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ENANTIOSELECTIVE MUKAIYAMA-ALDOL AND ALDOL-DIHYDROPYRONE ANNULATION REACTIONS CATALYZED BY A TRYPTOPHAN-DERIVED OXAZABOROLIDINE

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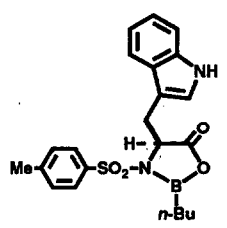
Summary: *The (S)-tryptophan derived catalyst **1**, has been used to effect enantioselective Mukaiyama-aldol and aldol-dihydropyrone annulation reactions of trimethylsilyloxy olefins and dienes.*

Recent research in this group has led to the development of **1** as a catalyst for highly enantioselective Diels-Alder reactions, for example that of cyclopentadiene and 2-bromoacrolein to give the 2*R* adduct **2** with >200 : 1 enantioselectivity.[1] On the basis of this result and subsequent mechanistic studies transition-state assembly **3** has emerged as the most likely representation for these transformations. The three-dimensional arrangement of the catalyst and α,β-enal complex which is depicted in **3** was strongly indicated by low temperature ^{1}H NOESY studies and the bright orange-red color (charge transfer absorption) associated with it.[2] The donor-acceptor interaction between the catalyst and the α,β-enal favors the positioning of the formyl carbon above the indole nitrogen π-cloud with parallel π-stacking and the carbonyl bond lying above the center of the indole 5-membered ring (**4**). Assuming that this mode of binding would be favored generally for aldehydes, it appeared possible that carbonyl addition reactions of aldehydes might be enantioselective for attack at the corresponding (*re*) face of the formyl group as shown in **4**. This further assumes that the free energies of activation for the various competing pathways from complex **4** are nearly the same so that the geometry of the predominating complex will control the absolute stereochemistry of the major product. This paper describes the catalytic enantioselective Mukaiyama-aldol reaction and the catalytic aldol-dihydropyrone annulation reaction between various aldehydes and ketone enol trimethylsilyl ethers using **1** as catalyst. Relevant studies of other catalytic aldol and cycloaddition processes have recently been reported by several research groups.[3,4]



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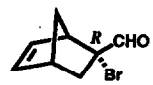

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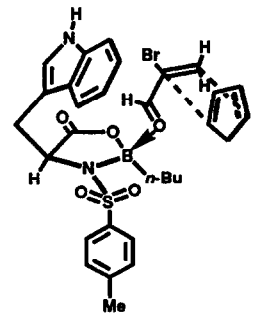

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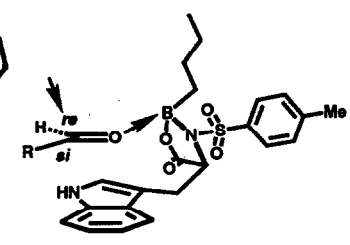

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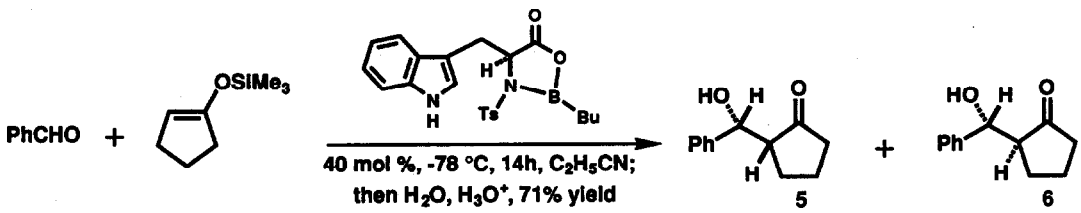
The reaction of several aldehydes with terminal trimethylsilyl enol ethers derived from methyl ketones was conducted at -78 °C in propionitrile as solvent in the presence of 20 mole % of **1** as catalyst. The results of these experiments are summarized in Table I. In general the reactions were clean and only the aldol product and uncoupled aldehyde or methyl ketone were detected after acidic aqueous workup. Enantioselectivities were in the range 96:4 to 93:7 and the major enantiomer in several cases was found to have the expected absolute configuration, as indicated in Table I. Although the absolute configuration of some of the products has not been determined, it seems likely that in view of the uniformly good enantioselectivity the absolute stereochemistry shown in Table I prevails. The level of enantioselectivity of the processes listed in Table I is lower when methylene chloride is used as solvent or when the B-methyl analog of **1** is used as catalyst.

