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A Novel Three-Component [3+2] Cycloannulation Process for the Rapid and Highly Stereoselective Synthesis of Pyrrolobenzoxazoles

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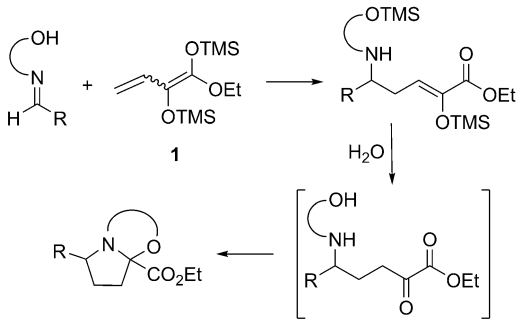
Dedicated to Professor Lutz F. Tietze on the occasion of his 70th birthday

The rapid assembly of novel heterocyclic scaffolds is an important and currently intensely investigated research topic primarily in the light of its relevance to medicinal chemistry.[1] In particular, domino reactions that lead to multiple bond-forming events in a one-pot operation are highly attractive processes due to their flexibility, operational simplicity, and reaction efficiency.[2] Ideally, such processes are accompanied by the generation of new reactive functional groups and full stereochemical control over newly formed stereogenic centers.

The pyrrolidine motif is among the most important heterocyclic ring systems and can be found in numerous biologically active natural products, pharmaceuticals, and agrochemicals.[3] In addition, pyrrolidines may be attached to other heterocyclic rings to give fused heterocycles, such as those found, for example, in pyrroloindoline, pyrrolobenzodiazepine, and pyrroloisoquinoline alkaloids.[4] Standard methodology to access the pyrrolidine ring system in a direct manner is mainly based upon [3+2] cycloaddition processes, namely azomethine ylide–alkene,[5] trimethylenemethane–imine,[6] and allene–imine cycloadditions.[7] In addition, [3+2] annulation reactions of imines with allylsilanes[8] and cyclopropane derivatives[9] have been developed.

We report, herein, a novel three-component, one-pot [3+2] cycloannulation process that gives previously unknown tetrahydropyrrolo [2,1-*b*]benzoxazoles in good yields and generates four new σ bonds and two new stereogenic centers with excellent diastereoselectivity.[10] Moreover, we demonstrate that this process can be rendered enantioselective with a suitable chiral scandium catalyst.

We have recently developed the Brønsted acid catalyzed, enantioselective, vinylogous Mannich reaction of acyclic vinylketene silyl-*O,O*-acetals that gives rise to functionalized δ-amino α,β-unsaturated esters in high yields and good-to-excellent enantio- and diastereoselectivities.[11] We reasoned that an additional silyloxy group in the 2-position of the vinylketene silyl *O,O*-acetal could further extend this reaction pathway. Under acidic aqueous reaction conditions the vinylogous Mannich product should in principle undergo hydrolytic cleavage of the newly formed silyl enol ether to give a highly reactive α-keto ester, which in turn could engage the previously formed amine in concert with a suitable secondary nucleophile in a cyclocondensation reaction generating an *N,O*-acetal spontaneously (Scheme 1). Accordingly, the envisioned bissilyldienediolate **1** would formally constitute the equivalent of an α-keto ester homoenolate and react as a 1,3-zwitterionic synthon at the same time.[12] Johnson and co-workers recently reported aldol reactions of in situ formed metallodienediolates of the same type as **1**, but observed opposite α-regioselectivity as a result of the different atomic orbital coefficients in metal versus silyl-containing dienolates.[13] In addition, Marsden et al. employed a related bimetaldienediolate in highly α-regioselective alkylation reactions.[14]



Scheme 1. Envisioned strategy.

