ORGANIC LETTERS

2002
Vol. 4, No. 17
2933−2936

Enantioselective Conjugate Addition of Silylketene Acetals to β-Enamidomalonates. Synthesis of β-Amino Acid Derivatives

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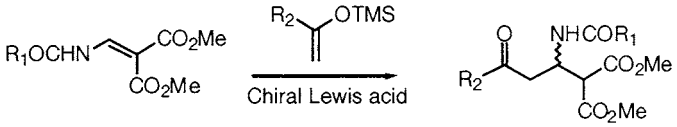
Received June 10, 2002

ABSTRACT



Conjugate addition of silylketene acetals or enolsilanes to enamidomalonates proceeds with excellent chemical efficiency and good selectivity using $Cu(OTf)_2$ and a chiral bisoxazoline. The effect of the Lewis acid, ligand, the *N*-acyl substituent, and the nucleophile on yield and selectivity for the addition product have been evaluated.

New protocols for enantioselective conjugate addition continue to attract interest.[1] In this context, several recent reports have underscored the utility of malonate-type acceptors in these reactions. These systems not only provide a new structural motif for acceptors but also show enhanced reactivity toward nucleophiles. The addition of chiral ionic nucleophiles to malonates has been reported by Beak[2] and Alexakis.[3] Evans and co-workers reported a highly selective addition of neutral silyl ketene acetals to alkylidene and arylidene malonates using catalytic amounts of chiral Lewis acids.[4] Additionally, Jørgensen has shown that indoles add conjugatively to malonates using chiral Lewis acids.[5] The use of proline as a catalyst in the addition of ketones to alkylidene malonates has also been demonstrated.[6] The addition of silyl ketene acetals to enamido methylene-oxobutanoate has been reported by Saito and co-workers.[7] A single example of silyl ketene acetal addition to enamidomalonates in a racemic fashion was also reported in Saito's work. We have recently shown[8] that chiral ionic nucleophiles add to enamido malonates with high selectivity, thus providing a new route for accessing β-amino acid derivatives.[9] Analogously, addition of neutral nucleophiles to enamidoma-

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(4) (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134. Also see: (b) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865. (c) Evans, D. A.; Scheidt, K. A.; Johnston, J. S.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (d) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (e) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

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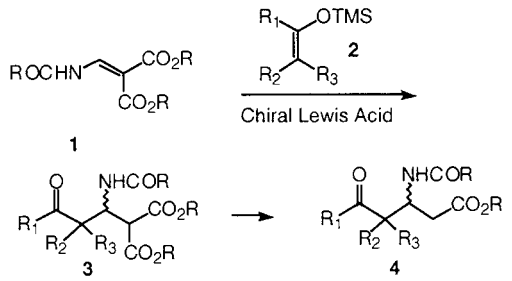
(7) Saito, S.; Uedo, E.; Kato, Y.; Murakami, Y.; Ishikawa, T. *Synlett* **1996**, 1103. For Diels−Alder reactions with ketene acetals and enamido substrates, see: Nishiuchi, M.; Honda, K.; Nakai, T. *Chem. Lett.* **1996**, 321. Ray, C. A.; Wallace, T. W.; Ward, R. A. *Tetrahedron Lett.* **2000**, *41*, 3501.

(8) Sibi, M. P.; Asano, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9708.

(9) For synthesis and biology of β-amino acids, see: *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. For a review, see: Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.

10.1021/ol026333d CCC: $22.00
Published on Web 08/02/2002

Scheme 1



lonates using chiral Lewis acids provides access to β-amino acid derivatives in an enantioenriched form and also information on the nature of the coordination between the substrate and the Lewis acid. Results from these studies are reported here (Scheme 1).

The β-heteroatom substituent in the malonate **1** raises several issues with regard to the conjugate addition. (1) Will neutral nucleophiles add effectively (**1** to **3**)? (2) Could these reactions be carried out using a catalytic amount of a chiral Lewis acid, and what will be the level of selectivity? (3) What will be the nature of the coordination between the amide and the Lewis acid, or will the Lewis acid preferentially coordinate to the 1,3-dicarbonyl unit of the malonate? (4) Can the product amino acid **4** be obtained easily from **3** by Krapcho decarboxylation?[10]

Our work began with the addition of the *O,S*-ketene silyl acetal **6** to the malonate **5** under the reaction conditions previously reported by Evans and co-workers (Scheme 2,

