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Trans-2- Arylcyclohexanols : Use as Auxiliaries in the Mukaiyama Aldol-Type Condensation between Silyl Enol Esters and Aldehydes

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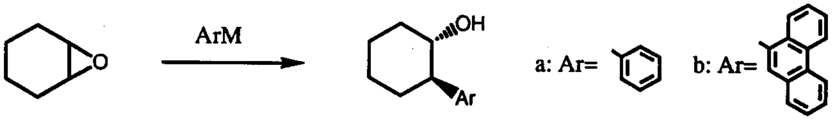
Abstract: *trans-2-Aryclohexanols 2a, 2b proved to be efficient auxiliaries in the Mukaiyama aldol-type condensation of silyl enol esters 4 with aldehydes.*

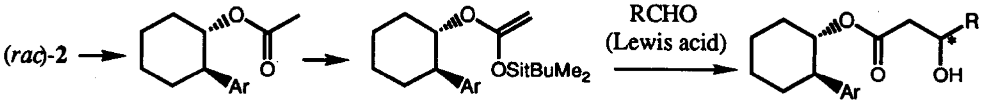
The purpose of the present paper is to test (*trans*)-2-phenylcyclohexanol (**2a**), an easily accessible inducer[1], in the stereoselective Mukaiyama aldol type condensation between silyl enol esters and aldehydes. In order to enhance the stereoselectivity we have also modified this auxiliary, by increasing the size of the aromatic part (**2b**), a principle in the design of chiral auxiliaries which we have applied with success in the asymmetric reduction of β-ketoesters[2] as well as in the asymmetric Michael addition of primary amines to chiral crotonates[3] and in the asymmetric catalytical hydrogenation of chiral enaminoesters[4]. We show that good to excellent selectivities are obtained with these chiral inducers, in aldol condensation [**4**→**5**].

Although *racemic* (*trans*)-2-phenylcyclohexanol **2a** was easily prepared by addition of phenylmagnesium bromide to cyclohexene epoxide **1**[1], this method proved to be relatively inefficient to prepare the new bulkier analog **2b**. The latter auxiliary was in fact obtained with an excellent yield (95 %) by adding the corresponding lithio derivative (generated from the bromide : *n*-BuLi, 10 min at -78°C in Et_2O) to epoxide **1** in the presence of BF_3-Et_2O complex[5].



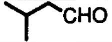
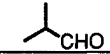
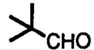
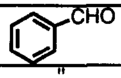
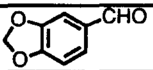
1 (*rac*)-**2**

The aldol condensation reaction between acetates **3**, derived from alcohols **2** and aldehydes was next examined. Preliminary experiments having established that the lithium enolates of acetates **3** furnish only a poor diastereoselectivity, we decided to condense the corresponding silyl enol esters **4** with various aldehydes, in the presence of a Lewis acid[7,8] [**4**→**5**].



3 **4** **5**

Table 1 gathers the results obtained in the conversion [**4**→**5**]. The diastereomeric ratios found in the resulting β-hydroxyesters **5** deserve the following comments[9]. As generally observed in such aldol condensations, the bulkier the aldehyde, the higher the selectivity (compare for example, entries 1 and 3 and 3 and 5) A significant increase in the selectivity was also obtained, at least with aliphatic aldehydes, by replacing the phenyl ring of the auxiliary by the phenanthryl nucleus (compare entries 1 and 2, 3 and 4, 5 and 6). *Very interestingly, (iPrO)$_3$ TiCl proved to be notably more effective than TiCl$_4$ in these Lewis acid-promoted condensations* (compare entries 6 and 7). Further work in order to generalize this methodology is in progress; in this respect the determination of the absolute configuration at the newly created stereogenic center in products **5**, by working in an optically active series, would give essential data to elaborate a model of asymmetric induction.

Entry	**3**	RCHO	Lewis acid	**5** Yields (from **3**)	**5** Diast. ratio
1	**3a**		TiCl$_4$	72^a (95)^b	59/41
2	**3b**	"	TiCl$_4$	55 (95)	64/36
3	**3a**		TiCl$_4$	70 (90)	77/23
4	**3b**	"	TiCl$_4$	40 (90)	84/16
5	**3a**		TiCl$_4$	65 (95)	82/18
6	**3b**	"	TiCl$_4$	40 (90)	88/12
7	**3b**	"	(iPrO)$_3$TiCl	40 (90)	96/4
8	**3a**		TiCl$_4$	50 (90)	72/28
9	**3b**	"	TiCl$_4$	50 (80)	73/27
10	**3a**		TiCl$_4$	40 (95)	80/20
11	**3b**	"	TiCl$_4$	45 (90)	80/20

a: Isolated yields b: Yields taking into account recovered acetates **3**

References and Notes

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5 Eis, M.J.; Wrobel, J.E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.

6 **2b** : mp 100-102°C; IR (KBr): 3400 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$): δ 1.2-2.4 (m, 9H) 3.2 (m, 1H) 3.9 (m, 1H) 7.6 (m, 6H) 8.3 (m, 1H) 8.6 (m, 2H).

7 For recent examples of stereoselective aldol reactions between chiral ester titanium enolates and aldehydes, see : Yi Bin Xiang; Olivier, E.; Ouimet, N. *Tetrahedron Lett.*, **1992**, *33*, 457.

8 [**3** $\rightarrow$ **4**] : LDA (1.5 eq, THF; -78°C, 40 min) then TBDMSCl, (2 eq), HMPA (2 eq), -78°C $\rightarrow$ 20°C, 2hours. [**4** $\rightarrow$ **5**]: Lewis acid, RCHO, CH$_2$Cl$_2$, -78°C, 2hours.

9 Diastereomeric ratios in hydroxy esters **5** were determined by ^{1}H NMR (if necessary, after adding EuFOD) and ^{13}C NMR spectroscopy. In the following NMR data, only the major diastereomer is described. **5** (Ar = 9-phenanthryl, R = *t*-Bu): oil; IR (neat) 3520, 1725 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.43 (s, 9H) 1.48-2.23 (m, 11 H) 2.79 (dd, J = 5.4 Hz, J = 7.5 Hz, 1H) 3.54 (m, 1H) 5.25 (m, 1H) 7.5-7.6 (m, 5H) 7.75 (m, 1H) 8.17 (m, 1H) 8.55 (m, 1H) 8.65 (m, 1H); ^{13}C NMR (50 MHz, CDCl$_3$) δ 24.9 25.2 26.1 32.7 33.7 36.7 43.3 5.2 76.6 122.3 123.3 123.7 126.1 126.4 126.7 128.4 129.8 130.3 131.2 131.6 137.3 173.0.

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