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Enantioselective Nucleophilic Formylation and Cyanation of Conjugated Enones *via* Michael Addition of Formaldehyde SAMP-Hydrazone

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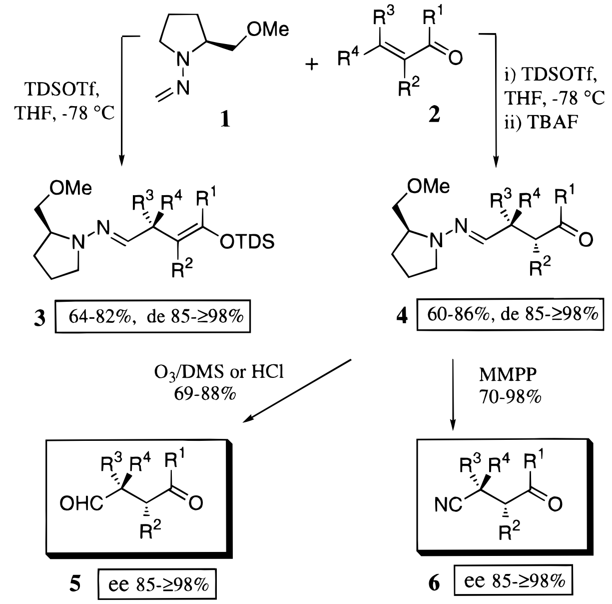
The Michael addition of carbon nucleophiles to conjugated enones is one of the most powerful methods for carbon−carbon bond formation. Due to its relevance in the synthesis of biologically active compounds, much effort has centered on carrying out this reaction in a stereoselective way.[1] The asymmetric introduction of nonfunctionalized fragments has been satisfactorily solved by addition of organometallics.[2] Likewise, chiral 5-oxocarbonyl compounds have been commonly synthesized from enones by asymmetric addition of silyl enol ethers,[3] enamines,[4] imines,[5] malonates,[6] aminocarbene complex anions,[7] and other enolate and aza-enolate equivalents. Many fewer possibilities can be found for asymmetric acylations (→1,4 diketones), a good approach being the addition of metalated aminonitriles.[8] To complete this scenario, a good methodology for the asymmetric addition of a formyl anion equivalent (→4-oxoaldehydes) should be of great interest.[9]

Taking advantage of their aza-enamine character, we have recently reported on the use of formaldehyde dimethyl-[10] and SAMP-hydrazones[11] as *neutral* formyl anion and cyanide equivalents in their Michael additions to conjugated nitroalkenes. We now report the dimethylthexylsilyl (TDS) triflate-promoted[12] regio- and diastereoselective addition of formaldehyde SAMP-hydrazone [(*S*)-**1**] to prochiral cyclic and acyclic conjugated enones (**2a**−**g**) (Scheme 1). The reaction proceeds in few minutes at −78 °C in THF, and both the silyl enol ethers **3**, primary products of the reaction, and the corresponding deprotected ketones **4** can be isolated in good yields and with excellent de's (85−≥98%). The results of these additions are collected in Table 1.

Scheme 1



Emphasis should be given to the fact that *quaternary* stereogenic centers[14] (entries b and e) are easily created with high diasteroselections and with the highest yields within the series. Interestingly, the reaction takes place in the presence of Et$_3$N with similar results.[15] The diastereoselectivities observed, which are highly dependent on temperature, are not much affected when reaction mixtures are allowed to warm up before quenching. Thus, the process is essentially irreversible, and kinetically controlled products are obtained. Experiments changing the order of addition of the reagents demonstrated that hydrazone−TDSOTf complexes are irreversibly formed and that the precomplexed ketone is the reactive species. Racemization-free cleavage of the chiral auxiliary to yield the desired 4-oxoaldehydes **5** has been performed in good yields by either ozonolysis[16] or HCl-mediated hydrolysis. High-yielding oxidative cleavage of adducts **4** to 4-oxonitriles **6** has also been easily achieved by treatment with magnesium monoperoxyphtalate hexahydrate (MMPP·6H$_2$O),[17] giving additional worth to this methodology. The results of the synthesis of compounds **5** and **6** are summarized in Table 2.

The absolute configuration of the adduct (*R*,*S*)-**4f** was determined by X-ray structure analysis,[18] and that corresponding

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[1] Recent reviews: (a) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *20*, 87−170. (b) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *20*, 227−407.

[2] Review: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771−806. Recent examples: Wang. Y.; Gladysz J. A. *J. Org. Chem.* **1995**, *60*, 903−909 and references cited therein.

[3] Lohray, B. B.; Zimbiniski, R. *Tetrahedron Lett.* **1990**, *31*, 7273−7276.

