b]
1		**1b**	82[c]
2		**1c**	89
2a		**1c**	85[d]
3		**1d**	95
4		**1e**	90[e]
5		**1f**	74
6		**1g**	89
7		**1h**	83
8		**1i**	95
9		**1j**	60
10		**1k**	95
11		**1l**	75
12		**1m**	94
13		**1n**	93
14		**1o**	93

[a] Reactions performed with **13** (1.0 mmol), $ArB(OH)_2$ (2.0 mmol), $Pd(PPh_3)_4$ (2.5 + 2.5 mol-%) and CuTC (2.0 mmol) in THF (1.5 mL) for 2× 30 min at 90 °C with microwave heating. [b] Isolated yield. [c] 2× 15 min heating intervals. [d] Performed on a 5 mmol scale with 3× 2.5 mol-% of $Pd(PPh_3)_4$ over 3× 30 min heating. [e] Performed on a 0.5 mmol scale.

The procedure gives access to alkylated aryl derivatives (Table 2, entry 2), alkoxy-functionalized aryl derivatives (entries 3–5), condensed aryl or biaryl derivatives (entries 6–8), heteroaryl (entry 9), and various halogenated aryl derivatives (entries 10–14). Some limitations were noted in case of hindered arylboronic acids, or with some functionalized boronic acids; likewise, alkyl boronic acids were unreactive (Figure 1).

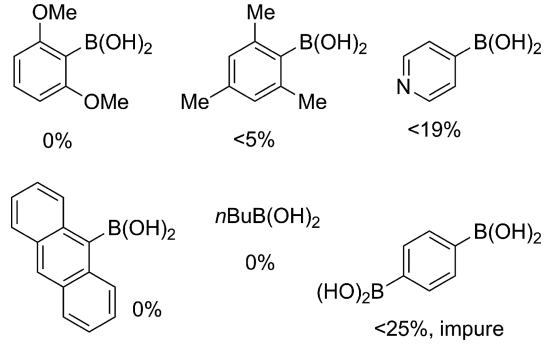
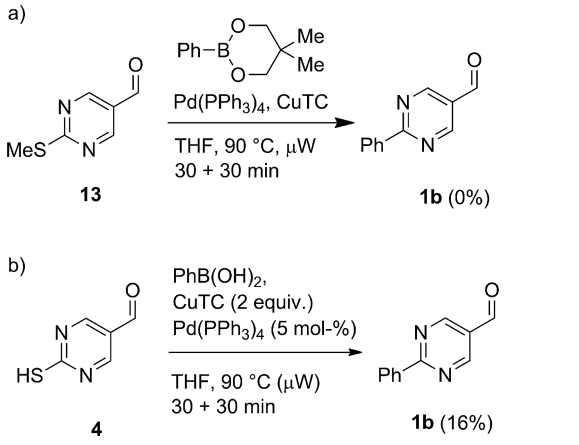


Figure 1. Limitations of the desulfurative coupling of **13** with boronic acids. Reaction conditions were those of Table 2, yields were determined by qNMR spectroscopic analysis of crude reaction mixtures.

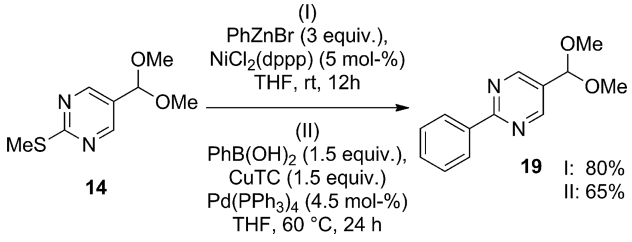
Alternative routes to 2-aryl-pyrimidine-carbaldehydes through desulfurative coupling have also been considered and evaluated in the course of this work. In contrast to boronic acids, boronate esters are not suitable nucleophiles in the desulfurative coupling reaction with **13** (Scheme 6, a).

