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Non-chelation Controlled 1,3-Asymmetric Induction in β-Chiral Acylsilanes

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Abstract : The diastereoselectivity of nucleophilic adition to β-chiral acylsilanes is examined, and our method is applied to the stereoselective synthesis of calcitriol lactone, a major metabolite of vitamine D_3.

In this communication, we wish to report an unprecedented 1,3-asymmetric induction in the reaction of β-chiral acylsilanes with nucleophiles to form a C-C bond, and its application to the highly stereoselective construction of the C-23 position of calcitriol lactone.[1,2,3]

We have reported that α-chiral acylsilanes exhibit quite high diastereofacial selectivity in nucleophilic additions (1,2-asymmetric induction) and behave as aldehyde equivalents[4]. This method of using α-chiral acylsilanes was developed to achieve diastereoselective additions to those α-chiral carbonyl compounds for which chelation controlled asymmetric inductions are impossible, and the high diastereoselectivity observed in the study prompted us to examine the potential for expanding the use of chiral acylsilanes to obtain stereoselectivity, and thus, to investigate 1,3-asymmetric induction of β-chiral acylsilanes in a non-chelation controlled manner.

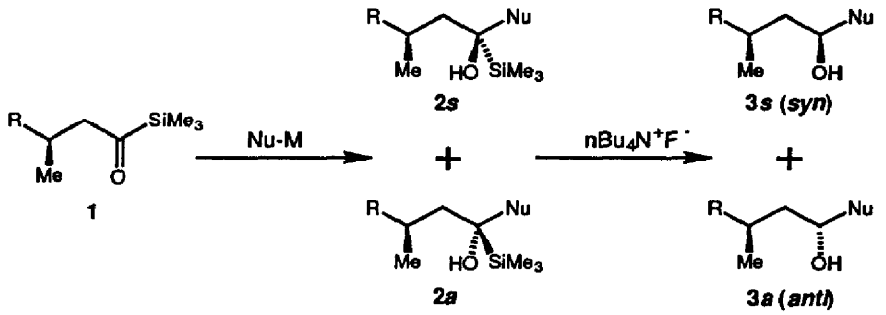
At first, we prepared some simple β-chiral acylsilanes **1** (R = Ph[5], Cyclohexyl[6], ^{t}Bu[7]), and examined the stereoselectivity of their reactions with several nucleophiles as summarized in **Table I**[8]. In the case of **1** (R = Ph) n-BuLi, which was chosen as the representative organometallic reagent, gave no selectivity and similar results were observed in the reaction of **1** (R = Cyclohexyl). However, in both cases (R = Ph, Cyclohexyl) higher diasteroselectivity (2 : 1 to 6 : 1) was observed in the Ti(IV) catalyzed reactions compared with the corresponding aldehyde. In particular methallyl-TMS / Ti(IV) gave good results. In the Ti(IV) catalyzed reactions, the degree of selectivity was not as high as that observed with α-chiral acylsilanes, but as the substituent became more bulky (R = ^{t}Bu), higher selectivity was observed. For this acylsilane (R = t-Bu) the product ratios became 12 : 1 in the reaction with allyl-TMS / Ti(IV) and 13 : 1 with methallyl-TMS / Ti(IV).

As shown in the reaction of **1** (R = ^{t}Bu), β-chiral acylsilanes having a bulky substituent showed selectivity sufficient for synthetic purposes, so we next applied this 1,3-asymmetric induction to the stereoselective synthesis of natural products.

We chose and prepared β-chiral acylsilane **4**[9], as the stereochemistry of the major product would be the same as calcitriol lactone[1,2,3] at its C-23 position. The reaction of **4** with some nucleophiles were examined as shown in **Table II**[8]. The selectivity was low in reactions with common organometallics such as alkyllithiums and Grignard reagents, but allyl- and methallyl-TMS / Ti(IV) showed excellent selectivity, yielding product ratios of 26 : 1, 36 : 1 respectively[8]. Compared to the corresponding aldehydes, the stereochemistry of the major products observed was reversed, and the degree of selectivity was dramatically increased.

Basaed on Felkin's and Ahn's models[10,11], we propose that this reaction proceeds via the transition states shown in **Scheme I**. Considering the coordination of Ti(IV) catalyst with the carbonyl oxygen to occur at less hindered side, four transition states which are relatively free from the steric strain are possible, of which the least

