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Ytterbium triflate-catalyzed reactions of imines with a chiral non-racemic silyloxypyrrole

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Abstract

In the presence of a catalytic amount of ytterbium triflate the reactions of various aromatic imines with a chiral non-racemic silyloxypyrrole proceeded smoothly to afford the corresponding aldol-type adducts in good yields and diastereoselectivities.

In the search of new methods of access to variously substituted γ-lactams, we recently reported a simple one-step preparation of the chiral lactam **1**,[1] which was proved to be easily substituted at several positions of the five-membered ring.[1–3] It has been shown that the silyloxypyrrole **2**, easily accessible from **1**, reacted with achiral aldehydes at the C-5 position of the pyrrolidine ring to give **3** in good yield and with high diastereoselectivity.[3]

In this paper, we report the reaction of several imines **4** with silyloxypyrrole **2**. As far as we know, there is no example in the literature of such a reaction. Indeed, the reaction of silyloxyfuran with potential N-acyl iminiums has been extensively reported[4] and some examples exist with imines or imine equivalents.[5] In the silyloxypyrrole series only a few examples of condensation with potential N-acyl-iminium were reported.[6]

Following the report on the silyloxyfuran condensation with imines[5] and our previous work on aldehydes, we first examined the reaction of the chiral non-racemic silyloxypyrrole **2** with imines in the presence of boron trifluoride etherate ($BF_3{\cdot}Et_2O$) in methylene chloride. Unfortunately, under these conditions, no reaction occurred and lactam **1b** was the only product recovered from the reaction mixture for attempts made at different temperatures ranging from –78°C to rt.

We turned to the use of lanthanide triflate reported by Kobayashi et al.[7] as catalyst for the condensation of aldimines with silyl enol ethers, ketene silylacetals, allyltributylstannane. Indeed,

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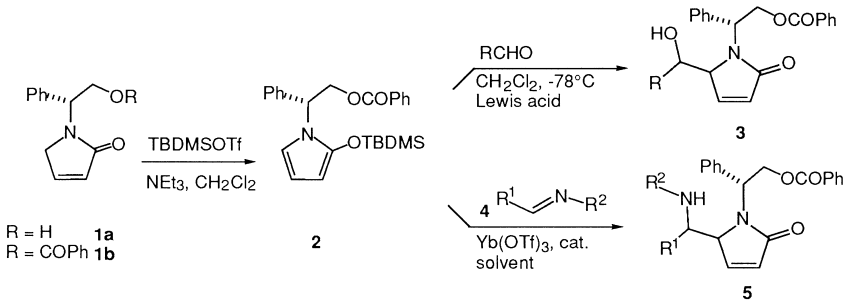
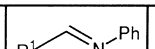
the reaction of silyloxypyrrole **2** with imines, in the presence of a catalytic amount of ytterbium triflate, proceeded smoothly and underwent the formation of adduct **5** (Scheme 1). The reaction was studied with various imines (1 equiv.) using a 10% mol. amount of $Yb(OTf)_3$, in different experimental conditions, and the results are reported in Tables 1 and 2. The imines were prepared by the condensation of amine and aldehyde without solvent.



Scheme 1.

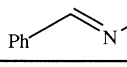
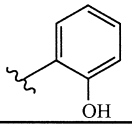
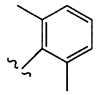
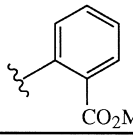
Table 1
$Yb(OTf)_3$-catalyzed condensation of imines derived from aniline with silyloxypyrrole **2**

entry		solvent	Temp (°C)	Yield[(a)] (%)	Diastereomeric ratios [(b)]	Erythro /Threo selectivity
a	Ph	CH_2Cl_2	-70	70 (84)	53 / 23 / 18 / 6	76 / 24
		CH_3CH_2CN	-45	62	49 / 26 / 15 / 9	75 / 25
b		CH_2Cl_2	-70	74 (87)	60 / 14 / 13 / 12	74 / 26
		CH_3CH_2CN	-45	53	32 / 33 / 22 / 13	65 / 35
c		CH_2Cl_2	-70	90	52 / 48	100 / 0
d	Me or Et	CH_2Cl_2 or CH_3CH_2CN	-70 or -45	0	-	-

[(a)] yields indicated in brackets were obtained with 1.5 equiv. of imine. [(b)] Determined by ^{1}H NMR and HPLC.