As mentioned, mercaptoaldehyde **4** was unsatisfactory as an electrophile for coupling with arylboronic acids under the conditions used for alkynylation of the same substrate.[12a] Even under the optimized conditions of Table 2, a very low yield of **1b** was obtained (Scheme 6, b). Conversely, methyl thioether **13** – the preferred substrate for boronic acid coupling – was not a suitable electrophile for alkynylation.[27] These results illustrate that desulfurative couplings of mercapto- (vis. **4**) and thioether (vis. **13**) derivatives of the same heterocyclic core structure may give complementary results.[28] Finally, acetal **14** proved to be a viable substrate in desulfurative Negishi coupling,[29,30] or under common Liebeskind–Srogl conditions (Scheme 7).[13,14]

In the absence of a formyl group in **14**, the choice of reaction conditions is less constrained by chemoselectivity issues. Whereas a protecting group approach towards targets **1** through acetalization (**13**→**14**), cross-coupling



Scheme 6. Unsuccessful approaches to 2-arylpyrimidine-5-carbaldehydes. (a) Boronic ester coupling. (b) Dehydrosulfurative arylation of **4**.



Scheme 7. Desulfurative coupling of acetal **14** with boron and zinc reagents.

(**14**→**19**) and acetal hydrolysis (**19**→**1b**; not performed) seems viable, it offers no advantage over the direct coupling reaction (**13**→**1b**; Table 2).

Conclusions

The synthesis of 2-aryl-substituted Soai-type aldehydes **1** as desirable targets of interest for the study of asymmetric autocatalysis has been achieved in two steps starting from Arnold's vinamidinium cation **9**, or in one step from the readily available aldehyde **13** through a palladium-catalyzed de-methylsulfanylative Liebeskind–Srogl coupling with arylboronic acids. The literature on desulfurative coupling methodology points to a number of advantages of coupling reactions with sulfur-centered leaving groups:[9] (i) The possibility to perform chemoselective reactions if multiple leaving groups are present in one substrate;[9b,13b,31] (ii) the easier availability and/or higher stability of thioethers over some halogenated heterocyclic electrophiles;[13d,14a,14b,30a] (iii) the potential for stereospecific syntheses of alkenes when starting from pure (*E*)- or (*Z*)-alkenyl sulfides;[9b,31] (iv) the potential for chemoselective activation of sulfur leaving groups under mild conditions;[13b,32] (v) the advantage of performing coupling reactions under base-free conditions;[13d,32] (vi) the potential for orthogonal functionalization of thioether substrates (as opposed to more reactive halogenated substrates) prior to the coupling step.[33] Economy of steps is seldom an argument for choosing a desulfurative coupling route, and methylsulfanyl leaving groups are often introduced in additional synthetic steps.[34] Our work highlights the utility of Liebeskind–Srogl type desulfurative couplings for realizing short synthetic routes to heterocyclic targets, if the synthetic strategy is based on a heterocyclic condensation event that introduces, at the same time, a thioalkyl leaving group.[35]

Experimental Section

General: Experimental details are provided in the Supporting Information.

2-(Methylthio)pyrimidine-5-carbaldehyde (13): A mixture of 2-(dimethylamino)methylenepropane-1,3-bis(dimethyliminium) dichloride hydrochloride monohydrate[12a] (10.38 g, 34.2 mmol), *S*-methyl isothiouronium sulfate (**16**; 7.45 g, 26.8 mmol), and sodium acetate trihydrate (14.61 g, 107.4 mmol) in water (100 mL) was heated at 90 °C for 1 h. After cooling of the reaction mixture to room temp., the product was extracted with dichloromethane (3× 100 mL). The organic phase was washed with 6 M HCl (6 mL), brine (2× 100 mL), and dried with $MgSO_4$. After filtration, the solvent was evaporated to give **13** (4.07 g, 77%) as a white or slightly yellow solid with a purity of 99% (by ^1H NMR analysis). ^1H NMR (250 MHz, $CDCl_3$): δ = 2.64 (s, 3 H, SCH_3), 8.92 (s, 2 H, CH), 10.02 (s, 1 H, CHO) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 14.6, 124.6, 158.2, 179.1, 188.5 ppm.