Table I



Entry	R	Nu-M	Solv.	Yield(%) (2*s*+2*a*)	Ratio[c] (2*s*:2*a*)	Yield(%) (3*s*+3*a*)	Ratio[c] (3*s*:3*a*)	Ratio[c],[f] (3*s*:3*a*)
1	Phenyl	nBu-Li	THF	55	1 : 1	72	1 : 1[d]	(1 : 1)[d]
2	Phenyl	Allyl-SiMe3[a]	CH_2Cl_2	97	2 : 1	100	2 : 1[d]	(1 : 1)[d]
3	Phenyl	Allyl-SnMe3[a]	CH_2Cl_2	98	2 : 1	60	2 : 1[d]	(1 : 1)[d]
4	Phenyl	Methallyl-SiMe3[b]	CH_2Cl_2	75	6 : 1	74	6 : 1[d]	(2 : 1)[d]
5	Phenyl	Methallyl-SnMe3[b]	CH_2Cl_2	100	5 : 1	63	5 : 1	(1.5 : 1)
6	Cyclohexyl	nBu-Li	THF	80	3 : 1	65	e)	e)
7	Cyclohexyl	Allyl-SiMe3[a]	CH_2Cl_2	86	2 : 1	87	2 : 1	(1 : 1)
8	Cyclohexyl	Allyl-SnMe3[a]	CH_2Cl_2	89	2 : 1	72	2 : 1	(1 : 1)
9	Cyclohexyl	Methallyl-SiMe3[b]	CH_2Cl_2	78	5 : 1	85	5 : 1	(1 : 1)
10	Cyclohexyl	Methallyl-SnMe3[b]	CH_2Cl_2	80	5 : 1	65	5 : 1	(1 : 1.5)
11	tButyl	nBu-Li	THF	89	1.4 : 1	75	1.4 : 1	(1 : 1)
12	tButyl	Allyl-SiMe3[a]	CH_2Cl_2	71	12 : 1	92	12 : 1	(1 : 1)
13	tButyl	Allyl-SnMe3[a]	CH_2Cl_2	46	6 : 1	75	6 : 1	(1 : 1)
14	tButyl	Methallyl-SiMe3[b]	CH_2Cl_2	77	13 : 1	83	13 : 1	(2 : 1)
15	tButyl	Methallyl-SnMe3[b]	CH_2Cl_2	74	9 : 1	90	9 : 1	(1.5 : 1)

a) in the presence of $TiCl_4$ b) in the presence of $6TiCl_4$-$5Ti(OiPr)_4$ c) determined by 400MHz ^1H NMR
d) determined by HPLC e) not determined f) ratio in the reaction of corresponding aldehyde with nucleophile

strained is $S_2^{\neq}$. Hence, the syn selectivity is well explained. Moreover, we assume that the observed higher selectivity in entries 4 and 7 of Table II, compared with the case of simple acylsilanes (Table I), can be attributed to the nearly frozen rotation of the bond between C-17 and C-20 of **4**. Further investigations are required to explain the low selectivity observed with allyl and methallyl trimethyltin.

In conclusion, β-chiral acylsilanes having sterically different substituents at their β-position and no ability to chelate can be effectively utilized as key intermediates for natural product synthesis. Product **6***s* (entry 7 of **Table II**) obtained as above can be taken on to calcitriol lactone, a major metabolite of vitamin D_3, thus demonstratuing the synthetic potential of 1,3-asymmetric induction in chiral acylsilanes.

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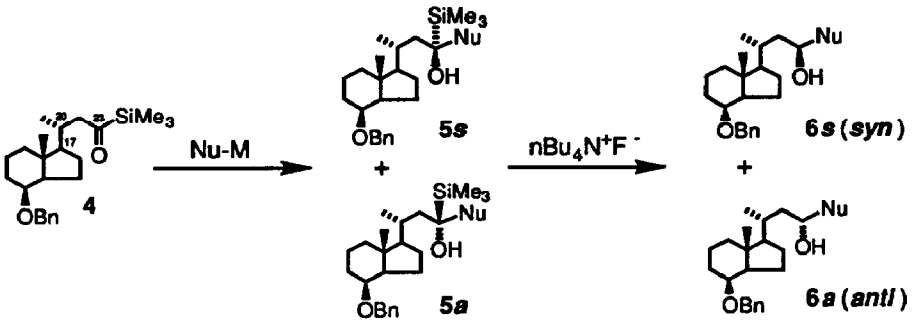
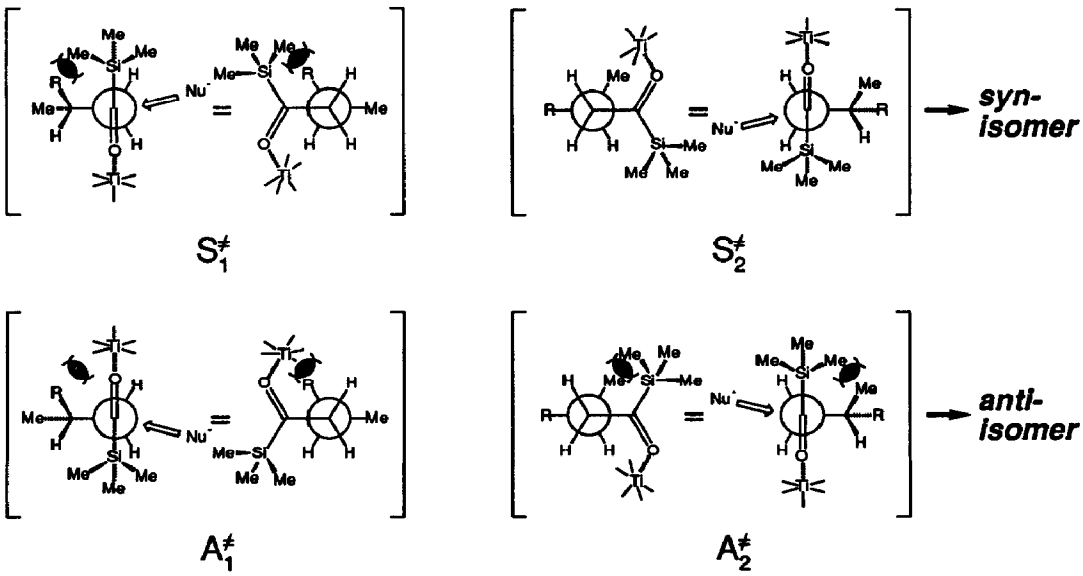
Table II



