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New Approach to the Stereoselective Synthesis of Tertiary Methyl Ethers

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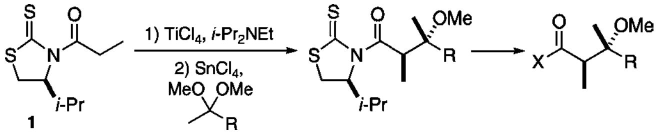
ABSTRACT



The Lewis acid-mediated addition of titanium enolates from 1 to dimethyl ketals of aliphatic methyl ketones followed by removal of the chiral auxiliary furnishes enantiomerically pure derivatives containing a tertiary methyl ether and a contiguous stereocenter in a straightforward manner.

Despite the tremendous advances recently disclosed in the asymmetric synthesis of biologically active natural products, the stereoselective construction of quaternary chiral centers still represents a foremost challenge.[1] In this context, only a scarce number of methodologies enable the simultaneous installation of two contiguous stereocenters, one of them being a tertiary alcohol or ether as represented in Figure 1.

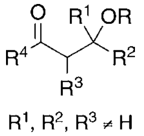


Figure 1. Aldol-like motif containing a quaternary stereocenter.

At first glance, such structures should be available through stereoselective aldol-like additions to ketones, but their attenuated reactivity and the difficult differentiation of the enantiotopic faces of their C═O bond make these reactions more elusive than the related additions to aldehydes.[2−4] Thus, considering that the higher reactivity of oxonium cations could overcome these limitations and taking advantage of our experience on the Lewis acid-mediated addition of chiral titanium enolates to dimethyl and dibenzyl acetals,[5] we envisioned that the addition of these enolates to ketals might

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(1) For reviews on the construction of quaternary chiral centers, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (d) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (f) García, C.; Martín, V. S. *Curr. Org. Chem.* **2006**, *10*, 1849. (g) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (h) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853.

(2) For chiral auxiliary based approaches, see: (a) Bartrolí, J.; Turmo, E.; Belloc, J.; Forn, J. *J. Org. Chem.* **1995**, *60*, 3000. (b) Jacobson, I. C.; Reddy, G. P. *Tetrahedron Lett.* **1996**, *37*, 8263. (c) García Ruano, J. L.; Barros, D.; Maestro, M. C.; Slawin, A. M. Z.; Page, P. C. B. *J. Org. Chem.* **2000**, *65*, 6027. (d) Dixon, D. J.; Guarna, A.; Ley, S. V.; Polara, A.; Rodríguez, F. *Synthesis* **2002**, 1973.

(3) For catalytic based approaches, see: (a) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. (c) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164.

(4) For reductive aldol approaches, see: (a) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292. (b) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440.

(5) (a) Cosp, A.; Romea, P.; Talavera, P.; Urpí, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2001**, *3*, 615. (b) Cosp, A.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **2001**, *42*, 4629. (c) Cosp, A.; Larrosa, I.; Vilasís, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Synlett* **2003**, 1109. (d) Cosp, A.; Llàcer, E.; Romea, P.; Urpí, F. *Tetrahedron Lett.* **2006**, *47*, 5819. (e) Gálvez, E.; Parelló, R.; Romea, P.; Urpí, F. *Synlett* **2008**, 2951. (f) Gálvez, E.; Romea, P.; Urpí, F. *Org. Synth.* **2009**, *86*, 81.

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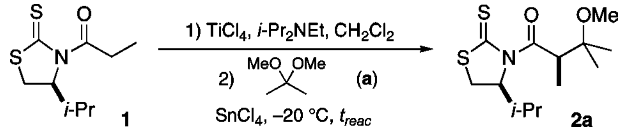
afford the corresponding tertiary methyl ethers in a straightforward and stereoselective manner.[6,7] Herein, we describe a new entry to *β*-methoxy-α,*β*-dimethyl carboxylic (R, R^1, R^3 = Me in Figure 1) adducts through the Lewis acid-mediated addition of titanium enolates from (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**1**)[8] to dimethyl ketals and their conversion into a broad array of enantiopure derivatives.[9]

