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Highly Stereoselective $TiCl_4$-Mediated Aldol Reactions from (*S*)-2-Benzyloxy-3-pentanone

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Stereoselectivity of $TiCl_4$-mediated aldol reactions from (*S*)-2-benzyloxy-3-pentanone is dramatically improved when the reaction is carried out in the presence of 1.1 equiv of tetrahydrofuran (THF) or 1,2-dimethoxyethane (DME). The resultant 2,4-*syn*-4,5-*syn* adducts are then obtained in diastereomeric ratios up to 97:3, which proves that the appropriate choice of the Lewis acid ($TiCl_4$−THF or DME vs Ti(*i*-PrO)Cl_3) engaged in the process permits access to both *syn*-aldol adducts.

Titanium(IV) enolates have been increasingly employed in C−C bond-forming processes since Evans reported that they can be directly prepared from the corresponding carbonyl precursors with a titanium(IV) Lewis acid and a tertiary amine.[1] Particularly important in the aldol arena, titanium enolates participate in such a wide scope of highly stereoselective reactions that they constitute nowadays an appealing alternative to the more classic boron and lithium counterparts.[2] Unfortunately, there is a lack of information concerning the aggregation state and the distribution of ligands around the metal, which hampers the development of new methodologies.

Regarding these elusive issues, Evans speculated that the titanium enolates from chiral *N*-propanoyl-1,3-oxazolidin-2-ones might be considered as six coordinated *Z*-chelated ate complexes.[1a] Crimmins took advantage of this model and established that the stereochemical outcome of the titanium-mediated aldol reactions from related 1,3-oxazolidine-2-thione auxiliaries depends on the base and the equivalents of $TiCl_4$ involved: Evans *syn*-aldol adducts are obtained with an excellent diastereoselectivity (dr >97:3) when 2.5 equiv of sparteine are used through a putative nonchelated transition state, while reactions with 2 equiv of $TiCl_4$ give non-Evans *syn*-aldol diastereomers (dr >95:5), presumably due to a chelated transition state resulting from the abstraction of a chloride ion by the second equivalent of Lewis acid.[3] In the first case, sparteine can be replaced by a combination of 1.1 equiv of *i*-Pr_2NEt and 1.0 equiv of an achiral additive as *N*-methyl-2-pyrrolidinone (NMP), which suggests that the second equivalent of that base simply operates as a ligand for titanium.[4,5] Furthermore, Ghosh reported the dramatic enhancement on the stereoselectivity of the titanium-mediated chloroacetate aldol reactions from indan-derived chiral auxiliaries produced by additives as acetonitrile, NMP, or triphenylphosphine.[6] Irrespective of the improvement on the stereoselectivity observed for these processes, the manner in which such additives interact with the titanium center is still unclear and, as a consequence, the intermediates or the transition states affecting titanium enolates are mainly proposed to account for the experimental results.

In this context, we have observed that the stereochemical outcome of the titanium-mediated aldol reaction of chiral α-benzyloxy ethyl ketone **1** (Scheme 1) relies on the Lewis acid engaged on the process.[7,8] Indeed, the same experimental procedure using $TiCl_4$ or Ti(*i*-PrO)Cl_3 leads to different *syn*-aldol adducts, so that the substitution of a chloride by an isopropoxide ligand on the Lewis acid determines the configuration of the resulting aldol. Unfortunately, the diastereoselectivity of both processes is rather different. The aldol reaction based on Ti(*i*-PrO)Cl_3 affords 2,4-*anti*-4,5-*syn*-aldols in high diastereomeric ratios, but the $TiCl_4$-mediated counterpart furnishes 2,4-*syn*-4,5-*syn*-aldol adducts in an impractical manner (Scheme 1).[7a,9] Thus, considering that it would be highly advantageous to get a better stereocontrol on the latter reaction, we envisaged that the presence in the reaction mixture of additives able to act as Lewis bases and bind to metal center might have an influence on the diastereoselectivity of the process. Herein, we disclose our studies on the impact of achiral nonionic additives on the $TiCl_4$-mediated aldol reactions from ketone **1**[10] that eventually permits direct access to aldol adducts **2** and **3** in a highly stereocontrolled manner.