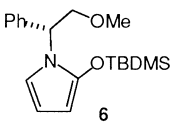
We first examined the reaction of imines derived from aniline and various aldehydes by varying the solvent and the temperature. From Table 1 it can be seen that imines formed from aromatic aldehydes led to the corresponding adduct **5** in high yields irrespective of the solvent. Nevertheless, the reaction was not efficient with aliphatic aldimines, probably due to their high potency to isomerize to enamines. The reaction was fairly diastereoselective, giving rise to mixtures of diastereomers. Nevertheless, in most cases the major isomer was formed in more than 50% yield and could be isolated.[8] Furthermore, the *erythro/threo* selectivity (vide infra for determination of the relative configuration) was good in every case. Experimental conditions induced small variations in the diastereoselectivity, showing better results at –70°C in CH_2Cl_2. All the assays described below were undertaken using these conditions.

Table 2
$Yb(OTf)_3$-catalyzed condensation of imines derived from benzaldehyde with **2** (CH_2Cl_2, –70°C)

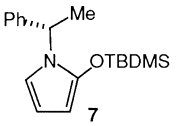
entry		Yield (%)	Diastereomeric ratios [(a)]	Erythro / threo selectivity
a	Ph	70	53 / 23 / 18 / 6	76 / 24
e	CH_2Ph	90	56 / 24 / 15 / 5	80 / 20
f		67	60 / 35 / 5 / –	95 / 5
g		18	64 / 22 / 14 / –	86 / 14
h		80	70 / 15 / 9 / 5	85 / 15

[(a)] Determined by ^1H NMR and HPLC.

Silyloxypyrroles **6**, **7** and **8** were prepared and checked on the reaction with imine **4b** derived from 2-furfural and aniline. Good yields but lower diastereoselectivity ratios were observed (an average ratio of 45:25:25:5 was found in each case), confirming that silyloxypyrrole **2** gave the best results.



6



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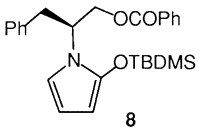

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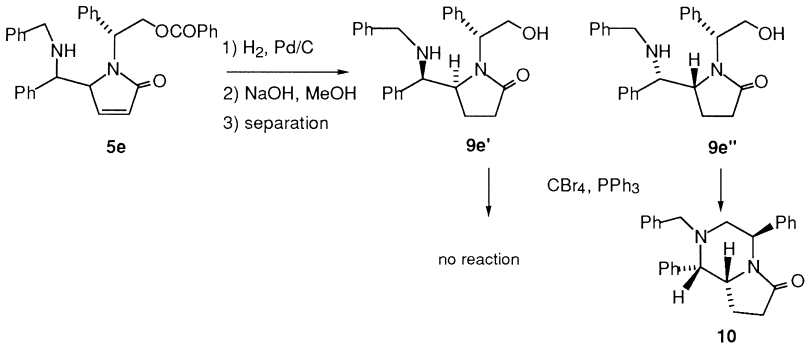
We also examined the influence of the *N*-substituent R^2 of imines **4** derived from benzaldehyde upon the diastereoselectivity. It can be seen from the results reported in Table 2, that *ortho*-substitution on the aromatic ring underwent significative improvement of the diastereoselectivity.

The relative configuration of the different diastereomers was difficult to determine. Careful examination of ^1H NMR data indicated that the two major diastereomers possessed the same relative configuration at the two new created chiral centers: the diagnostic protons exhibited a small coupling constant which was indicative for an *erythro* configuration. This has been proved by chemical transformations of one isomer of **5e** ($R^1 = Ph$, $R^2 = CH_2Ph$) to a bicyclic derivative. The crude reaction mixture of **5e** was submitted to hydrogenation (H_2, Pd/C, MeOH, 80%) and hydrolysis (NaOH, MeOH) to furnish compounds **9e** from which the two major isomers were separated by column chromatography on silica gel giving pure **9e′** (major, 42%) and **9e″** (minor, 18%). These two isomers were separately treated with CBr_4/PPh_3 (THF, Et_3N, rt). Surprisingly, only **9e″** cyclized to compound **10**[9] (52%) (Scheme 2), while the major amino lactam **9e′** was found to be unreactive.

