ELECTROPHILIC α-FORMYLATION OF CARBONYL COMPOUNDS USING NOR-EPHEDRINE-DERIVED 2-METHOXY OXAZOLIDINES. A NOVEL ASYMMETRIC FORMATION OF QUATERNARY STEREOCENTERS

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Abstract. The $BF_3 \cdot Et_2O$ promoted addition of enamines and silylenolethers, to the nor-ephedrine-derived orthoamides 1 or 5 has been studied. A judicious choice of the type of nucleophile and electrophile leads to useful selectivities. When a quaternary α-carbonyl stereocenter is created, the direct removal of the chiral auxiliary is possible and renders the overall process an efficient asymmetric carbonyl α-formylation.

Recently we reported the synthesis and use of orthoamide 1 as a chiral formyl cation equivalent.[1] Addition of silylketeneacetals and silylenolethers to 1 in the presence of a suitable Lewis acid, afforded the corresponding adducts 2 with high and predictable selectivity via the postulated cationic intermediate 3[2] (Scheme I).

Scheme I
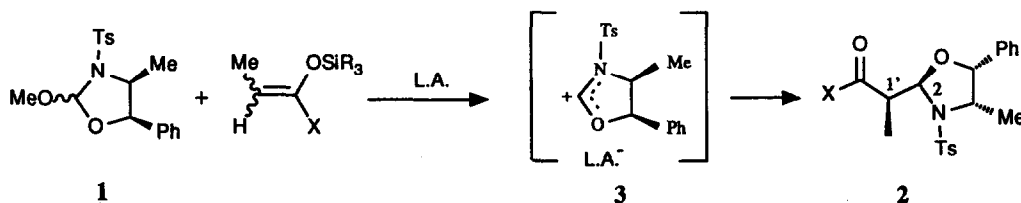
Further studies have now shown that enamines are excellent nucleophilic partners[3] for orthoamide 1 and complement silylenolethers in terms of optimal selectivity for the preparation of highly pure trans substituted 2-(2'-oxo-alkyl)-oxazolidines.

Scheme 2 compares this new method with the silylenolether-based one. Although a direct auxiliary removal at this stage is of no interest owing to the achiral nature of β-ketoaldehydes, the synthesis of these adducts in a stereohomogeneous fashion is desirable in view of the expected stereochemical control of the subsequent carbonyl functionalization[6].

We then decided to apply this method to the asymmetric generation of quaternary stereocenters as it represents a synthetic challenge especially in the field of natural products.[7] Treatment of silylenolether 4[8] with orthoamide 1 in the presence of $BF_3 \cdot Et_2O$, gave adduct 6[9] with a disappointing diastereoisomeric ratio of 63:37 (Scheme III). $NaBH_4$ reduction of 6 followed by $BF_3 \cdot Et_2O$ mediated methanolysis gave the corresponding dimethylacetal with concomitant release of the chiral auxiliary. Subsequent PDC oxidation afforded the β-keto acetal 8 in 25% e.e. as determined by Eu(hfc)$_3$-aided ^{1}H-NMR analysis.