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[1] (a) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049.

[2] (a) Ghosh, A. K.; Shevlin, M. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 63−125. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506−7525.

[3] (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883−7884. (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902.

[4] Crimmins, M. T.; She, J. *Synlett* **2004**, 1371−1374.

[5] Toru has also reported the effect of bases and phosphorous additives on the titanium mediated aldol reactions of α-seleno ketones and esters: Nakamura, S.; Hayakawa, T.; Nishi, T.; Watanabe, Y.; Toru, T. *Tetrahedron* **2001**, *57*, 6703−6711.

[6] (a) Ghosh, A. K.; Kim, J.-H. *Org. Lett.* **2004**, *6*, 2725−2728 and references therein. (b) For the influence of triphenylphosphine on titanium-mediated Mukaiyama-like aldol reactions, see: Palazzi, C.; Colombo, L.; Gennari, C. *Tetrahedron Lett.* **1986**, *27*, 1735−1738.

[7] (a) Solsona, J. G.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519−522. (b) Solsona, J. G.; Romea, P.; Urpí, F. *Tetrahedron Lett.* **2004**, *45*, 5379−5382. (c) Solsona, J. G.; Nebot, J.; Romea, P.; Urpí, F. *Synlett* **2004**, 2127−2130.

[8] For parallel studies on β-hydroxy ketones, see: (a) Solsona, J. G.; Nebot, J.; Romea, P.; Urpí, F. *J. Org. Chem.* **2005**, *70*, 6533−6536. (b) Ward, D. E.; Beye, G. E.; Sales, M.; Alarcon, I. Q.; Gillis, H. M.; Jheengut, V. *J. Org. Chem.* **2007**, *72*, 1667−1674.

[9] Moreover, the experimental procedure must be followed very carefully because small changes in the amounts of the reagents can modify the diastereoselectivity of the process.

[10] (a) Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414−1416. (b) Ferreró, M.; Galobardes, M.; Martín, R.; Montes, T.; Romea, P.; Rovira, R.; Urpí, F.; Vilarrasa, J. *Synthesis* **2000**, 1608−1614.

10.1021/jo071048z CCC: \$37.00

SCHEME 1. Stereoselective Titanium-Mediated Aldol Reactions from Ketone 1

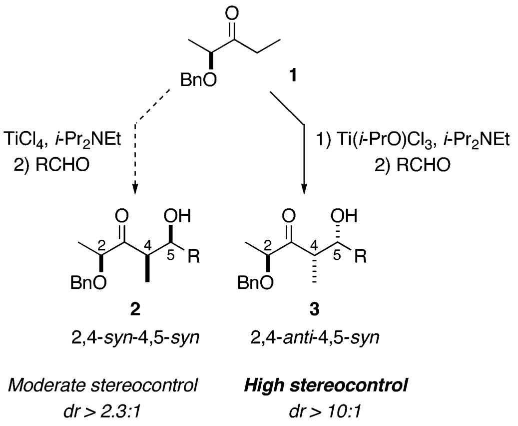
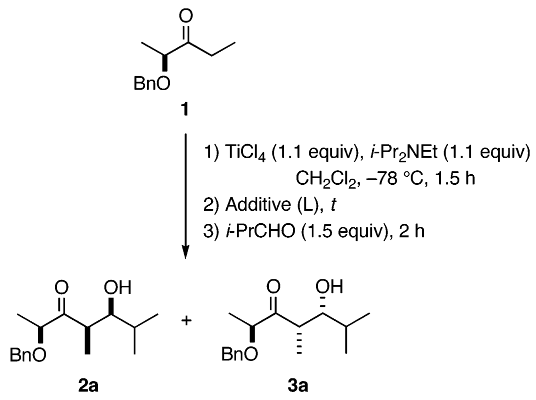


TABLE 1. Preliminary Studies on the TiCl$_4$-Mediated Aldol Reaction of 1 and Isobutyraldehyde



entry	additive, L	equiv	*t* (min)	dr[a] **2a**/**3a**	yield[b] (%)
1[c]				83:17	74
2	Ph$_3$P	1.1	10	91:9	55
3	Ph$_3$P	1.1	60	82:18	60
4	THF	1.1	10	93:7	70
5	THF	1.1	60	92:8	70
6	Ph$_3$P	2	10	75:25	60
7	THF	2	10	84:16	75

[a] Determined by HPLC. [b] Overall isolated yield. [c] See ref 7a.