Terminal trimethylsilyloxy (vinylidene) olefins appear to be the most favorable substrates for the enantioselective Mukaiyama aldol coupling as compared to more highly substituted cases of type $RCH{=}C(OSiMe_3)R'$ or $R_2C{=}C(OSiMe_3)R'$. Nonetheless, it is possible to obtain reasonably satisfactory results with members of the trisubstituted class. Thus, the reaction of 1-trimethylsilyloxycyclopentene with benzaldehyde in the presence of 40 mole % of **1** affords **5** ($[\alpha]_D^{23}$ + 199° (c=1.5,$CHCl_3$)) as the principal product (96:4 enantioselectivity, 94:6 diastereoselectivity ratio **5**:**6**).[5] On the other hand, silylketene acetals do not seem to react with high enantioselectivity under the standard conditions noted herein for catalysis by oxazaborolidine **1**, despite excellent reaction rates and yields. This interesting disparity is being investigated further.

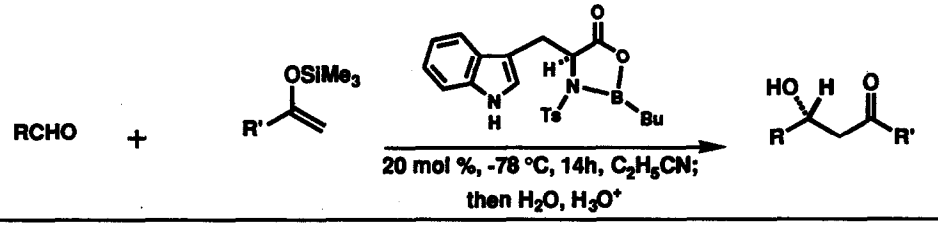


Catalyst **1** (20 mole %) was also applied to the conversion of aldehydes to 2-substituted 2,3-dihydro-4H-pyran-4-ones by reaction with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene in propionitrile at -78 °C for 14 h and subsequent acid treatment as summarized in Table II. The reaction of aldehydes with **7** in the presence of 20 mole % of **1** afforded mainly the Mukaiyama aldol product **8** which was isolated and converted to the dihydro-4H-pyran-4-ones **9** by treatment with trifluoroacetic acid in ether. Little, if any, of **9** was produced in the initial step (by what would correspond to a hetero Diels-Alder process).[6] In general, as indicated in Table II, good yields and moderate enantioselectivities were obtained with the predominating enantiomer being that corresponding to *re* face attack in **4**, as anticipated.

The following procedures are illustrative.

(*R*)-1-Hydroxy-1-phenyl-3-heptanone. To a solution of catalyst **1**[14] (0.056 mmol) in 0.5 ml of propionitrile at -78 °C in a dry 25 ml round-bottom flask was added benzaldehyde (0.028 ml, 0.28 mmol) followed by 2-trimethylsiloxy-1-hexene[15] (0.080 ml, 0.41 mmol). The reaction mixture was stirred for 14 h at -78 °C and then quenched by the addition of 10 ml of sat. aq. $NaHCO_3$. The mixture was extracted with ether (4 x 20 ml) and then the combined organic phases were dried ($MgSO_4$) and evaporated. The residue was dissolved in 4 ml of THF and 2 ml of 1 M HCl (aq), and the resulting solution was allowed to stand for 30 min. Saturated aqueous $NaHCO_3$ (20 ml) was added and the mixture was extracted with ether (4 x 25 ml).[16] The

Table I. Reaction of Trimethylsilyl Enol Ethers with Aldehydes.



