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Organocatalytic Asymmetric Synthesis of 5-(Trialkylsilyl)cyclohex-2-enones and the Transformation into Useful Building Blocks

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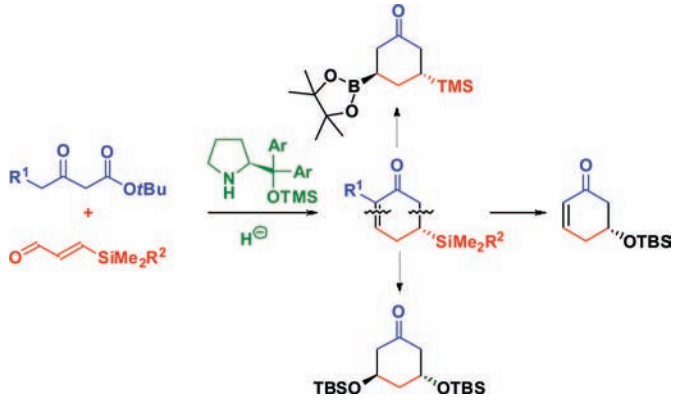
ABSTRACT



A simple organocatalytic approach to highly attractive chiral building blocks is presented. By the reaction of β-ketoesters with α,β-unsaturated aldehydes using a chiral TMS-protected prolinol as the catalyst, optically active 5-(trialkylsilyl)cyclohex-2-enones are formed in good yields and with 98−99% ee. The applications of 5-(trialkylsilyl)cyclohex-2-enones for the formation of 5-(hydroxy)cyclohex-2-enones and the A-ring of 19-*nor*-1α,25-dihydroxyvitamin D_3 are also presented.

Organocatalysis is a spreading field in modern organic synthesis.[1] Various new methodologies have been developed to construct chiral building blocks, which are employed in the synthesis of natural products and biologically active compounds.[2]

Chiral 5-(trialkylsilyl)cyclohex-2-enones[3] **1** and 5-(hydroxy)cyclohex-2-enones **2** are very important building blocks in organic synthesis (Figure 1). The trialkylsilyl-substituted cyclohexenones have been used for the synthesis of, e.g., Sarcodictyenone[3a] **3** and Nicandrenone[3e] NIC-10 **4**. The 5-hydroxy-substituted cyclohexenones[4] **2** have been employed in a number of syntheses, such as 19-*nor*-1α,25-

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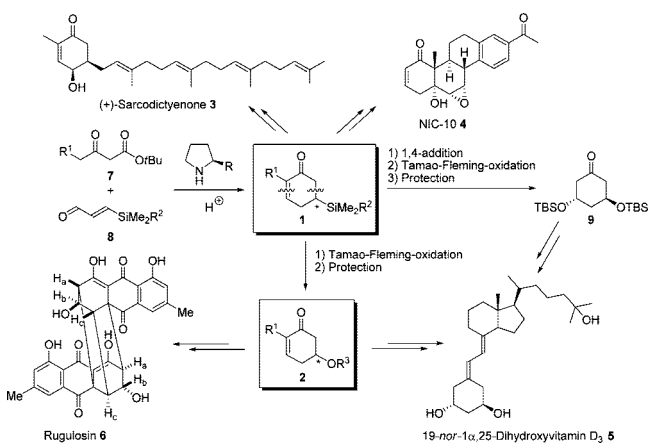

Figure 1. Synthesis of chiral 5-substituted cyclohexenone derivatives and their use in natural product synthesis.

dihydroxyvitamin D_3 **5**[4e,f] or Rugulosin **6**.[4a,b] Furthermore, the silyl and hydroxy group in **1** and **2**, respectively, can be used to control the stereochemistry of transformations at adjacent double bonds.[3k,5]

However, to the best of our knowledge, cyclohexenones of type **1** have so far only been synthesized by either enzymatic,[6] metal,[7] or cinchonidine[8] catalyzed kinetic resolutions. The hydroxy derivatives **2** can be constructed by enzymatic kinetic resolution,[4c] an enantioselective deprotonation strategy,[4d] a seven-step sequence as developed by Nicolaou et al.,[4a] or as Sato et al.[4i,9] have shown, in six or seven steps starting from commercially available compounds.

As a simple alternative, we envisioned an organocatalytic, asymmetric one-pot reaction sequence by which β-ketoesters **7** react under iminium ion catalysis with silicon-substituted α,β-unsaturated aldehydes[10] **8** in a Michael addition to an intermediate, which after acid-catalyzed decarboxylation and aldol condensation forms the desired 5-(trialkylsilyl)cyclohex-2-enones **1** (Figure 1). These products (**1**) (with R^2 = Ph) may then be converted by a Tamao−Fleming oxidation,[11] which after protection of the alcohol yields the 5-(hydroxy)cyclohex-2-enones **2**. Additionally, a short synthesis of the A-ring precursor[4e,f,12] of 19-*nor*-1α,25-dihydroxyvitamin D_3 **5** is developed by an analogous strategy. After the introduction of a second dimethylphenylsilyl (DMPS) substituent by a 1,4-addition to the cyclohexenone **1**, the Tamao−Fleming oxidation followed by alcohol protection delivers the bishydroxylated ketone.

