Enantioselective Conjugate Addition of Organomagnesium Amides to Enamidomalonates: Synthesis of Either Enantiomer of β-Amino Acid Derivatives

Mukund P. Sibi* and Yasutomi Asano

Department of Chemistry
North Dakota State University
Fargo, North Dakota 58105-5516

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Development of new methods for the synthesis of β-amino acids in enantiomerically pure form continues to attract interest.[1] Recently, we[2] and others[3] have shown that nitrogen nucleophiles add with high enantioselectivity to enoates to provide access to β-amino acid derivatives in a straightforward manner. However, there are drawbacks to this process: (1) the variation in the nucleophile is generally limited to hydroxylamines and azides, (2) addition to aryl-substituted enoates is generally inefficient, and (3) 1,2-addition to the starting material or the product by the amine nucleophile sometimes interferes.

An alternate and potentially a more general method is shown in Scheme 1. The process involves the conjugate addition of readily available carbon nucleophiles to a substrate in which the nitrogen is pre-installed, as in the enamidomalonates **1**. It was hypothesized that addition of an organometallic reagent to **1** would produce the amino acid derivative **2**, which after decarboxylation under Krapcho conditions,[4] would provide the β-amino acid esters **3**. The substrate choice was attractive for several reasons (1) a doubly activated substrate for efficient conjugate addition, (2) no *E*,*Z*-isomers, and (3) an electron-withdrawing acyl group on the nitrogen for increased reactivity in conjugate addition. In principle, introduction of asymmetry in the conversion of **1** to **2** could require either the acceptor or the nucleophile to be chiral or both. The addition of chiral nucleophiles to **1** in good chemical efficiency as well as enantioselectivity is detailed in this work.[5] Additionally, a convenient and interesting way to control the absolute stereochemistry of **2** is also presented.

Our experiments began with the establishment of reaction conditions for the conversion **1** to **2**. Grignard reagents were chosen as the nucleophile. Addition of 1.1 equiv of EtMgCl to the trifluoroacetamide derivative **4**[6] at −78 °C furnished the conjugate addition product **6a** in 46% yield (entry 1, Table 1).[7] This indicated that deprotonation was competitive with addition.

Scheme 1

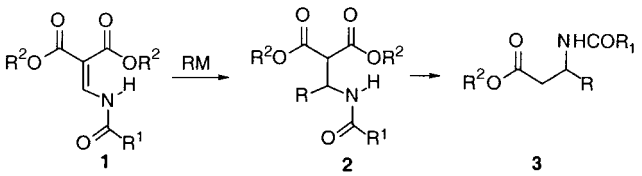
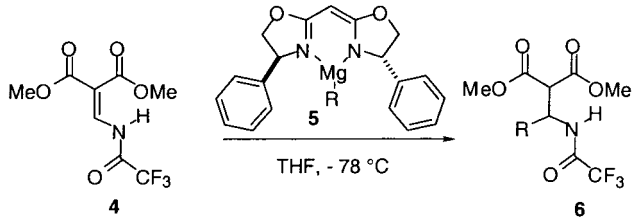


Table 1. Reaction Conditions for Addition to **4**[a]



entry	conditions	product	% yield	% ee
1	1.1 equiv EtMgCl	**6a** R = Et	46	−
2	2.1 equiv EtMgCl	**6a** R = Et	91	−
3	**5** R = Et, 2.2 equiv	**6a** R = Et	76	79
4	**4**, LiH, then add 1.1 equiv **5** R = Et	**6a** R = Et	86	83
5	**5** R = *i*-Pr, then 1.1 equiv EtMgCl	**6a** R = Et	22	28
		6b R = ^{i}Pr	62	78
6	**4**, LiH, **5** R=Br, then 1.1 equiv EtMgCl	**6a** R = Et	39	22
7	**4**, LiH, **5** R=Br, then 1.3 equiv **5** R = Et	**6a** R = Et	39	86
8	**4**, LiH, Ent **5** R=Br, then 1.3 equiv **5** R = Et	**6a** R = Et	34	89
9	**4**, LiH, add MgI_2, then 1.3 equiv **5** R = Et	**6a** R = Et	79	78

[a] For experimental details see Supporting Information.

Increasing the amount of EtMgCl to 2.1 equiv, gave a high yield of **6a** (entry 2). Recently, Nakamura has shown that σ-bound zinc reagents derived from bisoxazolines are good chiral nucleophiles.[8] The chiral organomagnesium amide **5** was prepared similarly by the treatment of 4,4′-diphenyldihydrobisoxazoline with 1 equiv of *n*-BuLi followed by the addition of the Grignard reagent.[9] Addition of **4** to 2.1 equiv of **5** gave **6a** in excellent chemical yield and high selectivity (79% ee, entry 3). This established that the conjugate addition indeed proceeds enantioselectively using chiral organomagnesium amides. The next experiment was designed to explore the necessity for a chiral nucleophile. Addition of 1 equiv of LiH to **4** generated the corresponding lithium salt to which **5** (R = Et) was added. The high enantioselectivity in this experiment suggests that the chiral donor is important (entry 4) and that only a stoichiometric amount of the chiral ligand is needed. The need for a chiral acceptor was investigated next. Compound **4** was treated with 1.1 equiv of **5** (R = *i*Pr) followed by another 1.1 equiv of EtMgCl (entry 5). The ee for **6a** in entry 5 is much lower than in entry 4, suggesting that the chiral nucleophile is the primary determinant of product stereochemistry. The formation of **6b** implied that deprotonation is marginally competitive with conjugate addition. A more unambiguous experiment to ascertain the role of chiral acceptor is shown in

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(6) See Supporting Information for the synthesis of **4** and other details.