TABLE 2. Influence of Additives (1.1 equiv) on the TiCl$_4$-Mediated Aldol Reaction of 1 and Isobutyraldehyde

entry	additive, L	dr[a] **2a**/**3a**	yield[b] (%)
1[c]		83:17	74
2	TMEDA	81:19	25
3	CH$_3$CN	84:16	89
4	NMP	90:10	67
5	Ph$_3$P=O	92:8	42
6	Ph$_3$P	91:9	55
7	Et$_2$O	81:19	72
8	THF	93:7	70
9	DME	94:6	60
10	1,4-dioxane	81:19	72

[a] Determined by HPLC. [b] Overall isolated yield. [c] See ref 7a.

Since TiCl$_4$-mediated aldol reactions based on ketone **1** provided particularly low stereocontrol in the case of aliphatic aldehydes,[7a] we chose isobutyraldehyde to test the influence of additives on such processes. Then, we focused our attention on the changes that two Lewis bases as triphenylphosphine (Ph$_3$P) and tetrahydrofuran (THF) produced on the TiCl$_4$-mediated aldol reaction of **1** and isobutyraldehyde. Keeping in mind that our main concern dealt with stereoselectivity, we decided to apply the previously optimized experimental procedure with deliberately extended reaction times. Importantly, enolization was carried out in the absence of those additives to avoid potentially undesired interactions with TiCl$_4$. The results are summarized in Table 1.[11]

As expected, diastereoselectivity was affected by the presence in the reaction mixture of either of the two Lewis bases. Moreover, diastereomeric ratios were dependent on the time elapsed between the addition of the Lewis base and the aldehyde to the enolate (compare entries 2 and 3 in Table 1) and, more importantly, on the amounts of Ph$_3$P or THF used (compare respectively entries 2 and 6, and 4 and 7 in Table 1). This behavior suggests that both additives might act as ligands that affect to the aggregation state of the enolate and the coordination sphere around the metal.

Having established the key issues of the modified experimental procedure, we next surveyed the influence of 1.1 equiv of other common Lewis bases that could potentially bind to the titanium. The results gathered in Table 2 reveal that they have a variable influence on the diastereoselectivity. The rationale for these results is at present elusive. Surprisingly, TMEDA afforded the worst diastereomeric ratio and yield (see entry 2 in Table 2),[12] whereas acetonitrile had apparently no influence on the process (see entry 3 in Table 2).[13] Otherwise, most of the additives improved the stereoselectivity, with ethers as THF or 1,2-dimethoxyethane (DME) the most suitable among them (see entries 8 and 9 in Table 2).[14]

Hence, our interest was centered on both additives and experimental conditions were evaluated in depth. After a considerable experimental optimization, it was established that enolization should be carried out for 30 min, followed by dropwise addition of a solution containing 1.1 equiv of additive (see the General Procedure in the Experimental Section). After 10 min, 1.5 equiv of freshly distilled aldehyde was added, and the resultant reaction mixture was stirred at −78 °C for 1.5 h. Unfortunately, the addition of DME slows down the aldol reaction and unreacted starting ketone **1** is usually observed in the crude reaction mixtures. Longer reaction times do not substantially improve the yields, and higher temperatures have a deleterious effect on the diastereoselectivity. Once optimized, the experimental procedure was next applied to a representative set of aliphatic, aromatic, and α,β-unsaturated aldehydes. Results are summarized in Table 3.