Scheme II : Addition of enamines[4] and silylenolethers [5] to orthoamide 1 in the presence of BF$_3$Et$_2$O
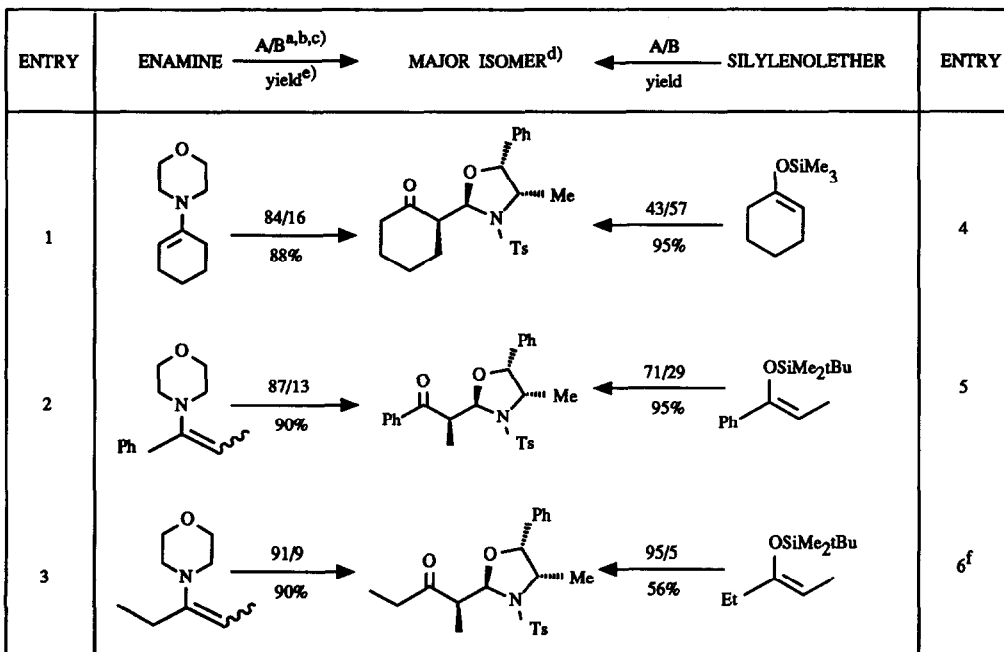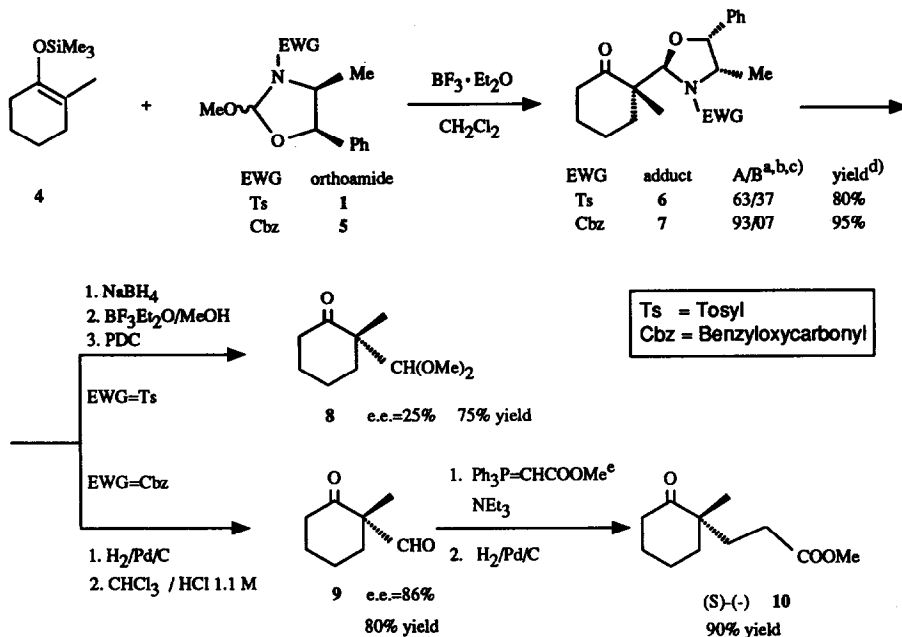

a) A/B represents the major against the minor isomer(s) ratio. b) Diastereoisomeric ratios were determined by ^{1}H-NMR spectroscopy. c) The stereochemistry of the minor isomer was not studied. d) In the case of entries 1 and 4 the absolute configuration has been determined by X-ray analysis. In the other cases the assignment is tentatively based on analogy with the previous cases. e) The yields reported here refer to diastereomeric mixtures isolated after flash chromatography. f) An A/B = 94/6 ratio and a 95% yield was obtained using TiCl$_4$ instead of BF$_3$ Et$_2$O.

This value therefore indicated that a poor enolether face discrimination took place in the condensation.

Interestingly, the addition of silylenolether **4** to the N-Cbz protected orthoamide **5**[10], afforded the corresponding adduct **7**[9] with a much more gratifying ratio of 93:7. Removal of the chiral auxiliary *via* hydrogenolysis followed by acid hydrolysis produced the β-ketoaldehyde **9** in 86% e.e. [Eu(hfc)$_3$; ^{1}H-NMR] and recyclable norephedrine. The (S) configuration of the aldehyde was established by its transformation into the known ester **10**[11] (Scheme III).

This example therefore provides a new entry towards enantiomerically enriched α,α-disubstituted β-ketoaldehydes and underlines the crucial role played by the N-Cbz group in this C-C bond formation.

In line with similar transformations,[12] the condensation under study is believed to proceed through an open staggered transition state that favors an antiperiplanar C=C (nucleophile) / C-O (heterocycle) disposition and places the less demanding substituent of the nucleophile in the inside position (Figure). Such a longitudinal developing of charges is expected to be more pronounced in the N-Cbz than in the N-Ts derivative, owing to the stronger participation (to the charge stabilization) of the oxygen lone pair in the former orthoamide. This argument might therefore well account for the dramatic improvement in the π-face discrimination of enolether **4** on passing from orthoamide **1** to **5**.

