Organic LETTERS

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Synthesis of Soai Aldehydes for Asymmetric Autocatalysis by Desulfurative Cross-Coupling

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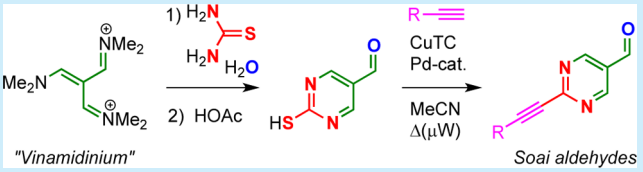
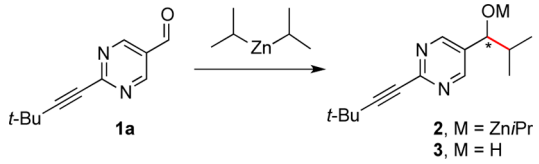
Supporting Information

ABSTRACT: Palladium-catalyzed dehydrosulfurative Liebeskind–Srogl coupling of terminal alkynes with 2-mercapto-1,3-pyrimidine-5-carbaldehyde under base-free conditions provides 2-(alkynyl)-1,3-pyrimidine-5-carbaldehydes, which are substrates for autocatalytic amplification of chirality according to Soai et al. The mercapto aldehyde acceptor is obtained by condensation of Arnold's vinamidinium salt with thiourea.



Soai and co-workers have described a remarkable asymmetric autocatalytic addition of aldehyde **1a** and Zn^{i}Pr$_2$ to

Scheme 1. Soai's Asymmetric Autocatalysis

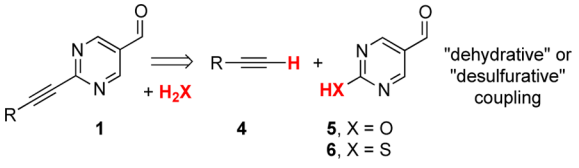


form alkoxide **2**, which is an asymmetric catalyst of its own formation (Scheme 1).[1,2] The strong asymmetric amplification[2,3] observed in the process means that addition of minute amounts of chiral inductors generates product **3** with considerable enantiomeric excess after hydrolysis.[2,4]

Some analogues of **1a** (R = *t*-Bu) with variable R groups, compounds **1**, have been prepared and tested in asymmetric amplification, e.g., R = *t*-BuMe$_2$Si,[5a] adamantyl,[5b] SiMe$_3$[5c] and others,[1,5d] but the involved five-step synthesis[1,4,6] hampers wider application and studies of those fascinating compounds.[7]

It occurred to us that recently introduced "dehydrative" coupling techniques,[8] in the instance with terminal alkynes (**4**) and a common electrophile **5**, might provide a shortcut access to targets **1** (Scheme 2).

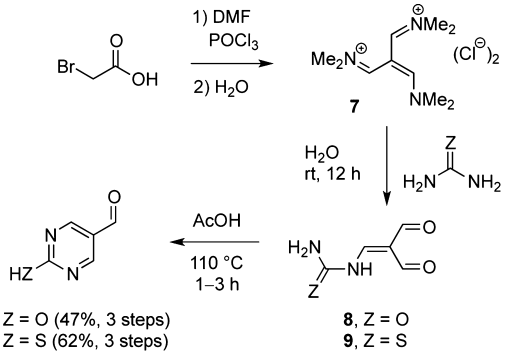
Scheme 2. Retrosynthetic Analysis of Soai-Type Aldehydes 1



While the envisioned dehydrative coupling of **5** has yet to be realized, we now report that the closely related dehydrosulfurative Liebeskind–Srogl[9,10] coupling of mercaptoaldehyde **6** with alkynes[11] indeed provides convenient access to a range of Soai-type aldehydes.

