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Highly Regio- and Enantioselective Organocatalytic Conjugate Addition of Alkyl Methyl Ketones to a β-Silylmethylene Malonate

Raghunath Chowdhury and Sunil K. Ghosh*

Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400085, India

ghsunil@barc.gov.in

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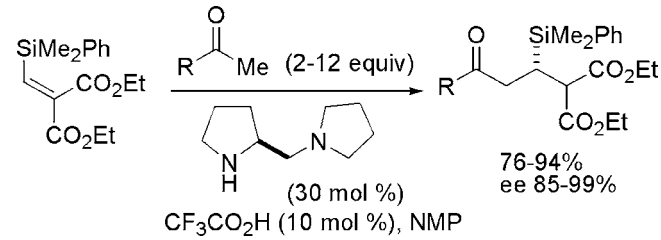
ABSTRACT



(*S*)-*N*-(2-Pyrrolidinylmethyl)pyrrolidine/trifluoroacetic acid (3:1) combination catalyzed the direct addition of alkyl methyl ketones to β-dimethyl(phenyl)silylmethylene malonate at the methyl terminal with high yield and excellent regio- and enantioselectivity. The silyl group played crucial roles in regioselection and substrate reactivity.

Chiral β-silyl carbonyl compounds[1] are popular targets because of their versatile nature. We are concerned for the asymmetric synthesis of intermediates of type **1** or **2** (Figure 1) containing a silicon group[2] positioned at β to both a ketone and an ester functionality because they could be synthons[3] for *privileged* structures containing chiral *N*- and *O*-heterocycles. Synthesis of silylated keto-ester **1** has been achieved by asymmetric desymmetrization[4] of 3-[dimethyl(phenyl)silyl]glutaric anhydride followed by selective alkylation of one of the carboxyl functionalities. Although high selectivity[5] was achieved in the desymmetrization process, it required specially designed *SuperQuat*[6] oxazolidinones. The desymmetrization of anhydrides with a limited type of carbon nucleophiles[7,8] has been reported recently to produce keto esters. Enantio-/diastereoselective conjugative silylation of unsaturated carbonyl compounds is also well-known.[9] However, the most suited chemical transformation that avoids additional reagents and waste production would be an atom-economic regio- and enantioselective conjugate addition of an alkyl methyl ketone to the β-silyl acrylate **3** or β-silylmethylene malonate **4**.[10]

Among the asymmetric Michael reactions developed in the field of organocatalysis,[11] direct addition of ketones or aldehydes to α,β-unsaturated aldehydes,[12] ketones,[13] sulfones,[14] and nitrostyrenes[15] provided satisfactory results.

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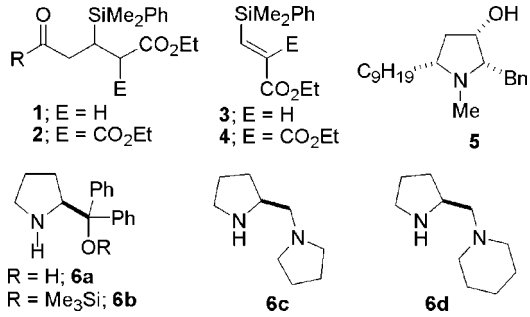

Figure 1. Structures of substrates, targets, and organocatalysts.

However, the addition of the same donors[16−20] to alkylidene malonates is less successful. Barbas III and co-workers[17] for the first time demonstrated that acetone can add to various aryl- and alkylidene malonates under organocatalysis with moderate yields and enantioselectivities. List et al.[18] have shown the natural proline-catalyzed direct addition of acetone to an arylidene malonate with good yield but poor enantioselectivity. Extension of this methodology to the three-component domino reaction[19] between ketones, aldehydes, and Meldrum's acid leading to the formation of two new C−C σ-bonds showed almost no enantioselectivity. Very recently, Tang et al.[20] reported that *N*-(pyrrolidin-2-ylmethyl)trifluoromethanesulfonamide catalyst gives Michael adducts in moderate to good yields and good to high enantioselectivities, depending upon the substituents present on the ketones and the arylidene malonates. Alkylmethylene malonates were not good acceptors for this reaction. Although cyclic ketones reacted with good diastereo- and enantioselectivities, acyclic ketones gave poor results.[17,20] Despite some success of these methodologies, reaction with acyclic nonsymmetrical ketones, especially the methyl ketones, remains very challenging. Besides yield and enantioselectivity, the regioselectivity of the addition is also an important issue.[21]

Herein, we report an efficient, highly regio- and enantioselective organocatalytic conjugate addition of acyclic methyl ketones to the β-silylmethylene malonate **4** providing the silylated keto-esters **2**. The potential of this new strategy has also been exemplified by synthesizing a known intermediate for the synthesis of (+)-preussin **5**,[22] a pyrrolidine natural product with interesting biological activities.

