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Asymmetric, catalytic, vinylogous aldol reactions using pyrrole-based dienoxy silanes. Enantioselective synthesis of α,β-unsaturated γ-butyrolactam synthons

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ABSTRACT

A practical, catalytic and enantioselective vinylogous Mukaiyama aldol reaction between 2-silyloxypyrrole donors and aromatic or heteroaromatic aldehyde acceptors is described. Using an enantiopure bisphosphoramide catalyst in conjunction with $SiCl_4$, a variety of α,β-unsaturated-δ-hydroxylated γ-butyrolactam compounds were synthesized in high yields and with good to excellent levels of site-, diastereo- and enantioselectivity.

Saturated and unsaturated pyrrolidine and pyrroline entities are enabling building blocks with which a variety of aminated natural and natural-like molecules and related frameworks can be constructed.[1] The design and development of asymmetric, catalytic methodologies that lead to the assembly of *N*-containing compounds in an enantio-enriched format therefore define a crucial field of research in organic synthesis.[2]

Within this context, one area of investigation is focused on the exploitation of enantiopure metal and metal-free catalysts to propel enantioselective vinylogous Mukaiyama aldol reactions (VMAR) using heterocyclic dienoxy silanes for efficient access to heteroatom-containing butenolide frameworks often found in complex, multifunctional natural architectures.[3,4]

Herein we disclose the results of our investigations highlighting the ability of the Denmark's bisphosphoramide/$SiCl_4$ catalyst system (**1**/$SiCl_4$ complex)[5,6] to guide a highly performing VMAR of silyloxy pyrrole nucleophiles with aromatic and heteroaromatic aldehydes that allow for preparation of a variety of α,β-unsaturated-δ-hydroxylated γ-butyrolactam structures with very high levels of site-, diastereo- and enantioselectivity.

The first phase of our investigation was aimed at optimizing conditions for the VMAR between *N*-Boc-pyrroles **2a–c** and benzaldehyde (**3a**) to give *syn*-configured lactam **4a** (Table 1).

We began with the vinylogous coupling of TBS–pyrrole **2a** to aldehyde **3a** (2.0:1.0 mol equiv ratio) in the presence of unpurified commercial grade $SiCl_4$ (1.1 mol equiv),[7] enantiopure bisphosphoramide ligand (*R*,*R*)-**1** (3.0 mol %) and DIPEA (10.0 mol %) in CH_2Cl_2 at −78 °C (entry 1), paralleling almost exactly the conditions Denmark exploited during his studies on catalytic, enantioselective vinylogous aldol additions of ketone- and amide-derived silyl dienol ethers to various aldehydes.[5] Here, the reaction went to completion in 20 h, with the expected aldol adduct **4a** recovered in a rather good 80% ee, as detected by chiral HPLC analysis (87% isolated yield, >99% de). The rate of the uncatalyzed racemic reaction was found to be considerable (roughly 21% substrate conversion in the absence of enantiopure bisphosphoramide **1**, under the same reaction conditions, entry 2), indicating a significant acceleration effect by the enantiopure ligand itself.

Indeed, several factors were found to increase the rate of the catalyzed pathway relative to the background reaction. In particular, variation of the $SiCl_4$ nature (purity, dilution and HCl content) and the silyl diene substrate led to remarkable effects, providing the bases for reaction optimization. Thus, for example, exposure of a mixture of TBS–pyrrole **2a** and **3a** to neat, freshly refluxed and redistilled $SiCl_4$ under an argon atmosphere resulted in selective minimization of the racemic background pathway (entry 3), with great acceleration of the corresponding enantiopure ligand-assisted reaction (entry 4). Under such conditions (0.25 M in CH_2Cl_2 on a 0.5 mmol scale), *syn*-configured unsaturated lactam **4a** was obtained in a remarkable 97% isolated yield, with exquisite