Scheme 2

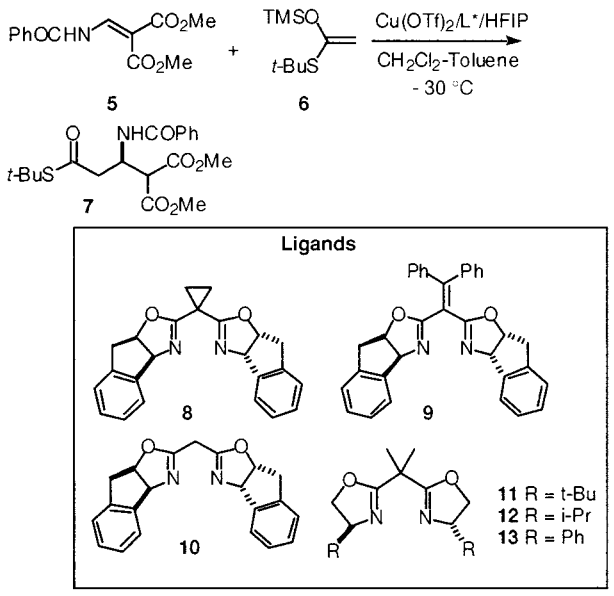


Table 1).[11] The methyl ester was chosen as the substrate based on the ease of its preparation as well as the literature precedent from the Evans group.[4,11] Initial reaction optimization was carried out by varying the amounts of the Lewis acid $Cu(OTf)_2$, the nucleophile, and hexafluoro 2-propanol (HFIP)[12] using ligand **8** as the chiral source.[13] Adding excess **6** using 10 mol % chiral Lewis acid at −78 °C to the substrate **5** and warming the reaction to room temperature gave the conjugate addition product **7** in high yield and 80% ee (entry 1). This illustrates that conjugate addition of neutral nucleophiles to enamidomalonates can be carried out with good selectivity using catalytic amounts of a chiral Lewis acid. Performing the reaction at −30 °C for a longer time led to an improvement in selectivity with as high as 89% ee (entry 2). Omission of HFIP as an additive had a negative impact on both yield and selectivity (entry 3), although in contrast to Evans' results, the HFIP is not absolutely necessary for turnover. It may be that in the absence of HFIP, the enamide may function as a proton source. Other variations in reaction conditions did not lead to an improvement in selectivity (entries 4 and 5). A series of ligands were evaluated next under the optimal conditions (see entry 2). In comparison to the cyclopropyl-substituted ligand **8**, two other ligands with variation in the substitution at the methylene bridge (dibenzylidene (**9**) or dihydrogen (**10**)) showed moderate selectivity in the conjugate addition (compare entry 2 with 6 and 7). Three other bisoxazolines **11**−**13** were also tested. Evans and co-workers have previously shown that *tert*-butyl box ligand **11** in combination with copper Lewis acids is very effective in conjugate addition to malonates (>95% ee).[11] In contrast, ligand **11** was only marginally effective in conjugate addition to **5** (entry 8). Ligands **12** and **13** were less efficient than **11** in the addition reaction (compare entry 8 with 9 and 10). These

Table 1. Effect of Ligand and Stoichiometry on Conjugate Addition

entry	substrate:Nu:HFIP:LA	ligand	time	yield (%)[a]	ee (%)[b]
1[c]	1:2.2:2:0.1	**8**	5 h	95	80
2	1:2.2:2:0.1	**8**	20 h	96	89
3	1:2.2:0:0.1	**8**	20 h	51	78
4[d]	1:2.2:2:0.1	**8**	55 h	89	72
5	1:2.2:2:0.3	**8**	8 h	95	76
6	1:2.2:2:0.1	**9**	20 h	95	63
7	1:2.2:2:0.1	**10**	20 h	95	68
8	1:2.2:2:0.1	**11**	20 h	87	60
9	1:2.2:2:0.1	**12**	20 h	96	44
10	1:2.2:2:0.1	**13**	20 h	96	32

[a] Isolated yield for column-purified material. [b] Determined by HPLC. [c] Reaction carried out at −78 °C and warmed to room temperature. [d] Reaction at −50 °C.

(10) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephen, W. P. *J. Org. Chem.* **1978**, *43*, 138.

(11) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994.