Initially, we chose acetone to obviate the regioselectivity issue and concentrated our effort to optimize the yield and enantioselectivity of the addition product **2a** (Figure 1, R = Me). The direct addition of acetone to malonate **4** using a catalytic amount of racemic amino acids for the synthesis of silylated ketodiester *rac*-**2a** has already been demonstrated by us,[23] as a part of our goal to develop silicon-based linkers for solid-phase organic synthesis.[24] Unfortunately, the asymmetric version of this reaction with a few natural amino acid catalysts in *N*-methylpyrrolidone (NMP) at room temperature resulted in very poor enantioselectivity (Table 1, entries 1−3). Reaction with simple pyrrolidines derived from proline, viz., diphenylprolinol **6a**[25] and its silyl ether **6b**,[26] was not effective for this addition (Table 1, entries 4 and 5). Pyrrolidine-based diamines derived from natural proline such as *N*-(2-pyrrolidinylmethyl)pyrrolidine **6c** and *N*-(2-pyrrolidinylmethyl)piperidine **6d** (Figure 1) are popular organocatalysts for aldol,[27] Michael,[17,28] and Mannich reactions.[29] Moreover, they can be easily made,[30] and also, Barbas III has used such catalysts for asymmetric addition of ketones to alkylidene malonates.[17] When pyrrolidine **6c** was used under the reported conditions,[17] addition of acetone to **4** was very slow, and the desired addition product **2a** was formed in poor yield but with moderate enantioselectivity (Table 1, entry 6). The catalytic ability of pyrrolidine **6c** was increased substantially with slight erosion of enantioselectivity by changing the solvent to NMP (Table 1, entry 7). Similarly, pyrrolidine **6d** also showed moderate yield and selectivity in NMP (Table 1, entry 8).

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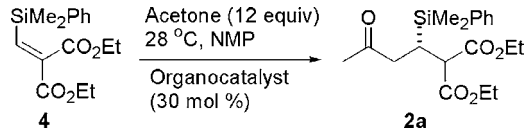
Table 1. Catalyst Screening for Direct Acetone Addition on Silylmethylene Malonate **4**



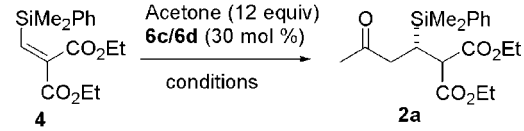
entry	catalyst	temp (°C)/time	% yield[a]	% ee[b]
1	(*S*)-Pro	28/1 day	75	<5
2	(*S*)-Trp	28/1 day	56	<5
3	(*S*)-Arg	28/5 days	42[c]	12
4	**6a**	28/7 days	trace	nd[d]
5	**6b**	28/7 days	trace	nd[d]
6	**6c**	28/6 days	10[e]	66
7	**6c**	28/3.5 days	61	55
8	**6d**	28/3.5 days	40[c]	55

[a] Yield of chromatographically homogeneous product. [b] Determined by HPLC. [c] Incomplete reaction. [d] nd = not determined. [e] Reaction was performed in THF as reported in ref 17b.

We next attempted to improve the yield and the enantioselectivity using the catalysts **6c** and **6d** in combination with different additives. Many research groups have used varying amounts of Bronstead acids as additives to accelerate the amine-catalyzed Michael addition of aldehydes and ketones to nitroolefins[28,31] resulting in good yields and stereoselectivities. Barbas III[17] has suggested that these reactions proceed through enamine intermediates[32] of the carbonyl donors. While investigating the role of acid in the formation of enamine from carbonyl compounds, Hine[33] has shown that the process was 15 times faster with the protonated primary amines than the free base. Therefore, the Michael reaction of acetone with silylidene malonate **4** was next examined with the pyrrolidine catalysts **6c** and **6d** in the presence of different organic acids in NMP.