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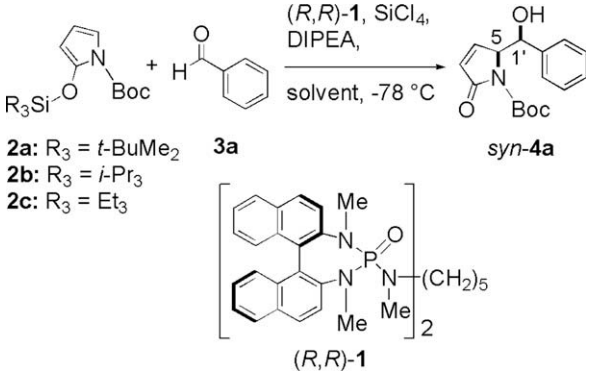
Table 1
Optimizing **1**/$SiCl_4$-catalyzed enantioselective VMAR between 2-silyloxypyrroles **2a–c** and benzaldehyde (**3a**) giving lactam *syn*-**4a**[a]



Entry	Pyrrole	(*R,R*)-**1** (mol %)	Solvent	Yield[b] (%)	dr[c] (*syn:anti*)	ee[d] (%)
1[e]	**2a**	3.0	CH_2Cl_2	91 (87)	99.5:0.5	80
2[e]	**2a**	None	CH_2Cl_2	21 (16)	90.0:10.0	Racemic
3[f]	**2a**	None	CH_2Cl_2	8 (6)	90.0:10.0	Racemic
4[f]	**2a**	3.0	CH_2Cl_2	>99 (97)	>99.5:0.5	>99
5[f,g]	**2b**	3.0	CH_2Cl_2	>99 (96)	>99.5:0.5	>99
6[f]	**2c**	3.0	CH_2Cl_2	60 (56)	99.6:0.4	>99
7[f]	**2a**	1.0	CH_2Cl_2	20 (18)	>99.0:1.0	95
8[f]	**2a**	3.0	Toluene	70 (61)	67.0:33.0	>99
9[f]	**2a**	3.0	THF	90 (84)	>99.5:0.5	94

[a] The reactions were carried out in the presence of pyrrole **2**/aldehyde **3a** (2.0/1.0 mol equiv), $SiCl_4$ (1.1 mol equiv), DIPEA (10.0 mol %), with a substrate concentration of 0.25 M (0.5 mmol scale) in the indicated solvent, with a 20 h reaction time (unless otherwise stated). For details, see Supplementary data.
[b] Based on ^1H NMR analysis of the crude reaction product. Yield of isolated *syn*-**4a** in parentheses.
[c] Determined by ^1H NMR analysis of the crude reaction product.
[d] Enantiomeric excess of *syn*-**4a** determined by chiral HPLC analysis.
[e] Commercial grade neat $SiCl_4$ used.
[f] Refluxed and redistilled, HCl-free, neat $SiCl_4$ used.
[g] 24 h reaction time.

levels of site-selectivity (γ-attack only), diastereoselectivity (>99.5:0.5% dr) and enantioselectivity (>99% ee). Almost identical behaviour was also observed with larger pyrrole silyloxy substituents, with TIPS–pyrrole **2b** emerging as an equally performing donor candidate (entry 5). Although in this instance the reaction rate was slightly reduced (>99% substrate conversion after 24 h), both yield and selectivity raised to nearly quantitative values for the (5*S*,1′*S*)-configured adduct *syn*-**4a**. On the other hand, when less encumbered TES–pyrrole **2c** was used as the donor component, less brilliant results were obtained, with a significant erosion of the yield, albeit with unaltered selectivity (entry 6). Finally, the solvent effect was evaluated, under the optimal conditions of entry 4. Moving to toluene solvent, both yield and diastereoselectivity decreased, while the use of THF still provided good results in terms of yield and selectivity (entries 8 and 9).

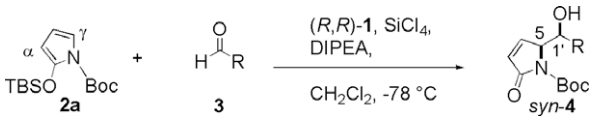
On the bases of the positive outcome of the initial study, we next investigated the bisphosphoramide **1**/$SiCl_4$-catalyzed VMAR of a range of aldehyde substrates, with the results summarized in entries 1–8 of Table 2. Due to the superior efficiency and selectivity exhibited by redistilled, HCl-free $SiCl_4$ in reaction involving ligand **1** and pyrrole nucleophile **2a**, the reaction scope of the electrophilic component was scrutinized by uniformly adopting the reaction conditions of entry 4 in Table 1 (alias entry 1 in Table 2).