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(13) For details on experimental procedures and characterization of the compounds prepared in this study, see Supporting Information.

studies clearly established that a combination of $Cu(OTf)_2$ and ligand **8** can provide excellent chemical yield and high selectivity in neutral nucleophile addition to enamidomalonates.

A brief study on the effect of Lewis acid on the conjugate addition was undertaken (Table 2) under the reaction

Table 2. Effect of Lewis Acid on Conjugate Addition

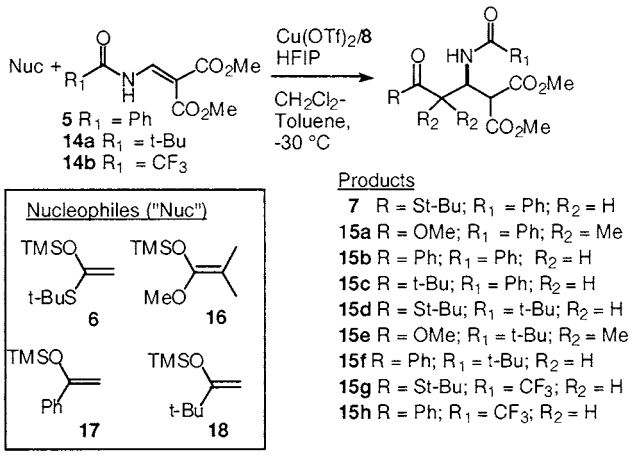
entry	Lewis acid (0.1 equiv)	time	yield (%)[a]	ee %[b]
1	$Cu(OTf)_2$	20 h	96	89
2	$Cu(SbF_6)_2$	12 h	95	63
3	$Zn(OTf)_2$	48 h	30	32
4	$Mg(OTf)_2$	48 h	21	36
5	$Mg(ClO_4)_2$	48 h	28	5

[a] Isolated yield for column-purified material. [b] Determined by HPLC.

conditions established for $Cu(OTf)_2$. Changing the triflate counterion to a more ionic antimony hexafluoride led to improvements in reactivity with a concomitant decrease in selectivity (compare entry 1 with 2). Magnesium and zinc Lewis acids were not very effective in the conjugate additions (entries 3−5).

Having established that the conjugate addition to enamidomalonates was feasible, we then set out to evaluate the scope of the reaction with respect to the nucleophile and the effect of the *N*-acyl substituent on the reaction (Scheme 3, Table 3).

Scheme 3



In comparison to the *O*,*S*-ketene silyl acetal **6** (entry 1), reaction with the *O*,*O*-ketene silyl acetal **16** (entry 2) was less selective under the optimized conditions for conjugate addition. Similar enhancement in selectivity with *O*,*S*-ketene silyl acetal was also observed by Evans and co-workers.[4] Reaction with enolsilyl ether **17** derived from acetophenone gave the addition product **15b** in excellent yield and moderate selectivity (entry 3). In contrast, reaction with pinacolone enolsilyl ether **18** was very slow and required higher

Table 3. Effect of the *N*-Acyl Group and the Nucleophile on Selectivity

entry	R_1	nucleophile	time	yield (%)[a]	ee (%)[b]
1	Ph	**6**	20 h	96	89
2	Ph	**16**	7 h	98	30
3	Ph	**17**	34 h	97	64
4	Ph[c]	**18**	40 h	39	40
5	*t*-Bu	**6**	36 h	97	83
6	*t*-Bu	**16**	12 h	98	16
7	*t*-Bu	**17**	22 h	74	73
8	CF_3	**6**	20 h	74	54
9	CF_3	**17**	20 h	95	67

[a] Isolated yield for column-purified material. [b] Determined by HPLC. [c] Reaction at room temperature.

temperatures and the selectivity was only modest (entry 4). These results suggest that a variety of nucleophiles can be used for the conjugate addition with variable selectivity and good chemical efficiency. Of the four different nucleophiles, the *O*,*S*-ketene silyl acetal gave the highest level of selectivity in these reactions. These results are consistent with the observations of Evans and co-workers on nucleophile addition to arylidene malonates.[14]

The effect of the *N*-acyl group on selectivity in the conjugate addition was also examined (Table 3). The *N*-pivaloyl group was equally effective as the *N*-benzoyl group in conjugate addition affording similar selectivity and efficiency (compare entry 1 with 5). The selectivity for the addition of the silylketene acetal **16** was low irrespective of the protecting group (compare entry 2 with 6). The enolsilyl ether **17** showed good reactivity and selectivity in the addition reaction (entry 7). Reactions with the electron-withdrawing *N*-acyl group, the trifluoroacetamide **14b**, were carried out. Addition of the thioketene acetal **6** under the standard conditions gave product **15g** in good yield and reduced selectivity. As was the case with other *N*-acyl groups, addition of **17** to **14b** was very successful and selectivity was good (entry 9). Thus, of the three *N*-acyl groups evaluated, the benzoyl and pivaloyl groups were equally effective with respect to yield and selectivity.