We were delighted to see that the addition of 10 mol % of AcOH or *p*-nitrobenzoic acid (PNBA) and 30 mol % of catalyst **6c** at 4 °C provided the desired product **2a** in good yield (Table 2, entries 1 and 2) with a significant improvement of enantioselectivity. To see the effect of temperature, the reactions using catalyst **6c** and with or without 10 mol % of AcOH were carried out at −10 °C for 7 days. Although this improved the enantioselectivity, the conversion was abysmally poor (Table 2, entries 3 and 4). Interestingly, trifluoroacetic acid (TFA) appeared to be a better additive, and using 10 mol % of it with 30 mol % of catalyst **6c** at −10 °C for 7 days gave a decent yield of the product **2a** with excellent enantioselectivity (Table 2, entry 5). Additional experiments with varying amounts of TFA (5−30%) (Table 2, entires 5−8) established 10 mol % of TFA to be optimum for the reaction. We also tried the reaction in DMF and toluene. Although the yield was comparable in these solvents, the enantioselectivity dropped (Table 2, entries 9 and 10). The other catalyst **6d** turned out to be poor, as revealed from the results in Table 2 (entry 11).

Table 2. Optimization of Direct Acetone Addition on Silylmethylene Malonate **4** Using Additives



entry	catalyst/ additive (mol %)	solvent/temp/time	% ee[a] (% yield)[b]
1	**6c**/AcOH (10)	NMP/4 °C/5 days	84 (72)
2	**6c**/PNBA (10)	NMP/4 °C/5 days	80 (79)
3	**6c**/nil	NMP/−10 °C/7 days	80 (<5)[c]
4	**6c**/AcOH (10)	NMP/−10 °C/7 days	88 (<5) [c]
5	**6c**/TFA (10)	NMP/−10 °C/7 days	90 (76)
6	**6c**/TFA (5)	NMP/−10 °C/7 days	88 (56)
7	**6c**/TFA (15)	NMP/−10 °C/7 days	88 (57)
8	**6c**/TFA (30)	NMP/−10 °C/7 days	90 (44) [c]
9	**6c**/TFA (10)	DMF/−10 °C/7 days	84 (78)
10	**6c**/TFA (10)	Tol/−10 °C/7 days	82 (88)
11	**6d**/TFA (10)	NMP/−10 °C/10 days	84 (44) [c]

[a] Determined by HPLC. [b] Yield of chromatographically homogeneous product. [c] Incomplete reaction.

Next we extended the optimized protocol for the Michael addition between **4** and methyl alkyl ketones to address the issue of regioselectivity. It is well established[28a] that in the presence of acid the prototropy of the reactive enamine is more favorable and the equilibration between the more and the less substituted enamine could occur. This leads to the formation of the more stable substituted enamine on thermodynamic grounds. But the regiocontrol of the reaction is often governed by Curtin−Hammett kinetics. Therefore, the balance between Curtin−Hammett kinetics and acidity decides the regioselectivity. Many research groups have addressed the issue of regioselectivity during aldol[34] and Michael[35] addition involving unsymmetrical ketone donors, by tuning the acidity of the α and α′ protons with suitable functional groups. When methyl isopropyl ketone was reacted with silylmethylene malonate **4** under the optimized conditions as described in Table 2, we obtained only one regioisomeric product, as revealed by ^{1}H NMR spectrum of the crude reaction product in very high yield and with

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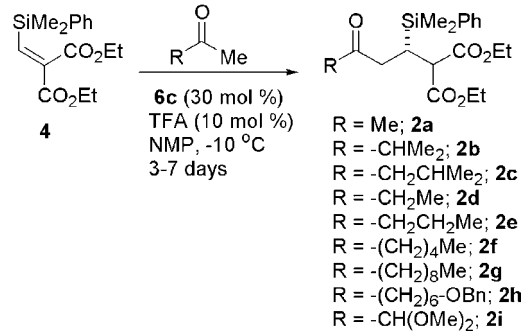
excellent enantioselectivity (Table 3, entry 2). Initially it was envisaged that the high regioselectivity might be an outcome of the steric crowding by the isopropyl group. However, this was discounted from the results with several other ketones, lacking any such steric congestion. In all the cases (Table 3, entries 3−9), only the addition product at the methyl terminal was obtained in excellent yields and enantioselectivities.