General Procedure for the Desulfurative Coupling of 13 with Arylboronic Acids: Into a microwave reactor glass vessel equipped with a stirring bar (1 cm) were successively added aldehyde **13** (154.2 mg, 1 mmol), the respective boronic acid (2 mmol), $Pd(PPh_3)_4$ (29 mg, 2.5 mol-%), and CuTC (381.5 mg, 2.0 mmol). The vessel was closed with a septum, and evacuated and filled with argon (3 times) through a steel cannula. Anhydrous THF (3 mL; 4 ppm H_2O) was added by using a syringe, the vessel was sealed with a septum that was suitable for use in the microwave reactor, and the reaction mixture was subjected to microwave irradiation (target temperature 90 °C, hold for 30 min). After cooling to 50 °C, additional $Pd(PPh_3)_4$ (29 mg, 2.5 mol-%) was added and microwave irradiation (90 °C, 30 min) was repeated. After cooling to room temp., a saturated solution of aq NH_4Cl (3 mL) and EtOAc (25 mL) were added and the mixture was filtered through Celite to remove insoluble solids. The filtrate was transferred into a separating funnel and the layers were separated. The aqueous phase was extracted with EtOAc (2× 25 mL) and the combined organic phase was washed with 2 M NaOH (2 mL) and brine (2× 20 mL), then dried with $MgSO_4$. After filtration and evaporation, the residue was purified by column chromatography on SiO_2.

2-Phenylpyrimidine-5-carbaldehyde (1b): Prepared according to the general procedure for 30 min (overall μW heating). Purification by column chromatography (CH_2Cl_2), yield 150 mg (82%); colorless solid. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.48–7.62 (m, 3 H, Ph-H), 8.52–8.60 (m, 2 H, Ph-H), 9.23 (s, 2 H, CH), 10.16 (s, 1 H, CHO) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 126.5, 128.9, 129.3, 132.3, 136.4, 158.6, 167.9, 188.9 ppm. HRMS (EI): *m/z* calcd. for $C_{11}H_8N_2O^+$ 184.0637; found 184.0639.

2-(*p*-Tolyl)pyrimidine-5-carbaldehyde (1c): (a) Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2) gave **1c** (177.7 mg, 89%) as a colorless solid. (b) Prepared according to the general procedure on a 5 mmol scale, with three additions of $Pd(PPh_3)_4$ (3× 2.5 mol-%) and 3× 30 min μW-heating

phases. Purification by column chromatography (CH_2Cl_2) gave **1c** (846.1 mg, 85%) as a colorless solid. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 7.33 (d, J = 8.2 Hz, 2 H, Ar-H), 8.44 (d, J = 8.2 Hz, 2 H, Ar-H), 9.18 (s, 2 H, CH), 10.12 (s, 1 H, CHO) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 21.8, 126.4, 129.5, 129.8, 133.8, 143.2, 158.7, 168.3, 189.0 ppm. HRMS (EI): m/z calcd. for $C_{12}H_{10}N_2O^+$ 198.0788; found 198.0794.

2-(4-Methoxyphenyl)pyrimidine-5-carbaldehyde (1d): Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2), yield 203.1 mg (95%); gray solid. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.91 (s, 3 H, OCH_3), 7.03 (d, J = 9.0 Hz, 2 H, Ar-H), 8.52 (d, J = 9.0 Hz, 2 H, Ar-H), 9.15 (s, 2 H, CH), 10.10 (s, 1 H, CHO) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 55.6, 114.4, 126.0, 129.2, 131.4, 158.7, 163.4, 167.9, 189.0 ppm. HRMS (EI): m/z calcd. for $C_{12}H_{10}N_2O_2^+$ 214.0737; found 214.0730.