We initiated our study by examining the reaction of bissilyldienediolate **1** with imine **2a** in aqueous CH_3CN in the presence of various Lewis acids (see Table 1 for a selection).[15] Among the Lewis acids screened, $Yb(OTf)_3$ and $Zn(OTf)_2$ emerged as optimal catalysts affording the desired tetrahydropyrrolo [2,1-*b*] benzoxazole **3a** as a single diastereomer in good yields of up to 82% within 48 h (Table 1, entries 4 and 7). The reaction time could be significantly reduced by increasing the amount of water employed. Thus, with 20 mol% of $Yb(OTf)_3$ in CH_3CN/water solvent (9:1) the reaction was completed within 3 h and delivered **3a** in

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Table 1. Initial optimization studies.[a]

2a 1 3a

Entry	LA	*t* [h]	Yield [%][b]
1	$Y(OTf)_3$	96	71
2	$La(OTf)_3$	48	58
3	$Sc(OTf)_3$	8.5	57
4	$Yb(OTf)_3$	24	79
5	$Cu(OTf)_2$	24	53
6	AgOTf	24	72
7	$Zn(OTf)_2$	48	82
8[c]	$Yb(OTf)_3$	3.5	82
9[c]	$Zn(OTf)_2$	21	73
10[c,d]	$Yb(OTf)_3$	4.5	74
11[c,e]	$Yb(OTf)_3$	15	74
12[c,f]	$Yb(OTf)_3$	4	81
13[c,g]	$Yb(OTf)_3$	6.5	74
14[h]	$Yb(OTf)_3$	4	84

[a] Reaction conditions (unless otherwise noted): imine **2a** (1.0 equiv, 0.20 mmol), diene **1** (3.0 equiv), Lewis acid (20 mol%), H_2O (5.0 equiv), MeCN (2 mL). [b] Yield of isolated product as a single diastereomer. [c] Reaction in MeCN/H_2O 9:1 (2 mL). [d] $Yb(OTf)_3$ (10 mol%). [e] $Yb(OTf)_3$ (1 mol%). [f] Diene **1** (2.0 equiv). [g] Diene **1** (1.2 equiv). [h] Three-component reaction: benzaldehyde (1.0 equiv, 1.30 mmol), 2-aminophenol (1.0 equiv), diene **1** (2.0 equiv) in MeCN/H_2O (9:1, 6.5 mL). TMS = trimethylsilyl, LA = Lewis acid.

identical yield (Table 1, entry 8). This observation is consistent with the assumption that hydrolysis of the silyl enol ether represents the slow step of this stepwise process and is further substantiated through detection of the initial vinylogous Mannich product after 1–2 h in significant amounts.[16] The catalyst loading could be reduced to only 1 mol% still generating the product in 74% yield within 15 h (Table 1, entries 10 and 11). Further investigations revealed that two equivalents of the nucleophile **1** were sufficient to achieve good results, whereas stoichiometric amounts gave rise to lower yields (Table 1, entries 12 and 13). More importantly, running the reaction in a three-component fashion with separate additions of benzaldehyde, 2-aminophenol, and nucleophile and in situ imine formation gave rise to even slightly improved results and isolation of isomerically pure **3a** in 84% yield (Table 1, entry 14,). This protocol was therefore employed for all further reactions.

The relative configuration of tetrahydropyrrolo [2,1-*b*] benzoxazole **3a** was unambiguously determined by X-ray crystallography.[17] As shown in Figure 1, benzoxazole **3a** forms a vaulted structure with both phenyl and ester substituents located on the convex face of the molecule, which most likely represents the thermodynamically favorable configuration.

Under the optimal reaction conditions, a variety of different aldehydes and 2-aminophenols were subsequently evaluated in this process giving the desired products as single diastereomers in generally good yields (Table 2). Aromatic aldehydes carrying both electron-donating and electron-withdrawing groups, as well as heteroaromatic aldehydes, proved to be good substrates. Moreover, different substitution patterns were readily tolerated. In addition, aliphatic and unsaturated aldehydes smoothly underwent the reaction to afford the desired tetrahydropyrrolo[2,1-*b*]benzoxazoles **3n–q** in moderate-to-good yields (Table 2, entries 14–17). Variation in the 2-aminophenol component was also possible