(7) The choice of the methyl group for an ester substituent and the trifluoroacetyl group for nitrogen protection was based on ease of preparation. The benzamide analogue reacted similarly (entry 3, Table 1) with 85% yield and 79% ee. A full account will discuss the effect of variations of these groups on chemical as well as selectivity efficiency.

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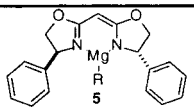
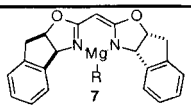
Table 2. Conjugate Addition of Different Nucleophiles to **4**[a]

			 5	 7
			Li Salt	Mg Salt	Mg Salt
Entry	Comp.	R	%yield (%ee)	%yield (%ee)	%yield (%ee)
1	**6 a**	Et	86 (83)	79 (78)	65 (-78)
2	**6 b**	*i*-Pr	78 (86)	72 (83)	62 (-80)
3	**6 c**	*n*-Bu	94 (81)	72 (81)	65 (-70)
4	**6 d**	$-(CH_2)_{17}CH_3$	85 (87)	71 (83)	68 (-70)
5	**6 e**	Cyclohexyl	82 (94)	69 (93)	64 (-74)
6	**6 f**	Vinyl	80 (82)	65 (86)	58 (-59)
7	**6 g**	Phenyl	88 (71)	70 (81)	65 (-56)

[a] For experimental details see Supporting Information.

entry 6. Formation of a magnesium diamide by treatment of **4-Li** with **5** (R = Br) followed by the addition of EtMgCl gave **6a** in low yield and ee (entry 6), suggesting that a chiral nucleophile is required for high selectivity. Further corroboration for this requirement is shown in entry 7, where addition of **5** (R = Et) to a chiral acceptor gave high selectivity for **6a**. The next experiment used enantiomeric **5** (R = Br) to prepare the chiral acceptor and addition of **5** (R = Et) (entry 8). The sense of stereoinduction for **6a** suggests that the chirality in the nucleophile controls the stereochemical outcome. The last control experiment involved conjugate addition to the N−Mg salt of **4**. Treatment of **4** with LiH followed by addition of MgI_2 gave the N−Mg salt (entry 9). Addition of **5** (R = Et) furnished **6a** with similar levels of selectivity as the Li salt (compare entry 4 with 9). It should be noted that the ligand could be recovered (∼80%) after the experiment. Compound **6** (R = Et) could be monodecarboxylated[4] to the corresponding amino acid ester uneventfully (**3**, R = Et, $R_1 = CF_3$, R_2 = Me).[6]

Having established that conjugate addition of chiral donors to **4** is feasible, we then undertook a brief study on the variation of its structure as well as the chiral ligand. Results from these experiments are tabulated in Table 2. Addition of a variety of nucleophiles derived from **5** to **4** either using the Li or Mg salt gave products **6a**−**g** in very good yield and selectivity (entries 1−7). There was very little variation in the yield or selectivity using the two methods. Examination of Table 2 indicates that alkyl, vinyl, and aryl nucleophiles are all compatible in this method.

We have shown previously[10] that bisoxazolines prepared from aminoindanol and phenylglycinol possessing the same sense of stereochemistry provide enantiomeric products in conjugate radical additions. On the basis of this precedence, we evaluated nucleophiles **7** in conjugate addition reactions to **4**. In contrast to reactions with **5**, conjugate addition using **7** (R = Et) was not very efficient (1.3 equiv 15% yield, 68% ee; 2.1 equiv, 35% yield, 63% ee). Addition of **7** (R = Et) to **4-Li** was also not possible. However, **7** added with good efficiency to the corresponding Mg salt (**4-MgI**). These results are also shown in Table 2. In general, the chemical yield as well as selectivity for **6a**−**g** in reactions with **7** were slightly lower than using **5**. *The most interesting outcome from reactions with* ***7*** *was that products* ***6a***−***g*** *had the opposite configuration as compared to reactions with* ***5***. Thus enantiomeric series of products are available with a simple change of the chiral ligand.

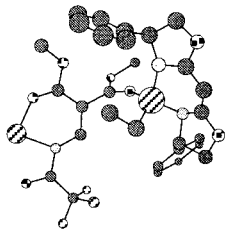


Figure 1.

A working model for the sense of stereoinduction is presented in Figure 1. The absolute stereochemistry for **6a** (entry 3, Table 1) was determined to be *R* by converting it to a known compound.[11] The control experiments suggest that deprotonation is not required and thus the chiral nucleophile[12] is the stereodetermining factor. Coordination of the ester carbonyl to the magnesium allows for alkyl transfer through a six-membered transition state (Figure 1). However, the inversion of stereochemistry with **7** is not easily rationalized using this model.

In conclusion, a general methodology for the preparation of *β*-amino acid esters has been developed. Experiments to gain a better understanding of the structure for the reactive complex, development of catalytic variants, and evaluation of copper and zinc nucleophiles in conjugate additions are underway.

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Supporting Information Available: Characterization data for compounds **3**−**6** and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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