We started our investigations by employing the reaction conditions for the synthesis of chiral 5-alkyl- or 5-aryl-substituted cyclohexenones.[13] Accordingly, *tert*-butyl acetoacetate **7a** was reacted with the DMPS-substituted α,β-unsaturated aldehyde **8a** in the presence of 10 mol % (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(trimethylsilyloxy)-methyl)pyrrolidine[14] under neat conditions to the Michael-addition intermediate, which was converted with catalytic amounts of *p*-TSA (20 mol %) to the corresponding 5-(dimethylphenylsilyl)cyclohex-2-enone by heating for 17 h at 80 °C (Table 1). The desired product was obtained in a low yield of 17%, but with a very good enantioselectivity of 93% ee. This result encouraged us to investigate the reaction conditions further.[15] The first step, the Michael reaction, usually proceeded with full conversion overnight. Nevertheless, benzoic acid and toluene were added to accelerate the reaction as long reaction times were observed in some cases under neat conditions. The problematic step turned out to be the decarboxylation−aldol condensation sequence. In general, low yields of the desired product were observed at long reaction times, low loadings of acid, and high temperatures. Therefore, a fine-tuning of these parameters was carried out (Table 1).

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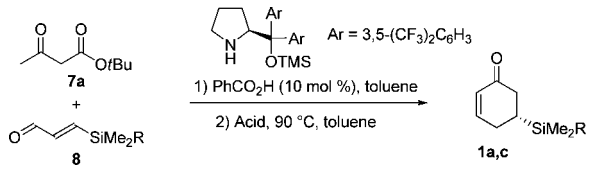
Table 1. Screening of the Reaction Conditions for the Decarboxylation−Aldol Reaction Step



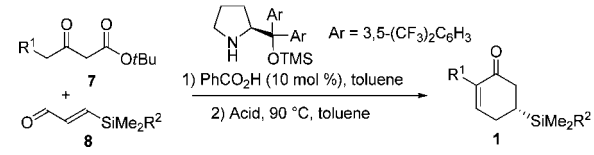
				R = Ph **1a**		R = Me **1c**	
entry	acid[a]	time [min]	acid [mol %]	yield[b] [%]	ee[c] [%]	yield[b] [%]	ee[c] [%]
1	TSA	35	20	35	98		
2	CSA	30	20	traces	n.d.		
3	MSA	30	25	49	97	45	99
4	MSA	35	25	50	99	43	99
5	MSA	40	20			32[d]	99
6	MSA	40	25	53	99	49[d]	99
7	MSA	40	30			60[d]	99
8	**MSA**	**40**	**35**	**57**[d,e]	**99**	**65**[d,e]	**99**
9	MSA	40	40			55[d]	99
10	MSA	45	25	47[d]	99	44	97
11	MSA	45	30	54[d]	99		
12	MSA	45	35	55[d]	99		
13	MSA	50	25	42	98		

[a] Reaction conditions: (1) Aldehyde (0.25), β-ketoester (0.37 mmol), catalyst (0.25 mmol), $PhCO_2H$ (0.025 mmol), toluene (0.13 mL), 15−17 h, rt. (2) acid, toluene (0.87 mL), 90 °C. [b] Isolated yield after column chromatography. [c] Determined by HPLC. [d] Reactions performed on a 1.00 mmol scale. [e] The isomerized products 5-(dimethyl(phenyl)silyl)cyclohex-3-enone and 5-(trimethylsilyl)cyclohex-3-enone were observed but could not be isolated purely after column chromatography.

First, different acids were used to catalyze the second step. The best yields were obtained with methanesulfonic acid (MSA) in comparison to *p*-TSA, while only traces of the desired product were observed with camphorsulfonic acid (CSA) (Table 1, entries 1−3). MSA was therefore chosen as the catalyst for further investigations. The optimizations showed that lower yields were obtained with lower catalyst loadings and longer reaction times (entries 4−13). In all cases, the products were formed with an excellent enantioselectivity of up to 99% ee. The best yields of 57% for the DMPS- and 65% for the TMS-substituted α,β-unsaturated aldehyde were in both cases obtained when the reaction was performed for 40 min at 90 °C with 35 mol % of MSA (entry 8).