[4] Hickmott, P. W. In *The Chemistry of Enamines*; Patai, S., Rappoport Z., Eds.; John Wiley & Sons: New York, 1994; pp 727-871.

[5] (a) Desmaële, D.; Pain, G.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 863−866. (b) For a recent review, see: d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459−505.

[6] (a) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571−1572. (b) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176−1178. (c) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805−8808.

[7] Anderson, B. A.; Wulff, W. D.; Rahm, A. *J. Am. Chem. Soc.* **1993**, *115*, 4602−4611.

[8] Enders, D.; Kirchhoff, J.; Mannes, D.; Raabe, G. *Synthesis* **1995**, 659−666 and references cited therein.

[9] The only precedent to our knowledge consists of addition of a chiral oxidized dithioacetal derived reagent which, upon a complicated two-step deprotection sequence, gave poor yields and ee's of the desired products: (a) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *Synthesis* **1981**, 74−76. (b) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1284−1286.

[10] Lassaletta, J. M.; Fernández, R. *Tetrahedron Lett.* **1992**, *33*, 3691−3694.

[11] (a) Fernández, F.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Tetrahedron Lett.* **1994**, *35*, 471−472. (b) Enders, D.; Syrig, R.; Raabe, G.; Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Synthesis* **1996**, 48−52.

[12] Attempts to carry out the reaction under the same conditions as for conjugated nitroalkenes (i.e., rt, no catalyst) failed. Other Lewis acids (ZnCl$_2$, TiCl$_4$, etc.) were also unsuccessfully tested. The use of trialkylsilyl triflates as promoters for the addition of soft nucleophiles to enones has recently been reported: Kim, S.; Park, J. H. *Synlett* **1995**, 163−164.

[13] The *cis* stereochemistry was assigned by comparison of the derived nitrile (*R*)-**6c** (vide infra) with the known racemic form: Cocker, W.; Grayson, D. H.; Shannon, P.V. R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1153−1162.

[14] The asymmetric creation of quaternary carbon centers has recently been reviewed: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

[15] This should allow the choice of Lewis acid-sensitive starting materials, although such possibility has not been tested.

[16] After ozonolysis, the chiral auxiliary SAMP can be recycled: Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933−2960.

[17] Fernández, F.; Gasch, C.; Lassaletta, J. M.; Llera, J. M.; Vázquez, J. *Tetrahedron Lett.* **1993**, *34*, 141−144.

[18] Complete crystallographic details for this compound will be published separately: Diánez, M. J.; Estrada, M. D.; López-Castro, A.; Pérez-Garrido, S. Dpto. Física Materia Condensada, Apartado de Correos 1065, E-41080 Seville, Spain.

[19] Jones oxidation of the volatile aldehyde (*R*)-**5a** gave the known (*R*)-3-oxocyclopentanecarboxylic acid [(*R*)-**7**, 84% from (*R*,*S*)-**4a**]. (*R*)-**7** had $[\alpha]^{21}_{D}$ +21.8° (*c* 1.9, CH$_3$OH). The maximum reported value for this compound is $[\alpha]^{21}_{D}$ +22.1° (*c* 1.9, CH$_3$OH): (a) Toki, K. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 333. (b) Sato, Y.; Nishioka, S.; Yonemitsu, O.; Ban, T. *Chem. Pharm. Bull.* **1963**, *11*, 829−834.

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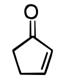
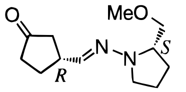
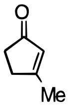
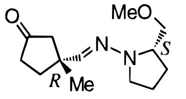
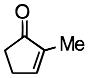
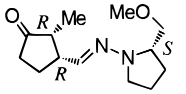
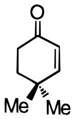
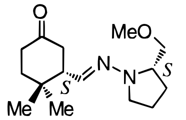
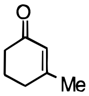
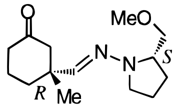
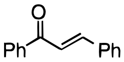
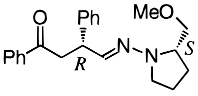
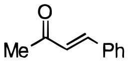
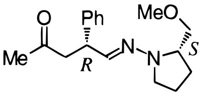
Table 1. Asymmetric Michael Additions of (*S*)-**1** to Enones **2**

entry	enone **2**	product **4**	yield **3** (%)	yield **4** (%)	de[a] (%)
a			64	69	95
b			76	80	≥98
c			77	83[b]	97
d			74	79	94
e			82	86	85
f			75	76	≥98
g			-[c]	60	95

[a] Determined by ^{13}C- and/or ^{1}H-NMR spectroscopy. [b] 95:5 Mixture of *cis* and *trans* isomers.[13] [c] Unstable compound.