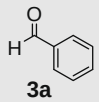
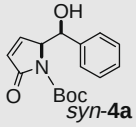
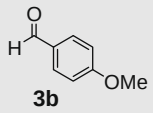
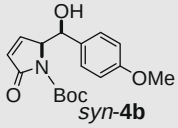
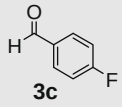
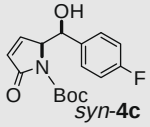
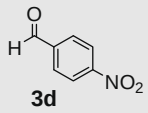
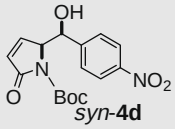
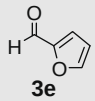
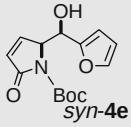
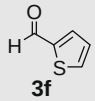
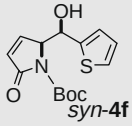
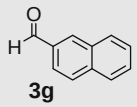
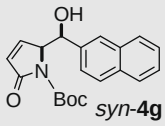
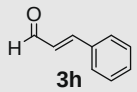
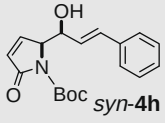
Indeed, complete γ-addition selectivity, good to excellent yields of pure isolated adducts and high diastereo- and enantioselectivity were generally observed in the reaction of **2a** with a survey of aromatic and heteroaromatic aldehydes **3a–g**. In all cases, the corresponding *syn*-configured α,β-unsaturated lactams **4a–g** were the sole or overwhelming isomers detected, with diastereo- and enantiocontrol consistently performed with aldehyde substrates of varied electronic and steric nature. Notably, the generality of the reaction was also tested on α,β-unsaturated aldehydes such as cinnamaldehyde (**3h**), which proved to be a pertinent substrate in this catalytic enantioselective VMAR reaction, giving rise to the corresponding adduct **4h** in high yield and with excellent *syn/anti* diastereoselectivity. Regrettably, in this instance, significant erosion of enantioselectivity was observed due to parasitic, concurrent activation of the racemic pathway (85% substrate conversion in the absence of ligand (*R,R*)-**1**, not shown).[8]

The relative 5,1′-*syn*-configuration of the emerging benzaldehyde lactam adduct *syn*-**4a** was unambiguously assigned based on comparison of the ^1H and ^{13}C NMR spectral data of our material with those of the racemic counterpart previously reported by H. Uno et al.[9] There, the ^1H–^1H $^3J_{5,1'}$ coupling constant for the *syn*-configured isomer ($^3J_{5,1'}$ = 6.1 Hz) was especially diagnostic, when compared to the smaller value for the corresponding 5,1′-*anti*-configured counterpart ($^3J_{5,1'}$ = 2.4 Hz). On these bases, we confidentially assigned the 5,1′-relative *syn* stereodisposition to the various lactam adducts **4b–h** shown in Table 2, whose ^1H–^1H $^3J_{5,1'}$ coupling constant values were invariably calculated in the 5.5–6.1 Hz range.

As for the absolute configuration assignment, we capitalized on an empirical, never-contradicted rule according to which a high $[\alpha]_D$ laevorotatory value pertains to 5*S*-configured unsaturated candidates of type **4**, while a dextrorotatory $[\alpha]_D$ value is attributed to 5*R*-configured isomers.[10] On these bases, we confidentially assigned a 5*S*,1′*S*-configuration to major *syn*-isomers **4** (see optical rotation values, Table 2) and a (5*R*,1′*S*)-configuration to the minor

Table 2
Substrate scope for the **1**/$SiCl_4$-catalyzed VMAR between pyrrole diene **2a** and aromatic and heteroaromatic aldehydes **3a–h** leading to the corresponding lactam adducts **4a–h**[a]