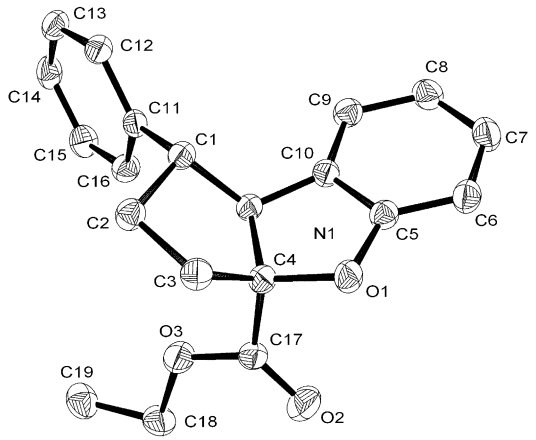
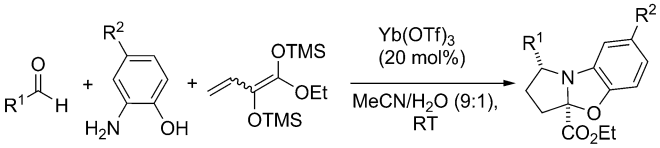
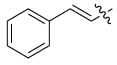


Figure 1. Crystal structure of (*rac*)-**3a**.

Table 2. Scope of the [3+2] cycloannulation process.[a]



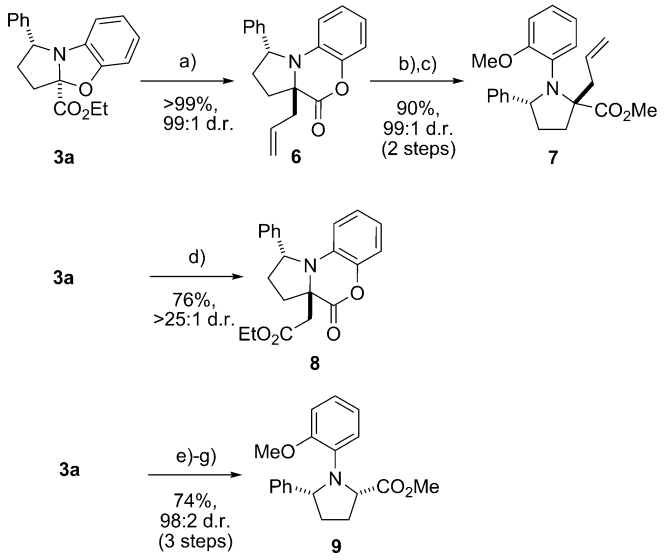
4 5 1 3

Entry	R^1	R^2	Product	*t* [h]	Yield [%][b]
1	Ph	H	**3a**	4	84
2	4-$MeOC_6H_4$	H	**3b**	3.5	64
3	4-MeC_6H_4	H	**3c**	4	75
4	4-*t*BuC_6H_4	H	**3d**	4	78
5	4-$NO_2C_6H_4$	H	**3e**	2	73
6	4-NCC_6H_4	H	**3f**	1	87
7	4-FC_6H_4	H	**3g**	3	71
8	4-ClC_6H_4	H	**3h**	4	62
9	3-ClC_6H_4	H	**3i**	1.5	75
10	2-ClC_6H_4	H	**3j**	2.5	84
11	2-BrC_6H_4	H	**3k**	4	79
12	2-naphthyl	H	**3l**	5	75
13	2-thiophenyl	H	**3m**	3	58
14		H	**3n**	1	63
15		H	**3o**	3	56
16	*t*Bu	H	**3p**	3	76
17	cyclohexyl	H	**3q**	2.5	70
18	Ph	Me	**3r**	4	63
19	Ph	*t*Bu	**3s**	3.5	70
20	Ph	Cl	**3t**	4	62

[a] Reaction conditions: aldehyde **4** (1.0 equiv, 1.30 mmol), 2-aminophenol **5** (1.0 equiv), diene **1** (2.0 equiv), $Yb(OTf)_3$ (20 mol%), MeCN/H_2O 9:1 (6.5 mL). [b] Yield of isolated product.

giving rise to products **3r–t** in equally good yields (Table 2, entries 18–20).