Entry	Nu-M	Solv.	Yield(%) (5s + 5a)	Ratio[c] (5s : 5a)	Yield(%) (6s + 6a)	Ratio[c],[d] (6s : 6a)	Ratio[e] (6s : 6a)
1	n-BuLi	THF	95	1.8 : 1	96	1.8 : 1	(1.9 : 1)
2	MeLi	Et_2O	100	1.8 : 1	93	1.8 : 1	(1.2 : 1)
3	Allyl-MgBr	Et_2O	83	2.2 : 1	100	2.2 : 1	(1.2 : 1)
4	Allyl-$SiMe_3$[a]	CH_2Cl_2	90	26 : 1	96	26 : 1	(1 : 2.1)
5	Allyl-$SnMe_3$[a]	CH_2Cl_2	85	8.3 : 1	84	8.3 : 1	
6	Methallyl-MgBr	Et_2O	93	2.1 : 1	97	2.1 : 1	(1.1 : 1)
7	Methallyl-$SiMe_3$[b]	CH_2Cl_2	90	36 : 1	52	36 : 1	(1 : 4)
8	Methallyl-$SnMe_3$[b]	CH_2Cl_2	70	3.3 : 1	92	3.3 : 1	

a) in the presence of $TiCl_4$ b) in the presence of $6TiCl_4$-$5Ti(OiPr)_4$ c) determined by 400MHz ^{1}H-NMR
d) determined by HPLC e) ratio in the reaction of the corresponding aldehyde with the nucleophile

Scheme I



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3. Synthesis of the A ring moiety in calcitriol lactone, see : Kobayashi, S.; Shibata, J.; Shimada, M.; Ohno, M. *Tetrahedron Lett.* **1990**, *31*, 1577, and references cited therein.
4. Nakada, M.; Urano, Y.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1988**, *110*, 4826.
5. Prepared as follows, starting from (S)-3-phenylpropionic acid : (1) $LiAlH_4$, (2) MsCl / Et_3N, (3) NaI, (4) 2-Lithio-2-TMS-dithiane, (5) NCS, $AgNO_3$, γ-collidine.
6. (S)-2-Cyclohexylpropionic acid, prepared by the known method (Levene, P. A.; Marker, R. E. *J. Biol. Chem.* **1932**, *93*, 563.) was converted to **4** (R = Cyclohexyl) as mentioned above.
7. (S)-2-*tert*-Butylpropionic acid was prepared by an asymmetric alkylation method (Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.), and the absolute configuration was determined by the optical rotation already reported, (see : Caporusso, A. M.; Giacomelli, G. P.; Lardicci, L. *Atti Soc. Tosc. Sci. Nat., Mem., Serie A*, **1973**, *80*, 40.). It was converted to **4** (R = t-Bu) as above.
8. The structures of the major products were determined by comparison (by 400 MHz ^{1}H-NMR, HPLC) with authentic samples prepared by W. S. Johnson's chiral template method. To avoid any errors arising from unusual stereoselections (see : Yamamoto,Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.), (2R,4R)- and (2S,4S)-pentanediol were both used, and the normal stereoselection was observed in each case.
9. Prepared as follows, starting from the Inhoffen-Lythgoe diol (Sardina, F.; Mourino, A.; Castedo, L. *J. Org. Chem.* **1986**, *51*, 1264): (1) TBSCl / imidazole, (2) BnBr / NaH, (3) n-$Bu_4N^+F^-$ (4) MsCl / Et_3N, (5) NaI, (6) 2-Lithio-2-TMS-dithiane, (7) NCS, $AgNO_3$, γ-collidine.

   We have also established a novel preparative method for acylsilanes, which is mild and general, and can be applied without any difficulty to α-chiral, α-alkoxy and multifunctionalized compounds, see ; Nakada, M.; Nakamura, S.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1991**, *32*, 4929.
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