Access to the heterocyclic pro-electrophiles started from Arnold's vinamidinium salts[12] as triformylmethane[12b,13] equivalents: aqueous solutions containing **7**[14] and either urea or thiourea precipitate enamides **8** or **9**, respectively.[13] The latter cyclize to the new pyrimidylaldehydes **5**/**6** upon brief heating in acetic acid (Scheme 3).[15,16]

Scheme 3. Synthesis of Aldehydes 5 and 6



Initial attempts at Sonogashira-type couplings of **5** via in situ tosylation[8e] or phosphonium salt activation[8a−d] protocols did not generate any of the desired products.[17]

The focus shifted to mercaptoaldehyde **6** as the potential starting material in a dehydrosulfurative Liebeskind–Srogl coupling,[9,10] as previously described for alkynes with oxazolinethione acceptors.[10b,d,11] However, established conditions for desulfurative alkynylations involving base[11] were unsatisfactory with the present substrates. After some experimentation,[18] we arrived at base-free alkynylation

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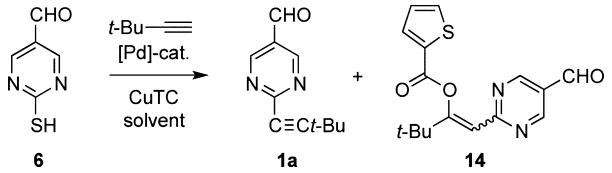
Table 1. Optimization of the Dehydrosulfurative Coupling of 6 with *tert*-Butylacetylene (4a)[a]



6 1a 14

					yield[b] (%)	
entry	cat. (mol %)	solvent	temp (°C)	time (h)	**1a**	**14**
1	none	THF	65	24	<0.5	
2	$[Pd_2Cl_2(allyl)_2]$ (5)	THF	65	24	44	3
3	$Pd(acac)_2$ (5)	THF	65	24	48	2
4	$Pd(dba)_2$ (5)	THF	65	24	54	2
5	$Pd(OAc)_2$ (5)	THF	65	24	57	2
6	$Pd(OAc)_2$ (5)	MeCN	65	2	22	
7	$Pd(OAc)_2$ + XPhos (5)	MeCN	65	2	23	
8	$Pd(OAc)_2$ + PPh_3 (5)	MeCN	65	2	39	
9[c]	$Pd(OAc)_2$ + PPh_3 (5)	MeCN	110	0.5	76	2
10[c]	$Pd(OAc)_2$ + PPh_3 (1)	MeCN	110	0.5	79	<1

[a]Reactions were performed under argon with **6** (0.5 mmol), **4a** (0.75 mmol), and CuTC (1 mmol) in the solvent (1.5 mL). [b]Yields of **1** and (*E*/*Z*)-**14** determined by qNMR with internal standard toluene. [c]Microwave (μW) heating was applied. CuTC = copper(I) thiophene-2-carboxylate; XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

conditions for **6** with *tert*-butylacetylene (**4a**) using various palladium catalysts and 2 equiv of CuTC (Table 1).

The reaction was performed in solvents such as 1,4-dioxane or THF with $Pd(OAc)_2$ as best catalyst precursor (Table 1, entries 1−6). Enol ester **14** is also formed by addition of thiophene-2-carboxylic acid, released from CuTC, to the triple bond of **1a**; consequently, it is the main product at prolonged reaction times.[18] Reactions in acetonitrile proceeded more selectively, but rather slowly, at 65 °C (Table 1, entry 6). While $Pd(OAc)_2$ catalyzes the reaction in the absence of added ligands (Table 1, entries 5 and 6), the addition of phosphanes (Table 1, entries 7−10) was preferred because this produced a homogeneously dissolved in situ catalyst. A metal/ligand ratio of 1:1 with PPh_3 was satisfactory for this purpose, whereas more specialized ligands provided no advantage (Table 1, entries 7 and 8).[18] To speed up the catalysis, it was performed in a microwave reactor at 110 °C, where satisfactory conversions were achieved in 30 min at a catalyst loading down to 1 mol % (Table 1, entries 9 and 10). Those conditions, at higher concentration, were then used in preparative couplings of various alkynes (Table 2).

The synthesis of **1a** (Table 2, entry 1) was scaled to 5 mmol (81% yield) and is limited only by the reactor volume and stirring efficiency in the heterogeneous reaction mixture of the microwave reactor. However, the reaction can also be performed in a pressure tube with thermal heating and magnetic stirring.[19] Alkyl-substituted, nonfunctionalized alkynes with variable steric requirements were successfully coupled (Table 2, entries 2−6), whereas phenylacetylene appeared to be less reactive and required more forcing conditions (Table 2, entry 7). However, this was not a general problem with arylacetylenes, since several substituted derivatives with either electron-attracting or -withdrawing substituents (entries 8a−e) gave fair yields under standard conditions.[20] Compound **1f** was amenable to X-ray crystal structure analysis (Figure 1).