Being *N,O*-acetals, pyrrolobenzoxazoles **3** could easily be converted into reactive iminium ions upon exposure to Lewis acids and further reacted with various nucleophiles (Scheme 2). Thus, treatment of **3a** with $BF_3{\cdot}Et_2O$, which



Scheme 2. a) $BF_3{\cdot}Et_2O$ (1.5 equiv), allyltrimethylsilane (2.5 equiv), 1 h, RT, CH_2Cl_2. b) $LiOH{\cdot}H_2O$ (5.0 equiv), 20 min, RT, $THF/H_2O/MeOH$ (3:1:1). c) NaH (5.0 equiv), MeI (10.0 equiv), 20 min, 0 °C, DMF. d) $BF_3{\cdot}Et_2O$ (1.5 equiv), ((1-ethoxyvinyl)oxy)trimethylsilane (2.0 equiv), 5 min, 60 °C, 1,4-dioxane. e) $BF_3{\cdot}Et_2O$ (3.0 equiv), $NaCNBH_3$ (2.0 equiv), 15 h, −30 °C, THF. f) $LiOH{\cdot}H_2O$ (2.0 equiv), 20 min, RT, $THF/H_2O/MeOH$ (3:1:1). g) NaH (4.0 equiv), MeI (10.0 equiv), 15 min, 0 °C, DMF.

proved to be optimal in this respect, and allyltrimethylsilane cleanly gave the allylated product **6** in quantitative yield as a single *trans*-diastereomer according to the crystal structure analysis (Figure 2).[18] Apparently, the phenyl group directs the attack of the incoming nucleophile to the opposite face

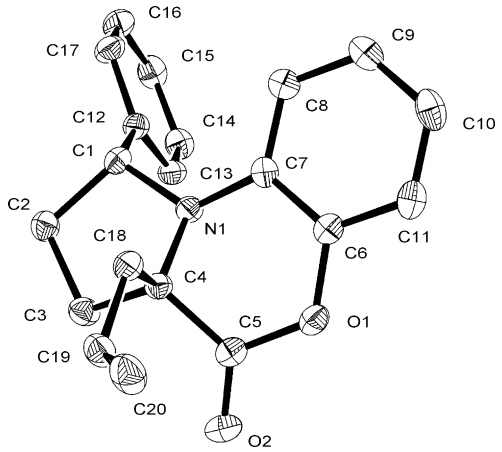
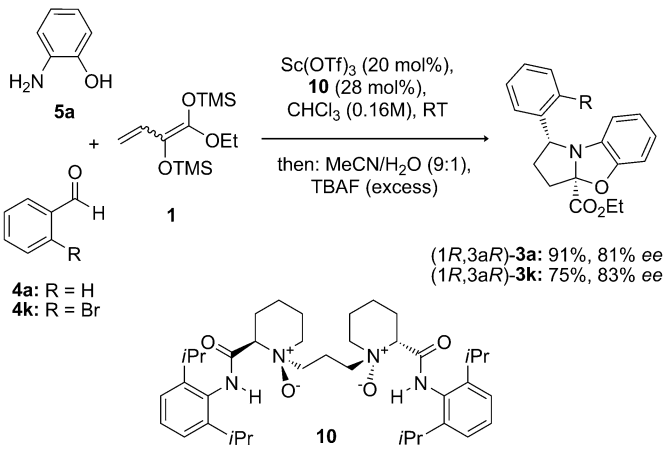


Figure 2. Crystal structure of (*rac*)-**6**.

of the iminium ion. Through concomitant transesterification with the liberated phenol, the bicyclic benzoxazinone **6** was obtained directly. This lactone was easily saponified with LiOH and further converted into methyl ester **7**, which constitutes an interesting proline derivative with a quaternary chiral center. This overall scheme could successfully be extended to the addition of a silylketene *O,O*-acetal in a Mukaiyama–Mannich reaction and to the hydride addition with $NaCNBH_3$, both of which occurred again with complete diastereoselectivity and delivered bicyclic benzoxazinone **8** and methyl ester **9** in good yields, respectively.