2-(3-Methoxyphenyl)pyrimidine-5-carbaldehyde (1e): Prepared according to the general procedure on a 0.5 mmol scale. Purification by column chromatography (CH_2Cl_2), yield 96.5 mg (90%); colorless solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.93 (s, 3 H, OCH_3), 7.12 (dd, J = 8.2, 2.4 Hz, 1 H, Ar-H), 7.44 (t, J = 8.0 Hz, 1 H, Ar-H), 8.11 (s, 1 H, Ar-H), 8.17 (d, J = 7.8 Hz, 1 H, Ar-H), 9.22 (s, 2 H, CH), 10.16 (s, 1 H, CHO) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 55.6, 113.6, 119.2, 122.0, 126.7, 130.0, 137.9, 158.7, 160.2, 168.0, 189.0 ppm. HRMS (EI): m/z calcd. for $C_{12}H_{10}N_2O_2^+$ 214.0737; found 214.0729.

2-(2-Methoxyphenyl)pyrimidine-5-carbaldehyde (1f): Prepared according to the general procedure. Purification by column chromatography (hexanes/EtOAc, 2:1), yield 160.4 mg (74%); yellow oil; purity 95% (NMR analysis). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, OCH_3), 6.96–7.06 (m, 2 H, Ar-H), 7.41 (ddd, J = 8.3, 7.4, 1.8 Hz, 1 H, Ar-H), 7.78 (dd, J = 7.6, 1.8 Hz, 1 H, Ar-H), 9.18 (s, 2 H, CH), 10.06 (s, 1 H, CHO) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 56.0, 112.1, 120.7, 125.7, 127.0, 132.3, 132.3, 158.0 (br), 158.2, 169.3, 188.9 ppm. HRMS (EI): m/z calcd. for $C_{12}H_{10}N_2O_2^+$ 214.0737; found 214.0731.

2-(Naphthalen-2-yl)pyrimidine-5-carbaldehyde (1g): Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2), yield 207.0 mg (89%); colorless solid. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.49–7.64 (m, 2 H, Ar-H), 7.86–8.06 (m, 3 H, Ar-H), 8.59 (dd, J = 8.7, 1.8 Hz, 1 H, Ar-H), 9.11 (s, 1 H, Ar-H), 9.24 (s, 2 H, CH), 10.15 (s, 1 H, CHO) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 125.4, 126.6, 126.8, 127.9, 128.2, 128.7, 129.7, 130.7, 133.3, 133.8, 135.5, 158.7, 168.2, 189.0 ppm. HRMS (EI): m/z calcd. for $C_{15}H_{10}N_2O^+$ 234.0788; found 234.0792.

2-(Naphthalen-1-yl)pyrimidine-5-carbaldehyde (1h): Prepared according to the general procedure. Purification by column chromatography (hexanes/EtOAc, 10:1), yield 194.5 mg (83%); colorless solid. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.50–7.66 (m, 3 H, Ar-H), 7.93 (dd, J = 7.3, 2.4 Hz, 1 H, Ar-H), 8.03 (d, J = 8.3 Hz, 1 H, Ar-H), 8.26 (dd, J = 7.3, 1.3 Hz, 1 H, Ar-H), 8.80 (d, J = 8.3 Hz, 1 H, Ar-H), 9.31 (s, 2 H, CH), 10.17 (s, 1 H, CHO) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 125.3, 125.7, 126.0, 126.3, 127.6, 128.9, 131.1, 131.2, 132.3, 134.3, 134.4, 158.3, 170.7, 189.0 ppm. HRMS (EI): m/z calcd. for $C_{15}H_{10}N_2O^+$ 234.0788; found 234.0779.

2-([1,1′-Biphenyl]-4-yl)pyrimidine-5-carbaldehyde (1i): Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2), yield 247.7 mg (60%); colorless solid. ^1H NMR (360 MHz, $CDCl_3$): δ = 7.36–7.85 (m, 7 H, Ar-H), 8.62 (d, J = 8.0 Hz, 2 H, Ar-H), 9.22 (s, 2 H, CH), 10.14 (s, 1 H, CHO) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 126.6, 127.4, 127.6, 128.2, 129.1, 130.0, 135.4, 140.3, 145.1, 158.7, 167.9, 189.0 ppm. HRMS (EI): m/z calcd. for $C_{17}H_{12}N_2O^+$ 260.0944; found 260.0945.