To establish the role played by the β-silyl group, other β-substituted methylene malonates, viz., diethyl esters of benzylidene, 4-fluorobenzylidene, and 3-phenylpropylidene malonates, were reacted with methyl ethyl ketone in the presence of catalyst **6c** under the optimized conditions. No reaction[36] took place indicating that the silyl substitution is crucial for the reactivity of the methylene malonate **4** as well as regioselectivity of the addition.

Table 3. Regioselctive Addition of Alkyl Methyl Ketones to Silylmethylene Malonate **4**

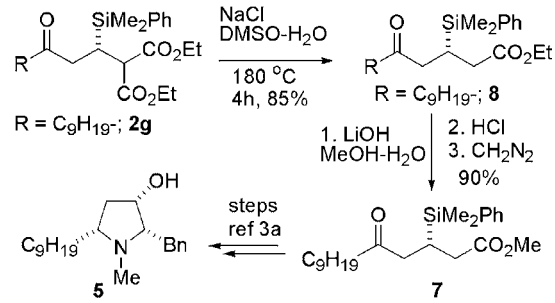


entry	ketone (equiv)	time	product (% yield)[a]	% ee[b]
1	MeCOMe (12)	7 days	**2a** (76)	90.0
2	$MeCOCHMe_2$ (12)	7 days	**2b** (82)	99.5
3	$MeCOCH_2CHMe_2$ (5)	6 days	**2c** (82)	96.7
4	$MeCOCH_2Me$ (12)	7 days	**2d** (81)	92.8
5	MeCO $(CH_2)_2Me$ (12)	7 days	**2e** (85)	91.2
6	$MeCO(CH_2)_4Me$ (5)	3 days	**2f** (94)	99.6
7	$MeCO(CH_2)_8Me$ (5)	3 days	**2g** (88)	91.1
8	$MeCO(CH_2)_6$-OBn (2)	6 days	**2h** (92)	91.3
9	$MeCOCH(OMe)_2$ (6)	7 days	**2i** (78)	85.4

[a] Yield of chromatographically homogeneous product. [b] Determined by HPLC; see the Supporting Information.

The absolute configuration of **2g** was assigned by converting it to a known keto ester **7**, an advanced precursor[3a,b] of (+)-preussin **5**. For this, the diester **2g** was subjected to Krapcho deethoxycarbonylation to give the monoester **8**,[37] which on hydrolysis[38] followed by esterification with diazomethane gave the methyl ester **7** (Scheme 1). Comparison of its optical rotation with the reported[3a] values established configuration of **7** to be (*S*) and, thus, of its progenitor **2g** also as (*S*). The absolute configurations of other products **2a**−**f** and **2h**−**i** were tentatively assigned to be (*S*) in analogy with **2g**.

Scheme 1. Synthesis of (+)-Preusssin **5**



Considering that the reaction goes via the enamine of the ketone, the stereochemical outcome for the formation of **2e** can be explained by a transition state assembly[13e,20] depicted in Figure 2. The malonate **4** approaches the enamine from the less hindered *si* face. The hydrogen bonding interaction of tertiary nitrogen, one of the carbonyl groups of **4**, and TFA activated the substrates by bringing them to proximity, demonstrating that a catalytic amount of TFA can speed up the reaction.

In conclusion, we have developed an organocatalytic asymmetric Michael addition of alkyl methyl ketones to a silylalkylidene malonate with high regio- and enantioselectivity. This is the first successful attempt to engage unsymmetrical methyl ketones to add via terminal carbon in such reactions, and the silyl group is the key to this success. The products thus obtained can easily undergo deethoxycarbonylation to give a variety of β-silylated keto esters with excellent synthetic potential. Further studies to use these silylated ketoesters for generation of skeletal and stereochemical diverse products are currently under active investigation.

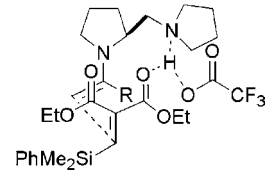


Figure 2. Potential transition state.

Supporting Information Available: Typical experimental procedure, full characterization data, and copies of ^1H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) Reaction of diethyl 4-fluorobenzylidene malonate with methyl ethyl ketone in the presence of catalyst **6c** and TFA in NMP at 28 °C gave a ~3:2 mixture of regioisomers with Me end addition product as the major. See the Supporting Information for details.

(37) Enantiomeric excess of **8** was found to be 90% by HPLC analysis.

(38) Hydrolysis of β-silyl esters do not epimerize the β-C center. See ref 3.