With the best conditions in hand, the scope of the reaction was investigated (Table 2). In all cases the products **1a**−**j** were formed with excellent enantioselectivity of up to 99% ee in good yields up to 69% (Table 2, entries 1−12). Different substituted β-ketoesters **7a**−**d**, aliphatic, allylic, and aromatic, as well as α,β-unsaturated aldehydes **8a**,**b** could be used. Generally slightly better yields were obtained in the case of the DMPS-substituted aldehyde **8a** (entries 7−12). The enantiomers **1b**,**d** of the products **1a** and **1c** were synthesized by using the enantiomer of the catalyst (entries 2 and 5). Additionally, the reaction could be performed on a 10 mmol scale delivering the products in yields of 59% and 61% (entries 3 and 6). The absolute configuration of

Table 2. Scope of the Reaction



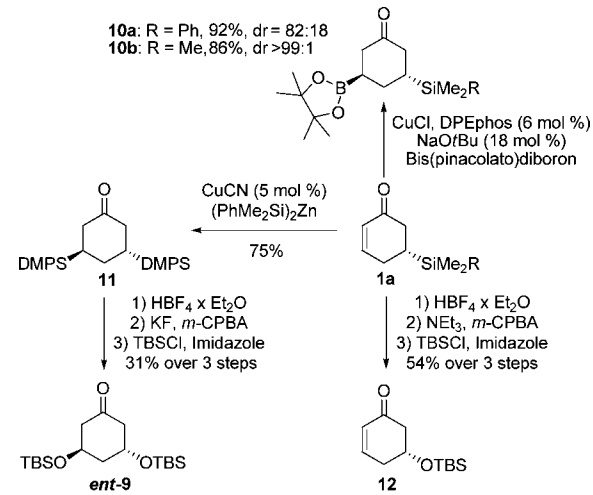
entry	R^1	R^2	yield[a,b] [%]	ee[c] [%]
1	**7a**-H	**8a**-Ph	**1a**-57	99
2	**7a**-H	**8a**-Ph	**1b**-55	99 (+)
3	**7a**-H	**8a**-Ph	**1a**-59[d]	99
4	**7a**-H	**8b**-Me	**1c**-65	99
5	**7a**-H	**8b**-Me	**1d**-69	99 (+)
6	**7a**-H	**8b**-Me	**1c**-61[d]	98
7	**7b**-Me	**8a**-Ph	**1e**-50	99
8	**7b**-Me	**8b**-Me	**1f**-42	98
9	**7c**-allyl	**8a**-Ph	**1g**-50	99
10	**7c**-allyl	**8b**-Me	**1h**-46	99
11	**7d**-Ph	**8a**-Ph	**1i**-52	99
12	**7d**-Ph	**8b**-Me	**1j**-47	98

[a] Reaction conditions: (1) Aldehyde (1.00 mmol), β-ketoester (1.5 mmol, 1.5 equiv), catalyst (10 mol %), $PhCO_2H$ (10 mol %), toluene (c = 2.0 mol/L), 15−17 h, rt. (2) MSA (35 mol %), toluene (c = 0.25 mmol/mL in total), 90 °C, 40 min. [b] Isolated yield after column chromatography. [c] Determined by HPLC. [d] Reaction performed on a 10 mmol scale.

the cyclohexenones was assigned by comparison of the α-value of the literature known compounds **1a** and **1c**.[6]

The 5-(trialkylsilyl)cyclohex-2-enones are important building blocks for natural product synthesis. In recognition of this, we wished to expand the scope of possible transformations, leading to the investigation of the copper[16] catalyzed 1,4-addition of bis(pinacolato)-diboron to the synthesized cyclohexenones (Scheme 1). Thereby trifunctionalized cyclohexanones of type **10** were formed in very good yields (86−92%) and diastereoselectivities up to *trans:cis* > 99:1. Interestingly, a higher diastereoselectivity was observed with the TMS-substituted cyclohexenone in comparison to the

Scheme 1. Transformations of the Cylcohexenones **1**



DMPS derivative. This may be due to interactions of the bulky DPEphos ligand with the DMPS group in the transition state.

Then, the short synthesis of the A-ring precursor **9** of 19-*nor*-1α,25-dihydroxyvitamin D_3 **5** was developed. The copper[17] catalyzed conjugated addition of bis(dimethylphenylsilyl)zinc resulted in formation of the disubstituted cyclohexanone **11** in a yield of 75% with a very good diastereoselectivity of *trans*:*cis* = 98:2. The cyclohexanone **11** was converted by a two-step Tamao−Fleming oxidation[18] to the corresponding diol and protected to bissilanolether ***ent*-9** in 31% over three steps without loss of enantiopurity to deliver the A-ring precursor.

Finally, the cyclohexenone **1a** was transformed into the corresponding protected 5-hydroxycyclohex-2-enone **12** by a Tamao−Fleming oxidation[18] followed by protection in a yield of 54% over three steps without loss of enantiopurity.

In conclusion, we have developed the first asymmetric synthesis which is not based on kinetic resolution of 5-(trialkylsilyl)cyclohex-2-enones in good yields with excellent enantioselectivities. Moreover, silicon-substituted α,β-unsaturated aldehydes were introduced to organocatalysis for the first time which might give rise to further interesting transformations. Finally, the synthesized cyclohexenone derivatives were transformed into interesting and important building blocks in shorter sequences than previously seen.

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Supporting Information Available: Experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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