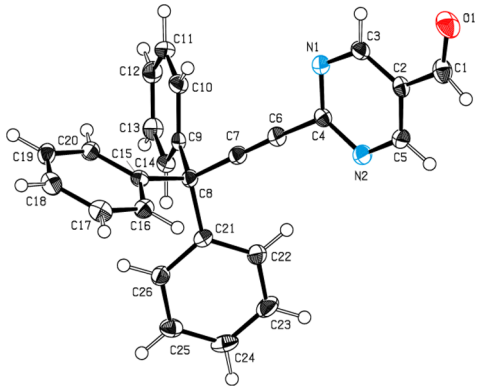


Figure 1. ORTEP representation of the molecular structure of **1f** (CCDC 971916). Ellipsoids are shown at the 50% probability level.

Besides the presence of aldehyde carbonyl, additional functionality is tolerated, such as ketone carbonyl (Table 2, entry 9), ester (Table 2, entries 10 and 11), or propargyl alcohols (Table 2, entry 12). Limitations of the alkyne structure included medium-chain 1-alkyn-ω-ols and trimethylsilyl acetylene (Table 2, entry 13) or certain propargyl derivatives (Table 2, entry 14). Occasionally, the coupling product could not be readily separated from enol ester side products (cf. **14**) by regular chromatography (examples not included in Table 2).

The mildness of the protocol and its potential for late-stage functionalization is also shown in the coupling of **6** with the contraceptive drug mestranol (**15**) that cleanly proceeds to aldehyde **16** (Scheme 4).

First experiments show that the nonbasic dehydrosulfurative alkynylation conditions are also suitable with a range of other heterocyclic substrates (Figure 2).

In conclusion, a synthesis of alkynylated pyrimidyl aldehydes, starting from readily accessible Arnold salt, via dehydrosulfurative coupling of alkynes with mercaptoaldehyde **6**, has been developed. This synthesis of Soai-type aldehydes **1** requires neither cryogenic reaction conditions nor highly air- and water-

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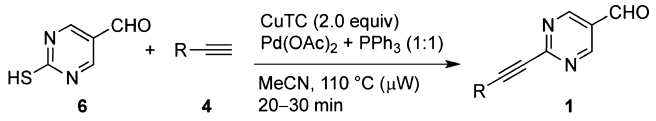
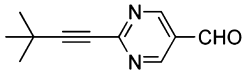
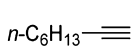
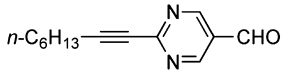
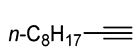
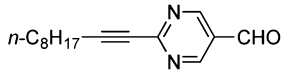
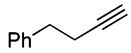
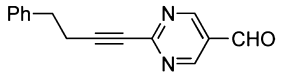
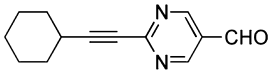
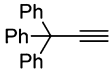
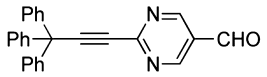
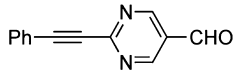
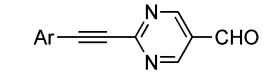
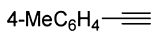
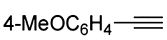
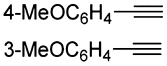
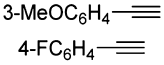
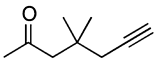
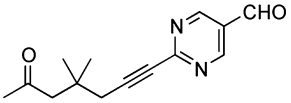
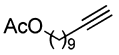
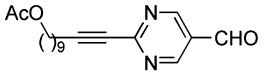
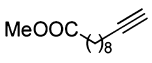
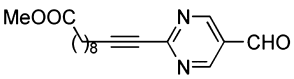
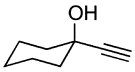
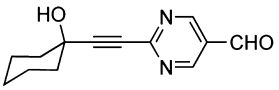
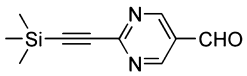
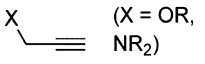
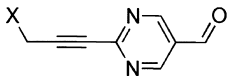
Table 2. Synthesis of 2-Alkynylpyrimidine-5-carbaldehydes by Liebeskind−Srogl Alkynyldehydrosulfuration of 6[a]



entry	alkyne	product		yield (%)[b]
1			**1a**	81–86
2			**1b**	70
3			**1c**	68
4			**1d**	55
5			**1e**	79
6			**1f**	87[c]
7			**1g**	16 (72)[d]
8a			**1ha**	60
8b			**1hb**	66
8c			**1hc**	64 (64)[d]
8d			**1hd**	54 (72)[d]
8e			**1he**	59 (69)[d]
9			**1i**	80
10			**1j**	59
11			**1k**	50
12			**1l**	59
13				–
14				complex mixture