Table 1. Lewis Acid-Mediated Addition of Titanium Enolates from **1** to 2,2-Dimethoxypropane (**a**)



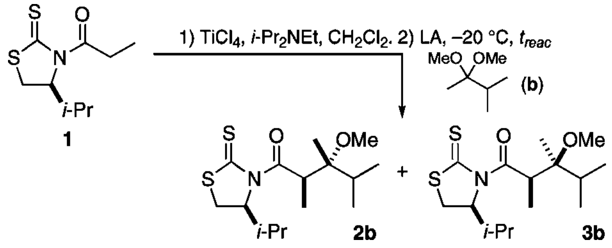
entry	$SnCl_4$ equiv	ketal equiv	t_{reac} (h)	yield (%)[a]
1	1.1	1	2	40
2	1.1	1	15	62
3	1.1	0.5	2	51
4	1.1	0.5	15	95
5	0.5	0.5	2	68
6	0.5	0.5	5	94

[a] Isolated yield of **2a** after chromatographic purification.

Preliminary studies with 2,2-dimethoxypropane (**a**) and $SnCl_4$ as Lewis acid showed that the corresponding adduct **2a** was consistently obtained as a single diastereomer, which proves the absolute control on the configuration of the α-stereocenter imparted by the chiral auxiliary (see Table 1). Moreover, the poor reactivity of ketal **a** required long reaction times (compare entries 1 and 2 in Table 1) and conferred to the stoichiometry a major role for the achievement of high yields (compare entries 2, 4, and 6 in Table 1).

Encouraged by these findings, we chose 2,2-dimethoxy-3-methylbutane (**b**) to study thoroughly the simultaneous construction of the two new stereocenters (see Table 2). Initially, we examined the influence of the Lewis acid and the stoichiometry on the yield and the diastereoselectivity of the coupling reaction. As expected, the yield was associated to the Lewis acid engaged in the process. A weak Lewis acid as $BF_3{\cdot}OEt_2$ was unable to produce the desired coupling, whereas the stronger $TiCl_4$ furnished a mixture of adducts in 56% yield; between them, the $SnCl_4$ afforded an intermediate yield (compare entries 1−3 in Table 2). However, $SnCl_4$ was much more stereoselective than $TiCl_4$ (dr 89:11 vs 79:21, compare entries 2 and 3 in Table 2). Furthermore, the diastereoselectivity turned out to be highly sensitive to the stoichiometry of the reaction. Indeed, the use of 0.5 equivalents of ketal produced **2b** as a single diastereomer in 63% yield (see entry 4 in Table 2). Otherwise, lowering the amount of $SnCl_4$ from 1.1 to 0.55 equiv improved the yield, but seriously eroded the diastereoselectivity (compare entries 4 and 5 in Table 2). These puzzling results suggest that the structure of the enolate can be altered by the presence of Lewis acids in the reaction mixture, which might be the cause of the different stereoselectivities observed across the whole optimization.[10] Finally, longer reaction times using the optimized conditions permitted the isolation of diastereomerically pure adduct **2b** in high yield (see entries 6 and 7 in Table 2).

Table 2. Lewis Acid-Mediated Addition of Titanium Enolates from **1** to 2,2-Dimethoxy-3-methylbutane (**b**)



entry	LA (equiv)	ketal equiv	t_{reac} (h)	dr[a] (**2b**:**3b**)	yield (%)[b]
1	$BF_3{\bullet}OEt_2$ (1.1)	1	3	–	–
2	$SnCl_4$ (1.1)	1	3	89:11	38
3	$TiCl_4$ (1.1)	1	3	79:21	56
4	$SnCl_4$ (1.1)	0.5	3	97:3	63
5	$SnCl_4$ (0.55)	0.5	3	86:14	72
6	$SnCl_4$ (1.1)	0.5	5	97:3	73
7	$SnCl_4$ (1.1)	0.5	15	97:3	75

[a] Determined by HPLC analysis of the reaction mixture. [b] Isolated yield of **2b** after chromatographic purification.