R	R'	Yield	ee	$[\alpha]_D^{23}$ [b]
Ph	C_6H_5	82[a]	89	+32.7° (*R*)[7]
c-C_6H_{11}	C_6H_5	67[a]	93	+63.6° (*R*)[c]
n-C_3H_7	C_6H_5	94	89	+65.4° (*S*)[8]
2-furyl	C_6H_5	100	92	+46.0°
Ph	*n*-C_4H_9	100	90	+59.8° (*R*)[9]
c-C_6H_{11}	*n*-C_4H_9	56[a]	86	+36.0° (*R*)[9]

[a] Balance of material is unreacted aldehyde. [b] c ≡ 0.5 ($CHCl_3$). [c] Proved by chemical correlation.

Table II. Reaction of 1-Methoxy-3-trimethylsilyloxy-1,3-butadiene with Aldehydes.

7 8 9

R	Yield of 9	ee	$[\alpha]_D^{23}$ of 9[a]
Ph	100	82[10]	-83°
c-C_3H_7	87	73[11]	-158°
2-furyl	83	67[12]	-255°
c-C_6H_{11}	80	76[13a]	-159°
$PhCH_2CH_2$	57	69[13b]	-69°

[a] c≡0.5 ($CHCl_3$).

combined organic phases were dried ($MgSO_4$) and evaporated to an oily residue. Silica gel chromatography (5-20% ethyl acetate–hexane) afforded 0.058 g (100%) of the known aldol product. HPLC analysis (Daicel AD column with 5% iPrOH–hexane) indicated an enantiomeric excess of 90% (R_t major 11.5 min; minor 13.8 min).

(2*R*)-2,3-Dihydro-2-phenyl-4H-pyran-4-one. To a dry 25 ml round-bottom flask fitted with a septum and stirbar under N_2 was added catalyst **1**[14] (56.0 μmol) in propionitrile (0.5 ml). After cooling to -78 °C freshly distilled benzaldehyde (28 μl, 280 μmol) was added with stirring followed by 1-methoxy-3-trimethylsilyloxybuta-1,3-diene (75 μl, 308 μmol). After 14 h at -78 °C the mixture was quenched by the addition of sat. aq. $NaHCO_3$ (5 ml), warmed to 23 °C and diluted with ether (10 ml). The aqueous phase was separated and extracted with ether (3 x 10 ml). The combined organic extracts were treated with trifluoroacetic acid (1 ml) and stirred for 1 h, and then quenched by the slow addition of sat. aq. $NaHCO_3$ (50 ml). After stirring an additional 30 min the organic phase was separated and washed with sat. aq. $NaHCO_3$ (3 x 15 ml), dried over $MgSO_4$ and concentrated *in vacuo* to yield 49 mg (100%) of (2R)-2, 3-dihydro-2-phenyl-4H-pyran-4-one[10] after chromatography (4 : 1 hexane–ethyl acetate). HPLC analysis revealed the pyrone had an ee of 82% (Daicel chiralcel OD column; 10% *i*-PrOH–hexane, 254 nm UV detector, 13.8 min (*S*) and 16.5 min (*R*)).[17]

References and Notes

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14. **Catalyst 1.** The catalyst was prepared according to the procedure of ref. 1. A dry 25 ml round-bottom flask fitted with a stirbar and a 10 ml pressure-equalized addition funnel (containing a cotton plug, 1.5 cm of sand and 1 cm of CaH_2 and functioning as a Soxhlet extractor) surmounted by a reflux condenser was charged with (*S*)-N-tosyltryptophan (40 mg, 112 μmol), butylboronic acid (14 mg, 137 μmol), THF (3 ml) and toluene (6 ml). A nitrogen atmosphere was secured and the solution was brought to reflux (bath temperature 170 °C). After 6 h the reaction mixture was cooled to room temperature and the addition funnel and condenser were quickly removed and replaced with a septum. The solvent was then removed *in vacuo* to leave a light yellow oil which was dissolved in propionitrile (1 ml).
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16. The N-tosyltryptophan ligand may be recovered from the aqueous phase with 90% efficiency by acidification to pH 1.5 and extraction with ethyl acetate.
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