[a]Reactions were performed at the 1 mmol scale under argon in closed glass vessels with **6** (1 equiv), alkyne (1.5−2.0 equiv), CuTC (2.0 equiv), $Pd(OAc)_2$ (1 mol %), and PPh_3 (1 mol %) in dry MeCN (1.5 mL) in a microwave (μW) reactor with variable power setting at 110 °C (hold temperature) for 22.5 min (hold time). [b]Isolated yield. [c]Performed on a 0.5 mmol scale in MeCN (1.5 mL) for 25 min. [d]Reaction performed with PhCCH (3.2 equiv), $Pd(OAc)_2$ (3 mol %), and PPh_3 (3 mol %) in MeCN (9 mL) under μW irradiation (130 °C, 30 min).

sensitive reagents. This approach illustrates the elegance of dehydrosulfurative Liebeskind−Srogl-type couplings,[9−11] which start from thio-heterocyclic building blocks as electrophiles rather than introducing leaving groups in extra synthetic steps.

■ ASSOCIATED CONTENT

Supporting Information

Additional screening results, detailed experimental procedures, and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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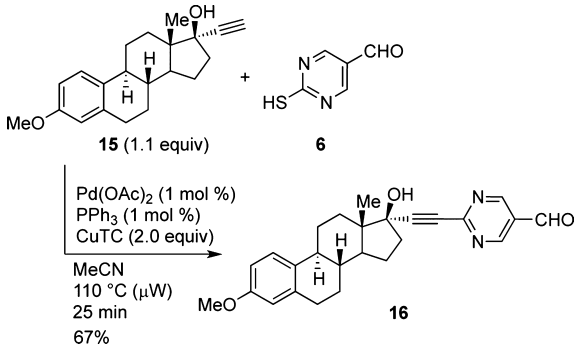
Scheme 4. Coupling of 6 with Mestranol



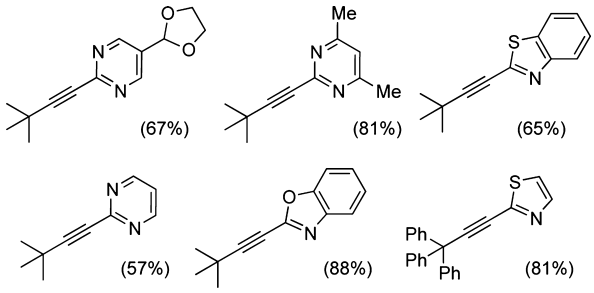


Figure 2. Additional products obtained from mercapto precursors by the standard protocol (cf. Table 2 for conditions).

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Notes

The authors declare no competing financial interest.

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(15) According to NMR data in DMSO-d_6, **5** and **6** favor the hydroxy or mercapto tautomer in that solvent, while **6** is also reversibly hydrated to 4-hydroxy-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde.

(16) Prolonged heating of **8**/**9** in acetic acid produces samples of **5**/**6** containing (thio)urea and ammonium salt impurities.

(17) Reaction of **5** with $POCl_3$ gives 2-chloro-5-dichloromethylpyrimidine rather than a monochloroaldehyde, implying preferential reaction of electrophiles at the formyl group.

(18) See the Supporting Information for additional screening results.

(19) The same 79% yield (qNMR) was obtained in a μW experiment (110 °C, 30 min) or a thermal experiment (oil bath, 115 °C, 40 min); the parameters of the thermal experiment were chosen to compensate for a slower heating rate and a temperature gradient. Differences in the outcome of catalytic reactions between μW and thermal heating are mostly due to such factors: Obermayer, D.; Gutmann, B.; Kappe, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 8321.

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