In an attempt to develop a catalytic, enantioselective process for this novel [3+2] cycloannulation, we eventually found a chiral scandium complex most suitable, which Feng et al. had established for a broad range of carbon–carbon bond-forming reactions.[19] Thus, the three-component reaction of benzaldehyde (**4a**), 2-aminophenol (**5a**), and the nucleophile **1** in $CHCl_3$ in the presence of $Sc(OTf)_3$ and the chiral *N,N*'-dioxide ligand **10** (28 mol%) with subsequent addition of tetra-*n*-butylammonium fluoride (TBAF) in CH_3CN/H_2O gave product **3a** in excellent yield and 81% enantiomeric excess (*ee*) (Scheme 3). Here, in the interest of conversion and enantioselectivity, the initial vinylogous Mannich reaction was performed under non-aqueous conditions, and desilylation and acetalization were effected subsequently through addition of TBAF. The corresponding *ortho*-bromo derivative **3k** was obtained likewise with 83% *ee*, and a crystal structure analysis revealed its absolute configuration (see the Supporting Information).[20]



Scheme 3. Catalytic, enantioselective reaction.

In conclusion, we have developed a novel Lewis acid catalyzed, stepwise [3+2] cycloannulation process, which converts bissilyldienediolate **1**, aldehydes, and 2-aminophenols directly into previously unknown tetrahydropyrrolo [2,1-*b*] benzoxazoles **3** in typically good yields and complete diastereoselectivity. On the basis of their *N,O*-acetal structure, benzoxazoles **3** were shown to be highly valuable synthetic intermediates with the potential to access proline derivatives with a quaternary stereogenic center with full stereochemi-

cal control. In addition, preliminary results document that a catalytic, enantioselective process is feasible with a chiral scandium catalyst, which gives products with currently up to 83% *ee*. Ongoing studies in our group are directed towards improving the scope, enantioselectivity, and applicability of this novel reaction.

Experimental Section

Synthesis of 3a: Benzaldehyde (138 mg, 1.30 mmol, 1.0 equiv) was added to a solution of $Yb(OTf)_3$ (162 mg, 0.26 mmol, 20 mol%) and 2-aminophenol (142 mg, 1.30 mmol, 1.0 equiv) in $MeCN/H_2O$ (9:1, 0.2 M). After 5 min, nucleophile **1** (714 mg, 2.60 mmol, 2.0 equiv) was added. Stirring was continued for 4 h at RT, until full conversion was indicated by TLC. The solvent was removed under reduced pressure, and silica-gel chromatography (hexane→hexane/diethyl ether 30:1) gave **3a** as a white solid (338 mg, 84%, single diastereomer, m.p. 138 °C). Additional details and full characterization data of all new compounds are provided in the Supporting Information.

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Keywords: asymmetric synthesis · domino reactions · heterocycles · Lewis acids · *N*,*O*-acetal

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[14] a) S. P. Marsden, R. Newton, *J. Am. Chem. Soc.* **2007**, *129*, 12600–12601; b) S. P. Marsden, R. Newton, *Synthesis* **2005**, 3263–3270.

[15] Brønsted acid catalyzed reactions of nucleophile **1** with imines give mixtures of α- and γ-regioisomers.

[16] The intermediate vinylogous Mannich product was characterized by HRMS and ^{1}H NMR spectroscopy measurements, see the Supporting Information.