Considering that the methyl group is less sterically hindered than the isopropyl group in **b**, the configuration of the major diastereomer **2b** was initially assigned as (2*R*,3*R*) in accordance to the pattern observed for related dimethyl acetals.[5] This stereochemsitry was later secured by X-ray diffraction analysis (Figure 2),[11] which also confirmed the existence of two intramolecular C−H•••X (X = O, S) interactions as occurs in other adducts.[12]

Once the best experimental conditions for ketal **b** were established, we next surveyed a wide range of ketals to determine the scope of the reaction.[13] The results are

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(6) For Mukaiyama aldol type reactions with dimethyl ketals leading to racemic mixtures of tertiary methyl ethers, see: (a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259. (b) Li, L.-S.; Das, S.; Sinha, S. C. *Org. Lett.* **2004**, *6*, 127.

(7) For a recent report on the enantioselective synthesis of tertiary ethers through allylation of aliphatic methyl ketones, see: Tietze, L. F.; Kinzel, T.; Schmatz, S. *J. Am. Chem. Soc.* **2008**, *130*, 4386.

(8) For the synthesis and acylation of the chiral auxiliary, see: (a) Baiget, J.; Cosp, A.; Gálvez, E.; Gómez-Pinal, L.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 5637. (b) Gálvez, E.; Romea, P.; Urpí, F. *Org. Synth.* **2009**, *86*, 70.

(9) For a review on the use of thiazolidinethiones in asymmetric synthesis, see: Velázquez, F.; Olivo, H. F. *Curr. Org. Chem.* **2002**, *6*, 303.

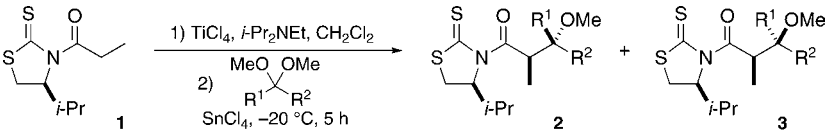
(10) A close dependence of diastereoselectivity on the stoichiometry has also been observed in some reactions involving dimethyl acetals. See ref 5e.

(11) Crystallographic data for **2b** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-713599, Copy of the data can be obtained free of charge on application to CCDC (e-mail: deposit@ccdc.cam.ac.uk).

(12) Cosp, A.; Larrosa, I.; Anglada, J. M.; Bofill, J. M.; Romea, P.; Urpí, F. *Org. Lett.* **2003**, *5*, 2809.

(13) Ketal **a** is commercially available. Ketals **b**−**m** have been prepared from the corresponding ketones following standard procedures reported in the literature, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.

Table 3. $SnCl_4$-Mediated Addition of Titanium Enolates from **1** to Dimethyl Ketals



entry	ketal	R^1	R^2	dr (**2**:**3**) [a]	yield (%) [b]
1	**b**	Me	*i*-Pr	97:3	73
2	**c**	Me	*i*-Bu	95:5	74
3	**d**	Me	CH_2CH_2Ph	86:14	67 (79)
4	**e**	Me	$CH_2CH_2CH{=}C(CH_3)_2$	82:18	67 (83)
5	**f**	Et	*i*-Pr	55:45	(45)
6	**g**	Me	Ph	60:40	(40)
7	**h**	Me	(*E*) CH=CHPh	–	–
8	**i**	Me	CO_2Me	–	–
9	**j**	Me	$CH_2CH_2CO_2Me$	82:18	75 (92)
10	**k**	Me	$(CH_2)_2CH_2OTIPS$	87:13	55 (65)
11	**l**	Me	$(CH_2)_2CH_2OBn$	79:21	53 (67)
12	**m**	Me	$(CH_2)_2CH_2NPhth$	76:24	58 (76)

[a] Determined by HPLC or ^1H NMR analysis of the reaction mixture. [b] Isolated yield of **2** after chromatographic purification. Overall yield is given in parentheses.