Table 2. Synthesis of 4-Oxoaldehydes **5** and 4-Oxonitriles **6**

	product **5** (**7**)			product **6**			
educt	yield (%)	$[\alpha]^{22}_D$	ee	yield (%)	$[\alpha]^{22}_D$	ee	conf
4a	(84)[a]	(−21.8)[a]	(99)[a]	90	+35.3	93[b]	(*R*)
4b	87	−22.0	≥98[c]	98	−54.2	≥98[c]	(*R*)
4c	94	+82.3	97[c]	70[d]	+63.6	97[c]	(*R*,*R*)
4d	78	+34.3	95[e]	83	−11.7	94[b]	(*S*)
4e	69	+5.5	85[c]	87	−24.3	84[b]	(*R*)
4f	79	−55.6[f]	*g*	95	+15.3	>98[h]	(*R*)
4g	88	−39.7[f]	*g*	91	+8.1	96[h]	(*R*)

[a] Characterized as its corresponding acid **7** (see ref 19). [b] Determined as de of its (2*R*,3*R*)-2,3-butanediol derived ketal. [c] Determined as de of compounds **4**. [d] Yield of pure (2*R*,3*R*)-isomer (see ref 13). [e] Determined by shift experiments using (*R*)-1-(9-antryl)-2,2,2-trifluoroethanol as cosolvent. [f] Maximum values measured for freshly obtained products. [g] Racemization occurs during ee determination with Eu(hfc)$_3$. [h] Determined by shift experiments using Eu(hfc)$_3$ in CDCl$_3$.

to **4a** has been assigned (*R*,*S*) by comparison of the optical rotation of the derived (+)-(*R*)-3-oxocyclopentanecarboxylic acid [(*R*)-**7**] with literature data.[19] Additionally, the empirical rule developed by Lemière *et al.*[20] was used to assign the 3*S* and 3*R* configuration to the (2*R*,3*R*)-2,3-butanediol-derived ketals of compounds **6d** and **6e**, respectively. Assuming uniform reaction pathways, the stereochemistry of b, c, and g series compounds has been assigned by analogy. Summarizing, the nucleophilic attack always occurs to the same face of the enone, irrespective of its stereochemistry.[21]

In conclusion, this paper describes a new simple and efficient methodology for the highly diastereoselective asymmetric Michael addition of a neutral masked formyl anion and cyanide equivalent to prochiral conjugated enones. The chiral formaldehyde SAMP-hydrazone and its enantiomeric RAMP-hydrazone[11b,22] can be used for the enantioselective synthesis of important chiral building blocks, some of them bearing quaternary stereogenic centers. In our opinion, the excellent enantioselectivity and predictable absolute configuration will prove to have many applications in the field of natural product synthesis.

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Supporting Information Available: Full experimental details, spectral and analytical data for compounds **3a**−**f**, **4a**−**g**, **5b**−**g**, **6a**−**g**, and **7**, ORTEP figure and tables containing bond lengths and angles for compound **4f**, detailed experiments for the determination of the absolute configuration of compounds **6d** and **6e** (11 pages). See any current masthead page for ordering and Internet access instructions.

JA9610500

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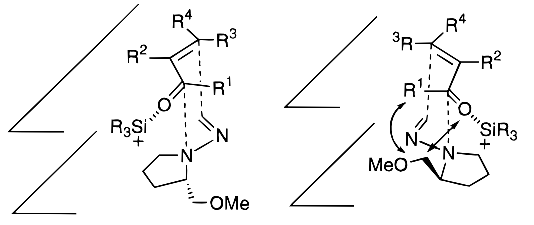
(20) Lemière, G. L.; Dommisse, R. A.; Lepoivre, F. C.; Alderweireldt, F. C.; Hiemstra, H.; Wynberg, H.; Jones, J. B.; Toone, E. J. *J. Am. Chem. Soc.* **1987**, *107*, 1363−1370. See supporting information for details.

(21) A chairlike geometry for the approach of the reactants is proposed. Thus, the steric repulsion between the CH$_2$OMe group and both the bulky TDS$^+$-chelated oxygen atom and the substituent R^1 should result in a much higher energy for **B** than for **A**, according to the absolute configuration and the high induction observed. Such geometries, stabilized by secondary orbital interactions, have been demonstrated to be operative for closely related systems: Pfau, M.; Tomas, A.; Lim, S.; Revial, G. *J. Org. Chem.* **1995**, *60*, 1143−1147.



A **B**

(22) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173−182.