Analysis of the diastereomeric ratios obtained for such aldehydes indicates that both additives have a dramatic influence on the stereochemical outcome of the process. Indeed, addition

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[11] Configurations of the resulting aldol diastereomers have been previously established. See ref 7a.

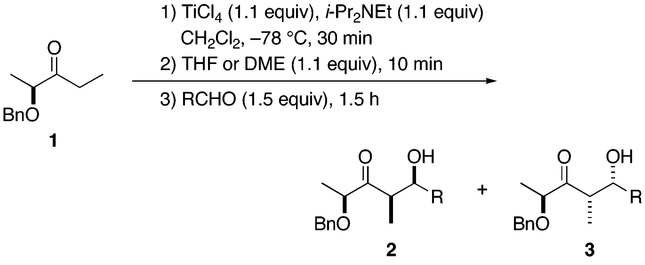
[12] TMEDA was successfully used by Crimmins on aldol reactions based on *N*-acyl oxazolidinethiones and thiazolidinethiones. See refs 3 and 4.

[13] Ghosh reported that acetonitrile produces a dramatic enhancement of diastereoselectivity on titanium-mediated chloroacetate aldol reactions. See ref 6a.

[14] In striking contrast, diethyl ether and 1,4-dioxane afford low diastereomeric ratios. In regard of the influence of ethers, it is worth recalling the large solvent effects (THF, Et$_2$O, *i*-Pr$_2$O) observed in aldol reactions based on *N*-acyl-1,3-oxazolidinones involving titanium enolates prepared from their lithium counterparts; see: Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489−2498.

of 1.1 equiv of DME produces a remarkable improvement on the diastereoselectivity for all the aldehydes, to the point that most of them afford 2,4-*syn*-4,5-*syn*-aldols **2** in dr (**2**/**3**) higher than 94:6 (compare entries 1, 4, 7, 10, 13, and 16 to 3, 6, 9, 12, 15, and 18, respectively). Similarly, THF improves the results previously obtained and also provides highly stereoselective aldol reactions (compare entries 1, 4, 7, 10, 13, and 16 to 2, 5, 8, 11, 14, and 17, respectively). Although the diastereoselectivity of these reactions is slightly poorer than that achieved with DME, the yields are consistently higher, which confer to THF a particular interest for aromatic and α,*β*-unstaurated aldehydes (see entries 11, 14, and 17).

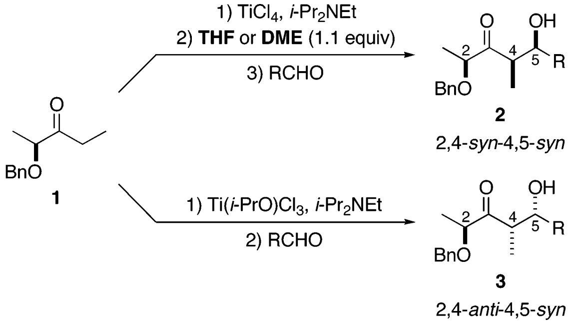
TABLE 3. Influence of THF and DME (1.1 equiv) on the $TiCl_4$-Mediated Aldol Reaction of 1



entry	additive, L	aldehyde	R	dr[a] **2/3**	yield[b] (%)
1[c]		**a**	$CH(CH_3)_2$	83:17	74
2	THF	**a**	$CH(CH_3)_2$	93:7	79
3	DME	**a**	$CH(CH_3)_2$	97:3	64
4[c]		**b**	$CH_2CH(CH_3)_2$	82:18	95
5	THF	**b**	$CH_2CH(CH_3)_2$	88:12	85
6	DME	**b**	$CH_2CH(CH_3)_2$	90:10	57
7[c]		**c**	CH_2CH_3	69:31	92
8	THF	**c**	CH_2CH_3	88:12	84
9	DME	**c**	CH_2CH_3	94:6	45
10[c]		**d**	Ph	93:7	91
11	THF	**d**	Ph	95:5	92
12	DME	**d**	Ph	97:3	56
13[c]		**e**	4-ClPh	91:9	96
14	THF	**e**	4-ClPh	94:6	91
15	DME	**e**	4-ClPh	94:6	64
16		**f**	$C(CH_3){=}CH_2$	92:8	83
17	THF	**f**	$C(CH_3){=}CH_2$	94:6	82
18	DME	**f**	$C(CH_3){=}CH_2$	96:4	41

[a] Determined by HPLC. [b] Overall isolated yield. [c] See ref 7a.