summarized in Table 3. Ketals from methyl ketones (R^1 = Me) containing alkyl R^2 groups furnished diastereomerically pure adducts **2** in good yields (see entries 1−4 in Table 3). As expected, the stereoselectivity of these ketals was highly dependent on the size of R^2 and it gradually decreased from **b** (R^2 = *i*-Pr) to **e** ($R^2 = CH_2CH_2R$). According to this trend, the replacement of the methyl by an ethyl as the R^1 group produced a dramatic erosion on the diastereomeric ratio for 3,3-dimethoxy-2-methylpentane (**f**, see entry 5 in Table 3) and afforded a mixture of adducts in low yield. Moreover, ketals from aryl and α,*β*-unsaturated methyl ketones were also troublesome (see entries 6 and 7 in Table 3). The results with the dimethyl ketal from acetophenone (**g**) were particularly disappointing because, in spite of our efforts, we were not able to obtain the desired adduct **2g** in synthetically useful yield and diastereomeric ratio. The behavior of the ketal from 4-phenyl-3-buten-2-one (**h**) was even worse, since no coupling was observed under any condition.

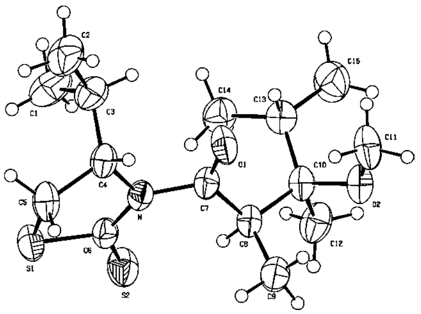


Figure 2. X-ray crystal structure of adduct **2b**.

Having recognized the carbon skeleton requirements to be fulfilled by the ketals and looking for pushing the frontier ahead, we centered our attention on the reactivity of ketals containing different functional groups. Piruvate-derived ketal **i** was our first choice. Unfortunately, it was completely unreactive and only starting materials were identified in the reaction mixtures. However, ketals **j**−**m** possessing an ester, a protected alcohol or amine far from the reacting center afforded adducts **2** in good yields and diastereoselectivities up to 87:13 (see entries 9−12 in Table 3). These results prove that dimethyl ketals from aliphatic methyl ketones are suitable substrates for such kind of transformations provided that no electronwithdrawing groups are close to the ketal center. Then, pure *anti* adducts **2** can be isolated by simple chromatographic purifications.

E oxocarbenium cation *Z* oxocarbenium cation

Figure 3. Methyloxocarbenium cations from methyl ketones.

Although a clear understanding of the mechanistic details of the above-mentioned coupling is hampered by the poor knowledge on the structure of the titanium enolate,[14] it is likely that it proceeds via an S_N1-like mechanism. Such scenario puts the formation and the reactivity of the oxocarbenium cation in a prominent position to rationalize the overall process. Thus, it is important to realize that any electronwithdrawing group close to the ketal prevents the formation of the required cation and the reaction does not

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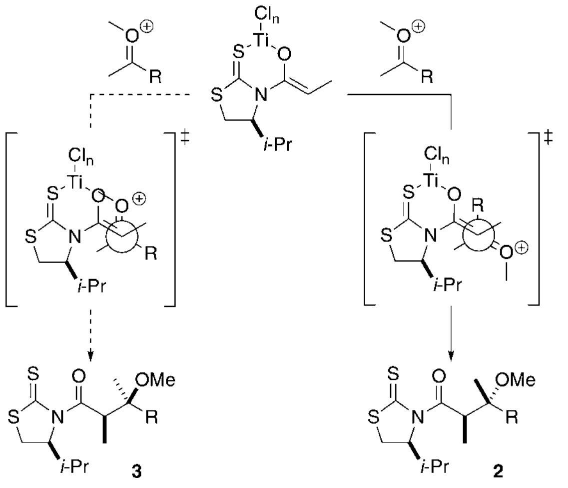
[14] For the biradical character of some titanium(IV) enolates, see: Moreira, I. de P. R.; Bofill, J. M.; Anglada, J. M.; Solsona, J. G.; Nebot, J.; Romea, P.; Urpí, F. *J. Am. Chem. Soc.* **2008**, *130*, 3242.