[17] Crystal data for (*rac*)-**3a**: $C_{19}H_{19}NO_3$; $M_r = 309.35\ g\,mol^{-1}$; crystal size: $0.30\times0.30\times0.20\ mm^3$; monoclinic; space group $P2_1/n$; $a = 11.7951(4)$, $b = 7.2664(2)$, $c = 17.9472(6)$ Å; $\alpha = 90$, $\beta = 91.571(3)$, $\gamma = 90°$; $V = 1537.64(8)$ Å^3; $Z = 4$; $\rho_{calcd} = 1.336\ g\,cm^{-3}$; $\mu = 0.090\ mm^{-1}$; $Mo_{K\alpha}$ radiation; $\lambda = 0.71073$ Å; $T = 180(2)$ K; 10190 measured and 3643 independent reflections; $\theta_{max} = 27.89°$; $R_{int} = 0.0238$; $R_1(I>2\sigma(I)) = 0.0354$; wR_2 (all data) $= 0.0977$; 284 parameters; $\Delta\rho_{max/min} = 0.272/-0.178\ e\,Å^{-3}$; structure determination by direct methods (G. M. Sheldrick, SHELXS-97, **1990**) and by least-squares refinement on F^2_o (G. M. Sheldrick, SHELXL-97, **1997**). CCDC-862018 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] Crystal data for (*rac*)-**6**: $C_{20}H_{19}NO_2$; $M_r = 305.36\ g\,mol^{-1}$; crystal size: $0.40\times0.30\times0.20\ mm^3$; orthorhombic; space group $Pna2_1$; $a = 15.5961(3)$; $b = 10.9133(2)$, $c = 9.2802(2)$ Å; $\alpha = 90$, $\beta = 90$, $\gamma = 90°$; $V = 1579.54(5)$ Å^3; $Z = 4$; $\rho_{calcd} = 1.284\ g\,cm^{-3}$; $\mu = 0.083\ mm^{-1}$; $Mo_{K\alpha}$ radiation; $\lambda = 0.71073$ Å; $T = 130(2)$ K; 18137 measured and 4824 independent reflections; $\theta_{max} = 30.50°$; $R_{int} = 0.0301$; $R_1(I>2\sigma(I)) = 0.0314$; wR_2 (all data) $= 0.0624$; 284 parameters; $\Delta\rho_{max/min} = 0.223/-0.172\ e\,Å^{-3}$; structure determination by direct methods (G. M. Sheldrick, SHELXS-97, **1998**) and by least-squares refinement on F^2_o(G. M. Sheldrick, SHELXL-97, **1997**). CCDC-862016 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] For a review, see: X. Liu, L. Lin, X. Feng, *Acc. Chem. Res.* **2011**, *44*, 574–587.

[20] See the Supporting Information for ORTEP picture of (1*R*,3a*R*)-**3k**. Crystal data for (1*R*,3a*R*)-**3k**: $C_{19}H_{18}BrNO_3$; $M_r = 388.25\ g\,mol^{-1}$; crystal size: $0.50\times0.40\times0.20\ mm^3$; monoclinic; space group $P2_1$; $a = 10.7744(9)$, $b = 7.2784(5)$, $c = 11.774(1)$ Å; $\alpha = 90$, $\beta = 108.23(1)$, $\gamma = 90°$; $V = 877.0(1)$ Å^3; $Z = 2$; $\rho_{calcd} = 1.470\ g\,cm^{-3}$; $\mu = 2.360\ mm^{-1}$; $Mo_{K\alpha}$ radiation; $\lambda = 0.71073$ Å; $T = 213(2)$ K, 15257 measured and 4048 independent reflections, $\theta_{max} = 27.96°$; $R_{int} = 0.0747$; $R_1(I>2\sigma(I)) = 0.0265$; wR_2 (all data) $= 0.0491$; 289 parameters; absolute structure parameter $-0.012(6)$; $\Delta\rho_{max/min} = 0.381/-0.351\ e\,Å^{-3}$; structure determination by direct methods (G. M. Sheldrick, SHELXS-97, **1990**) and by least-squares refinement on F^2_o (G. M. Sheldrick, SHELXL-97, **1997**). CCDC-862017 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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