SCHEME 2. Divergent Stereochemical Pathways of the Titanium-Mediated Aldol Reaction of 1



In summary, we have documented the influence of neutral Lewis bases on the $TiCl_4$-mediated aldol reactions based on chiral ketone **1**, with tetrahydrofuran and 1,2-dimethoxyethane the most suitable additives to achieve high diastereomeric ratios. Hence, it is possible to gain access to both 2,4-*syn*-4,5-*syn* (**2**) and 2,4-*anti*-4,5-*syn* (**3**) adducts through the appropriate choice of the Lewis acid used ($TiCl_4$−THF or DME vs Ti(i-PrO)Cl_3 respectively) (Scheme 2).

Although the mechanistic details of the reaction have been not disclosed, the aforementioned results lend support to the idea that the coordination sphere of the metal plays a crucial role on the stereochemical outcome of the process. Eventually, comparison of these results with previously reported studies on the effect of additives on the stereoselectivity of titanium-mediated aldol reactions suggests that the influence of ligands bound to the metal closely relies on the structure of the enolate, and in consequence, the space around the titanium must be carefully crafted to achieve highly stereoselective processes.

Experimental Section

General Procedure. Neat $TiCl_4$ (0.12 mL, 1.1 mmol) was added slowly to a solution of **1** (196 mg, 1 mmol) in CH_2Cl_2 (3 mL) at −78 °C under N_2. The resulting yellow mixture was stirred for 3 min, and i-Pr_2NEt (0.19 mL, 1.1 mmol) was added dropwise. The resulting dark red solution was stirred for 30 min at −78 °C, and a 0.55 M solution of THF or DME in CH_2Cl_2 (2 mL, 1.1 mmol) was slowly added. The mixture was stirred for 10 min at −78 °C, and freshly distilled aldehyde was added (1.5 mmol). The reaction was quenched after 1.5 h by the addition of satd NH_4Cl (5 mL). The mixture was diluted with Et_2O and washed with H_2O, satd $NaHCO_3$ and brine. The aqueous layers were extracted with Et_2O, and the combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oil was analyzed by ^1H NMR and HPLC and purified by flash chromatography.

(2*S*,4*R*,5*S*)-2-Benzyloxy-5-hydroxy-4,6-dimethyl-3-heptanone (2a): colorless oil. R_f (hexanes/EtOAc 90:10) = 0.10. HPLC (hexanes/i-PrOH 99:1) t_R = 10.3 min. $[\alpha]_D$= −19.7 (c = 1.0, $CHCl_3$). IR (film): ν 3510 (br), 2962, 2873, 1713, 1455, 1118 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40−7.30 (5H, m), 4.57 (1H, AB system, J = 11.7), 4.52 (1H, AB system, J = 11.7), 4.06 (1H, q, J = 6.8), 3.46 (1H, dd, J = 8.5, J = 2.6), 3.18 (1H, qd, J = 7.2, J = 2.6), 1.72−1.62 (1H, m), 1.39 (3H, d, J = 6.8), 1.11 (3H, d, J = 7.2), 1.00 (3H, d, J = 6.5), 0.83 (3H, d, J = 6.7). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 217.4, 137.5, 128.5, 128.0, 127.8, 79.4, 76.2, 71.8, 42.4, 30.6, 19.1, 18.9, 17.3. 9.5. HRMS (+ESI): m/z calcd for $C_{16}H_{24}O_3Na$ $[M + Na]^+$ 287.1618, found 287.1614.

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Supporting Information Available: Spectroscopic data and copies of ^1H and ^{13}C NMR spectra of aldols **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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