take place, as it probably occurs in the piruvate-derived ketal **i**. Furthermore, the resultant ion must be stable enough to undergo the nucleophilic atack of the enolate. In this context, we hypothesize that the lack of coupling observed for **h** is due to the competitive formation of a fully conjugated enol ether and the subsequent quenching of the enolate.[15]

Otherwise, we are aware that the oxocarbenium cations are configurationally labile and two diastereomers can operate in these processes. Regarding the cations from methyl ketones represented in Figure 3, the *E* isomer must be the most stable and can be identified as the reacting species leading to the major adduct **2**. However, the less sterically hindered the group R is, the more accessible is the oxocarbenium intermediate with the *Z* geometry, which challenges the control on the configuration of the quaternary stereocenter. Thereby, the remarkable difference on steric hindrance of both groups in ketal **b** (Me vs *i*-Pr) must only produce the *E* oxocarbenium intermediate that is responsible of the highest diastereomeric ratios observed in this case.

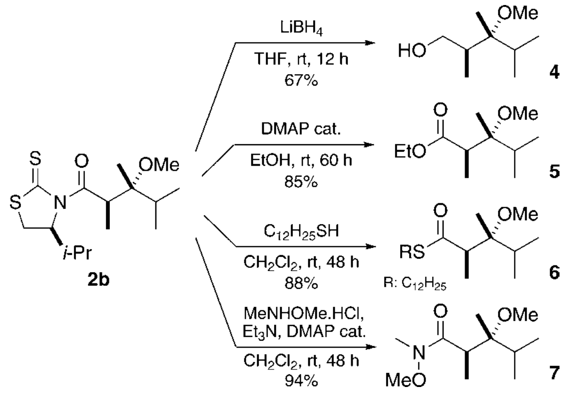
Scheme 1



Bearing in mind these considerations, the resultant *anti* stereochemistry might be explained by an open transition state that involves the approach of the oxocarbenium cation to the less hindered face (*Si* face) of a putative chelated *Z*-enolate (Scheme 1). Such approach determines the *R* configuration at the α-stereocenter. In turn, the configuration of the *β*-stereocenter is mainly ruled by the antiperiplanar approach of the *E*-oxocarbenium to the enolate to minimize the steric and dipolar interactions.[16]

Finally, the easy removal of the chiral auxiliary from **2** gives access to a wide range of enantiomerically pure fragments. For instance, the model adduct **2b** was converted into the corresponding alcohol **4**, ester **5**, thioester **6**, and Weinreb amide **7** in high yields under mild conditions as represented in Scheme 2.

Scheme 2



In summary, the Lewis acid-mediated addition of the titanium enolates from (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**1**) to dimethyl ketals from aliphatic methyl ketones and the subsequent removal of the chiral auxiliary give access to enantiomerically pure derivatives containing a tertiary methyl ether and a contiguous stereocenter in good yields and a straightforward manner.

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Supporting Information Available: Physical and spectroscopic data for adducts **2** and derivatives **4**−**7** and the X-ray crystallographic data for **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For kinetic studies on the reactivity of oxocarbenium ions, see: (a) Richard, J. P.; Williams, K. B.; Amyes, T. L. *J. Am. Chem. Soc.* **1999**, *121*, 8403. (b) Richard, J. P.; Amyes, T. L.; Toteva, M. M. *Acc. Chem. Res.* **2001**, *34*, 981.

(16) The main features of this mechanism are consistent with studies on ketone crotylation reactions, see: (a) Tietze, L. F.; Kinzel, T.; Schmatz, S. *J. Am. Chem. Soc.* **2006**, *128*, 11483. (b) Reference 7.