The examination of the ^1H NMR spectrum of **10** clearly established the relative configuration of the chiral centers from which can be deduced the *erythro* configuration of the corresponding



Scheme 2.

compound **5e**. The same *erythro* relative configuration for the major isomer of **5e** could be proposed on the basis of similar ^{1}H NMR behavior. This result is in sharp contrast with the major *threo* configuration found in the aldol reaction of **2** with aldehydes.

In summary, we found that chiral non-racemic silyloxypyrrole **2** can react with non-enolizable aldimines in the presence of a catalytic amount of $Yb(OTf)_3$ supplying a new short stereoselective approach for the preparation of 5-aminomethyl pyrrolidones.

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8. (a) Compound **5c** (major isomer): white amorphous solid; $[\alpha]_D$ –84 ($CHCl_3$, *c* 0.8); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.0 (broad s, 1H), 4.65 (m, 2H), 5.0 (dd, 1H, J = 6.0, 11.2 Hz), 5.35 (d, 1H, J = 3.7 Hz), 5.95 (dd, 1H, J = 6.0, 9.7 Hz), 6.15 (d, 2H, J = 8.1 Hz), 6.35 (dd, 1H, J = 1.7, 6.0 Hz), 6.65 (m, 2H), 6.9 (m, 3H), 7.2 (t, 1H, J = 6.0 Hz), 7.3 (t, 2H, J = 7.7 Hz), 7.6–7.4 (m, 9H), 7.75 (d, 1H, J = 8.1 Hz), 7.85 (d, 1H, J = 7.9 Hz), 8.05 (d, 2H, J = 7.1 Hz); ^{13}C (75.43 MHz, $CDCl_3$) δ (ppm): 53.2, 53.9, 63.8, 64.9, 113.5, 118.5, 121.4, 124.7, 125.6, 125.8, 126.6, 128.1, 128.3, 128.5, 128.7, 129.2, 129.4, 129.5, 129.8, 130.1, 133.1, 134.2, 136.1, 145.1, 145.7, 165.9, 172.4. (b) Compound **5c** (minor isomer): white amorphous solid; $[\alpha]_D$ +91 ($CHCl_3$, *c* 0.2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.8 (broad s, 1H), 4.85 (broad s, 1H), 4.95 (broad s, 1H), 5.15 (dd, 1H, J = 5.6, 11.1 Hz), 5.35 (dd, 1H, J = 9.5, 11.1 Hz), 5.9 (dd, 1H, J = 5.6, 9.3 Hz), 6.1 (d, 2H, J = 7.9 Hz), 6.3 (m, 2H), 6.6 (t, 1H, J = 6.5 Hz), 6.8 (dd, 1H, J = 1.4, 6.0 Hz), 6.9 (t, 2H, J = 8.3 Hz), 8.0–7.0 (m, 16H); ^{13}C (75.43 MHz, $CDCl_3$) δ (ppm): 52.9, 54.3, 63.6, 64.5, 113.8, 118.0, 121.5,124.9, 125.8, 126.7, 127.3, 128.4, 128.7, 128.8, 129.0, 129.7, 130.4, 133.1, 133.6, 134.3, 136.4, 133.1, 146.0, 166.2, 173.3.
9. Compound **10**: white amorphous solid; $[\alpha]_D$ –112 ($CHCl_3$, *c* 0.7); ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 1.45 (m, 1H), 2.0 (m, 2H), 2.35 (m, 1H), 3.05 (dd, 1H, J = 3.4, 12.8 Hz), 3.2 (dd, 1H, J = 5.4, 12.8 Hz), 3.4 (d, 1H, J = 13.6 Hz), 3.5 (d, 1H, J = 13.6 Hz), 3.85 (d, 1H, J = 5.0 Hz,), 4.35 (m, 1H), 5.4 (dd, 1H, J = 3.6, 4.7 Hz), 7.2–7.5 (m, 13H), 7.55 (d, 2H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 75.43 MHz) δ (ppm): 19.7, 30.0, 47.6, 51.7, 55.7, 59.38, 65.6, 127.4, 128.1, 128.5, 129.0, 130.4, 135.8, 138.3, 140.2, 174.5; MS (IC): 383 (MH^+); HRMS calcd. for $C_{26}H_{27}N_2O$: 383.21232; found: 383.21044.