2-(Thiophen-2-yl)pyrimidine-5-carbaldehyde (1j): Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2), yield 114 mg (60%); pale-yellow solid. ^1H NMR (360 MHz, $CDCl_3$): δ = 7.21 (dd, J = 5.0, 3.8 Hz, 1 H, Ar-H), 7.64 (dd, J = 5.0, 1.2 Hz, 1 H, Ar-H), 8.17 (dd, J = 3.8, 1.2 Hz, 1 H, Ar-H), 9.10 (s, 2 H, CH), 10.08 (s, 1 H, CHO) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 126.1, 129.1, 132.1, 133.2, 142.3, 158.9, 164.7, 188.5 ppm. HRMS (ESI): m/z calcd. for $C_9H_6N_2OS^+$ 190.0195; found 190.0195.

2-[4-(Trifluoromethyl)phenyl]pyrimidine-5-carbaldehyde (1k): Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2), yield 239.9 mg (95%); colorless solid. ^1H NMR (360 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.3 Hz, 2 H, Ar-H), 8.68 (d, J = 8.3 Hz, 2 H, Ar-H), 9.26 (s, 2 H, CH), 10.19 (s, 1 H, CHO) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 124.0 (q, $J_{F,C}$ = 272.5 Hz, CF_3), 125.89 (q, $J_{F,C}$ = 3.7 Hz), 127.1, 129.7, 133.7 (q, $J_{F,C}$ = 32.5 Hz), 139.6, 158.8, 166.7, 188.9 ppm. HRMS (EI): m/z calcd. for $C_{12}H_7N_2OF_3^+$ 252.0505; found 252.0501.

2-(3,4,5-Trifluorophenyl)pyrimidine-5-carbaldehyde (1l): Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2), yield 177.0 mg (75%); colorless solid. ^1H NMR (360 MHz, $CDCl_3$): δ = 8.24 (dd, $J_{F,H}$ = 8.6, $J_{F,H}$ = 6.8 Hz, 2 H, Ar-H), 9.22 (s, 2 H, CH), 10.18 (s, 1 H, CHO) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 113.7 (dd, $J_{F,C}$ = 17.7, $J_{F,C}$ = 5.5 Hz), 127.0, 132.5 (td, $J_{F,C}$ = 7.9, $J_{F,C}$ = 4.2 Hz), 142.7 (dt, $J_{F,C}$ = 258.5, $J_{F,C}$ = 15.6 Hz), 151.6 (ddd, $J_{F,C}$ = 250.3, $J_{F,C}$ = 10.3, $J_{F,C}$ = 3.7 Hz), 158.8, 165.1 (q, $J_{F,C}$ = 3.0 Hz), 188.7 ppm. HRMS (EI): m/z calcd. for $C_{11}H_5N_2OF_3^+$ 238.0348; found 238.0345.

2-(4-Fluorophenyl)pyrimidine-5-carbaldehyde (1m): Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2), yield 188.5 mg (94%); colorless solid. ^1H NMR (360 MHz, $CDCl_3$): δ = 7.14–7.26 (m, 2 H, Ar-H), 8.52–8.64 (m, 2 H, Ar-H), 9.20 (s, 2 H, CH), 10.15 (s, 1 H, CHO) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 116.1 (d, $J_{F,C}$ = 22.0 Hz), 126.6, 131.8 (d, $J_{F,C}$ = 9.0 Hz), 132.7 (d, $J_{F,C}$ = 3.0 Hz), 158.8, 165.8 (d, $J_{F,C}$ = 253.5 Hz), 167.2, 188.9 ppm. HRMS (EI): m/z calcd. for $C_{11}H_7N_2OF^+$ 202.0537; found 202.0532.