The absolute stereochemistry for one of the conjugate addition products was established by converting **7** to a known compound (Scheme 4). Compound **7** was decarboxylated under Krapcho conditions[10] to provide a desymmetrized glutarate. This established that the conjugate addition product could be converted to the β-amino acid derivative uneventfully. Selective hydrolysis of the thioester to the corresponding acid **19** was carried out using bromine.[15] Monodecarboxylation of the acid ester **19** using Barton protocol[16]

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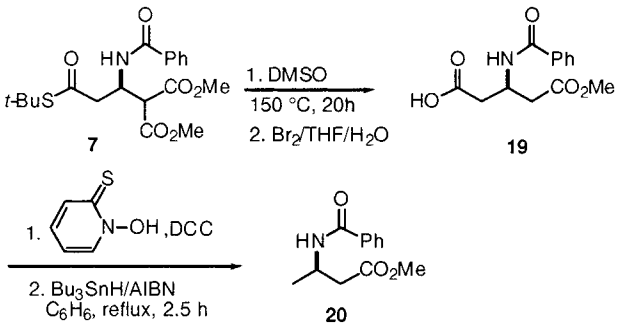
(16) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.

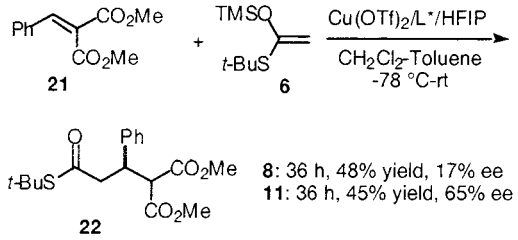
Scheme 4



furnished the known (*R*)-methyl 3-(benzoylamino)butanoate **20**.[17] It should be noted that the radical intermediate in the decarboxylation step is amenable for functionalization such as labeling (deuterium or tritium) and reactions with allylstannane or other radical acceptors.[18]

In an effort to arrive at a stereochemical model for the observed selectivity in the conjugate addition to **5**, two control experiments were carried out (Scheme 5). The level

Scheme 5



of enantioselectivity and the sense of stereoinduction for the conjugate addition product from **21** and **6** using $Cu(OTf)_2$ and ligands **8** or **11** were determined. The reaction using ligand **8** was nonselective affording **22** in 17% ee. This is in contrast to 89% ee observed for the reaction with **5** using the same chiral Lewis acid. The reaction of **21** and **6** with the chiral Lewis acid derived from $Cu(OTf)_2$/**11** gave a higher selectivity, and the sense of stereoinduction in the two experiments was the same.

A working model for the conjugate addition to **5** is presented in Figure 1. On the basis of the crystal structure

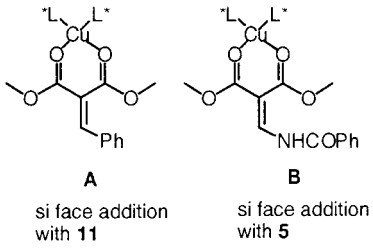


Figure 1.

and product stereochemistry, Evans and co-workers have proposed a model (structure **A**) for ketene acetal addition to arylidene malonates. The absolute stereochemistry for **7** (Scheme 4) is consistent with malonate **5** also undergoing a *si*-face addition. This suggests a similar coordination geometry for the ternary complex between **5** + $Cu(OTf)_2$ + **8** (structure **B**). The large variation in selectivity in addition to **5** and **21** using ligand **8** may indicate alternate coordination geometries (chelation involving the amide functional group resulting in either six or an eight-membered ring). With the limited amount of data at hand, it is not possible to definitively state which of these speculative models (**B** or others) are operative in the conjugate additions. Experiments are underway to gain a better understanding of the coordination in these systems and to further extend the addition chemistry to the preparation of more complex amino acids.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-9983680).

Supporting Information Available: Characterization data for compounds **5**−**22** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026333D

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