Scheme III : asymmetric α-formylation of silylenolether 4

EWG	orthoamide
Ts	1
Cbz	5

4

EWG	adduct	A/B[a,b,c]	yield[d]
Ts	6	63/37	80%
Cbz	7	93/07	95%

1. NaBH₄
2. BF₃Et₂O/MeOH
3. PDC

EWG=Ts

8 e.e.=25%   75% yield

CH(OMe)₂

Ts = Tosyl
Cbz = Benzyloxycarbonyl

EWG=Cbz

1. H₂/Pd/C
2. CHCl₃ / HCl 1.1 M

CHO

1. Ph₃P=CHCOOMe[e]
   NEt₃
2. H₂/Pd/C

COOMe

9 e.e.=86%
80% yield

(S)-(-) **10**
90% yield

a) A/B represents the major isomer against the minor isomer(s) ratio. b) Diastereomeric ratios were determined by ^{1}H-NMR spectroscopy. c) The stereochemistry of the minor isomer was not studied. d) The yields reported here refer to the diastereomeric mixtures isolated after flash chromatography. e) Aldehyde 9, deriving from the acid hydrolysis, was submitted *in situ* to the Wittig olefination.

Although a deeper understanding of the mechanistic details in this transformation must await further studies, it turns out that a very efficient discrimination has to be operative in the transition states even when the nucleophile substituents are of comparable size as in the case of silylenolether 4.[13]

Figure

EWG = Ts , Cbz

X = OSiMe₃ , OSiMe₂tBu , N_O

R₁ = Alkyl ; R₂ = H

R₁ = CH₃ ; R₂ = (CH₂) ring
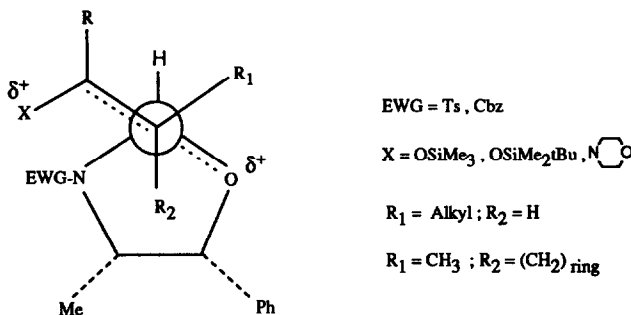
Work is in progress in order to rationalize the role of the N-protecting group and to extend the present method to the preparation of quaternary stereocenters of synthetic interest.

References and notes.

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4) Typical experimental procedure: to a stirred solution of the enamines (0.58 mmoles) and orthoamide **1** (0.29 mmoles) in CH_2Cl_2 (0.25 M) at -78°C was added $BF_3 \cdot Et_2O$ (1.16 mmoles). The reaction mixture was stirred for 4 h at -78°C (-30°C for entry 1), quenched with aqueous HCl in order to hydrolise the intermediate immonium ion and then worked-up as usual.

5) Typical experimental procedure: to a stirred solution of the silylenolethers (0.58 mmoles) and orthoamide **1** (0.29 mmoles) in CH_2Cl_2 (0.25 M) at -78° was added $BF_3 \cdot Et_2O$ (0.58 mmoles). The reaction was stirred for 1h (3 h for entry 6), quenched with phosphate buffer and then worked-up as usual.

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9) The successful reaction between silylenolether **4** and orthoamides **1** or **5** is indicative of the high reactivity of these cationic systems. In fact, whereas the TMSOTf catalysed addition to trimethylorthoformate proceeds uneventfully using cyclohexanone TMSenolether, it fails with the more substituted silylenolether **4** : see ref 12.

10) Orthoamide **5** was synthesized as a 1:1 epimeric mixture at C-2 by condensation between trimetylorthoformate and (1R,2S)-N-Cbz-nor-ephedrine in refluxing benzene and in presence of pyridinium tosylate.

11) Compound (S)-(**10**): $[\alpha]_D$ -30° (c 0.6, EtOH); [lit. $[\alpha]_D$ +33.8° (c 2.95, EtOH) antipode 90% optically pure; ref. 7c].

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13) As suggested by a referee, a differential X/EWG versus R/EWG interaction may in this case dictate the selectivity.