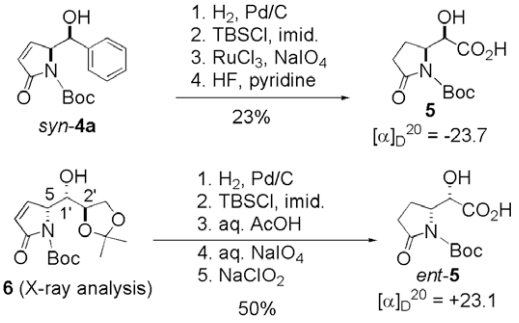


Entry	Substrate	Product	Yield[b] (%)	dr[c] (*syn:anti*)	ee[d] (%)	γ:α[c]	$^3J_{5,1'}$[e] (Hz)	$[\alpha]_D^{20}$[f]
1	 **3a**	 *syn*-**4a**	>99 (97)	>99.5:0.5	>99	>99:1	6.1	−347.5
2	 **3b**	 *syn*-**4b**	99 (96)	>99.5:0.5	>99	>99:1	6.0	−381.6
3	 **3c**	 *syn*-**4c**	97 (92)	>99.5:0.5	96.2	>99:1	5.8	−340.3
4	 **3d**	 *syn*-**4d**	82 (77)	84.0:16.0	73.6	>99:1	5.7	−278.3
5	 **3e**	 *syn*-**4e**	92 (87)	>99.5:0.5	74.6	>99:1	6.1	−286.0
6	 **3f**	 *syn*-**4f**	99 (93)	>99.0:1.0	88.4	>99:1	5.5	−222.3
7	 **3g**	 *syn*-**4g**	99 (85)	>99.0:1.0	99.0	>99:1	6.0	−280.0
8	 **3h**	 *syn*-**4h**	99 (94)	>99.0:1.0	45.1	>99:1	nd	−42.8

[a] The reactions were carried out in the presence of pyrrole **2a**/aldehydes **3** (2.0/1.0 mol equiv), $SiCl_4$ (1.1 mol equiv, refluxed and redistilled), DIPEA (10.0 mol %), with a substrate concentration of 0.25 M (0.5 mmol scale) in CH_2Cl_2, with a 20 h reaction time. For details, see Supplementary data.
[b] Based on ^{1}H NMR analysis of the crude reaction product. Yield of isolated *syn*-**4** in parentheses.
[c] Determined by ^{1}H NMR analysis of the crude reaction product.
[d] Enantiomeric excess of *syn*-**4** determined by chiral HPLC analysis.
[e] Coupling constant value between the H5 and H1′ protons of compounds *syn*-**4** as determined by the respective ^{1}H NMR spectra ($CDCl_3$, 300 MHz).
[f] Optical rotation values of compounds *syn*-**4** (*c* 1.0 g/100 mL, EtOH).

epimeric counterparts.[11,12] Decisive assessment of the absolute configuration of compound *syn*-**4a** was performed by chemical correlation to known D-glyceraldehyde-derived α,β-unsaturated lactam **6**, whose identity had been firmly established by single crystal X-ray analysis (5*R*,1′*S*,2′*R* absolute configuration).[13] As shown in Scheme 1, simple chemistry advanced *syn*-**4a** into carboxylic acid **5**, while **6** was elaborated into *ent*-**5** (the enantiomer of **5**). As expected, the optical rotation values of the two enantiomers were equal in absolute value but opposite in sign ($[\alpha]_D^{20} - 23.7$ for **5** versus $[\alpha]_D^{20} + 23.1$ for *ent*-**5**).

In summary, we present a reasonably general and practical methodology for catalytic, enantioselective, vinylogous aldol reactions that involve TBS–pyrrole donors and aromatic or heteroaromatic aldehyde acceptors. The process proceeds efficiently (77–97% isolated yields), with superb levels of site selectivity (γ-addition only), diastereoselectivity (84.0:16.0 to >99.5:0.5 dr)



Scheme 1. Chemical correlation of compound *syn*-**4a** to known D-glyceraldehyde-derived lactam **6**.

and enantioselectivity (73.6 to >99% ee for 5*S*,1′*S*-configured isomers).

Development of further vinylogous, enantioselective processes involving heterocyclic dienoxy silane nucleophiles and aliphatic aldehyde or imine substrates, and their application to synthesis of natural and natural-like bioactive compounds are the focus of ongoing studies.

Acknowledgements

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Supplementary data

Supplementary data (Experimental procedures and characterization data of compounds *syn*-**4**, **5** and *ent*-**5**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.181.

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11. Clean, base-promoted conversion (Et_3N, CH_2Cl_2) of major isomer *syn*-**4a** into the corresponding minor counterpart *anti*-**4a** proved their C5 epimeric relationship.
12. Heteroaromatic compounds *syn*-**4e** and *syn*-**4f**, in truth, are (5*S*,1′*R*)-configured, due to nominal change of the C1′ absolute configuration according to the Cahn–Ingold–Prelog priority rules.
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