2-(4-Chlorophenyl)pyrimidine-5-carbaldehyde (1n): Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2), yield 204.9 mg (93%); colorless solid. ^1H NMR (360 MHz, $CDCl_3$): δ = 7.50 (d, J = 8.6 Hz, 2 H, Ar-H), 8.50 (d, J = 8.6 Hz, 2 H, Ar-H), 9.20 (s, 2 H, CH), 10.15 (s, 1 H, CHO) ppm. ^{13}C NMR (91 MHz, $CDCl_3$): δ = 126.7, 129.3, 130.7, 135.0, 138.9, 158.7, 167.2, 188.8 ppm. HRMS (EI): m/z calcd. for $C_{11}H_7N_2O^{35}Cl^+$ 218.0241; found 218.0239.

2-(3-Chlorophenyl)pyrimidine-5-carbaldehyde (1o): Prepared according to the general procedure. Purification by column chromatography (CH_2Cl_2), yield 203.4 mg (93%); colorless solid. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.43–7.56 (m, 2 H, Ar-H), 8.45 (dt, J = 7.5, 1.7 Hz, 1 H, Ar-H), 8.56 (t, J = 1.7 Hz, 1 H, Ar-H), 9.23 (s, 2 H, CH), 10.17 (s, 1 H, CHO) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 127.0, 127.5, 129.5, 130.2, 132.3, 135.2, 138.3, 158.7, 166.9, 188.8 ppm. HRMS (EI): m/z calcd. for $C_{11}H_7N_2O^{35}Cl^+$ 218.0241; found 218.0238.

Supporting Information (see footnote on the first page of this article): General information, additional screening data, spectroscopic data and copies of ^1H and ^{13}C NMR spectra for all synthesized compounds.

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[20] Conditions: CuTC (1.4 equiv.), $PhB(OH)_2$ (1.4 equiv.), $Pd(PPh_3)_4$ (2 mol-%), THF, 80 °C, 24 h.

[21] Aldehyde **13** was independently shown to undergo standard acid-catalyzed acetalization with ethylene glycol (toluene, 110 °C, *p*TsOH) to give a 97% yield of dioxolane acetal **15**; see the Supporting Information.

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[24] Further experimental details are provided in the Supporting Information.

[25] Since **16** contains two isothiouronium cations per formula unit, this ratio corresponds to a 1.5 molar excess of *S*-methylisothiouronium over **9**.

[26] Use of microwave heating in desulfurative cross-coupling and addition of the catalyst in two separate portions has been recommended by Kappe et al., see ref.[10]

[27] Heating of **13** (1 equiv.) with 1-octyne (1.5 equiv.), CuTC (1.05 equiv.), $Pd(OAc)_2$ (4 mol-%) and PPh_3 (4 mol-%) in MeCN for 23 min at 110 °C gave no alkynylation product; starting material **13** was largely reisolated.

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[35] For other methods of condensation/coupling shortcuts, see: a) ref.[10c]; b) ref.[12a]; c) ref.[14c]

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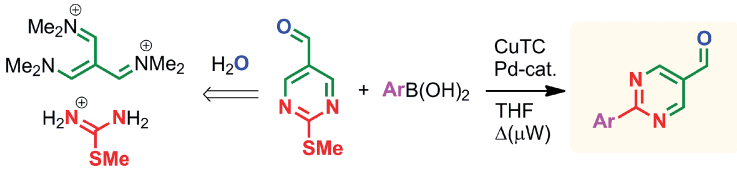
Cross-Coupling



2-Arylpyrimidine-5-carbaldehydes, which are of relevance as substrates in Soai's asymmetric autocatalysis, are prepared through Liebeskind–Srogl coupling of aryl boronic acids with 2-methylthiopyrimidine-5-carbaldehyde; the latter is obtained in a hydrolytic condensation of two symmetric amidinium salts.

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Synthesis of Soai Type 2-Arylpyrimidine-5-carbaldehydes through Desulfurative Cross-Coupling with Arylboronic Acids

Keywords: Asymmetric catalysis / Homogeneous catalysis / Palladium / Cross-coupling / Nitrogen heterocycles

