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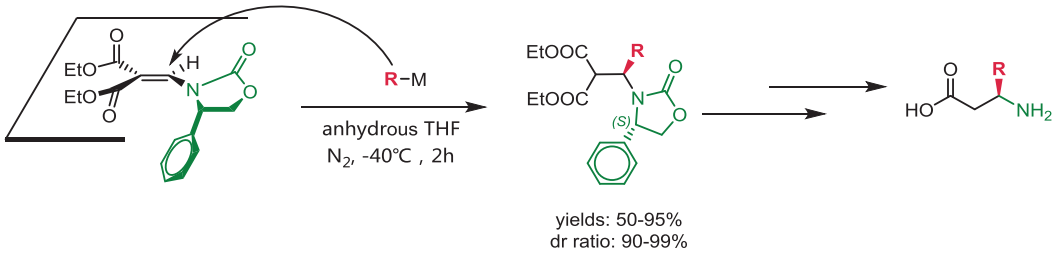
Substrate-controlled Diastereoselective Michael Addition of Alkylidene Malonates by Grignard Reagents



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Abstract: Herein is described a diastereoselective Michael addition of Grignard reagents to α, β- unsaturated diethyl malonates incorporated with a 2-oxazolidone chiral auxiliary. The catalyst-free Michael addition proceeds with good chemical efficiency and excellent stereoselectivity; and it provides new thoughts to the asymmetric synthesis of β-substituted β^3 amino acid derivatives.

Optically active β-amino acid derivatives are commonly found in various biologically active compounds from natural sources and organic synthesis.[1, 2] They have been also widely adopted as building blocks for the construction of α/β-peptide foldamers which can mimic biological function of natural α-peptide of enzymes, and are less susceptible to protease degradation than the latter ones.[3-7] Therefore, the development of synthetic procedures to prepare β-amino acids is a relevant endeavor. The synthesis of β-amino acids in enantiomerically pure forms continues to attract interest.[8-14]

The chirality conformation of β-amino acids is generally originated from chiral starting materials, chiral auxiliaries or chiral catalysts. Many approaches were developed for the preparation of substituted β-amino acids, such as hydrogenation of enamines catalyzed by rhodium or palladium with chiral phosphepine ligands[15, 16], addition of aromatic amines to α-β unsaturated imides catalyzed by palladium complex[17], thiourea catalyzed asymmetric Mannich reaction[18] and chiral amine catalysed aza-Michael addition[19-22]. Although various methods for the synthesis of substituted β-amino acids have been developed with good yield and stereoselectivity, arduous availability of chiral catalysts is still an unavoidable obstacle for the wide use of these methods. Thus, it is still desirable to develop novel catalyst-free strategies to construct these privileged skeletons.

The use of chiral auxiliaries is another important strategy to synthesize of β-amino acids. In this context, Goodman *et al.* reported pseudoephedrine as a chiral auxiliary for the synthesis of α-substituted β-amino acids[23]. Juaristi *et al.* accomplished diastereoselective synthesis of β-amino acids using hexahydrobenzoxazolidinones[3]. These methods provided practical approaches for the synthesis of α-substituted β-amino acids (β^2-amino acids). But for β-substituted β-amino acids (β^3-amino acids), it is still challenging.

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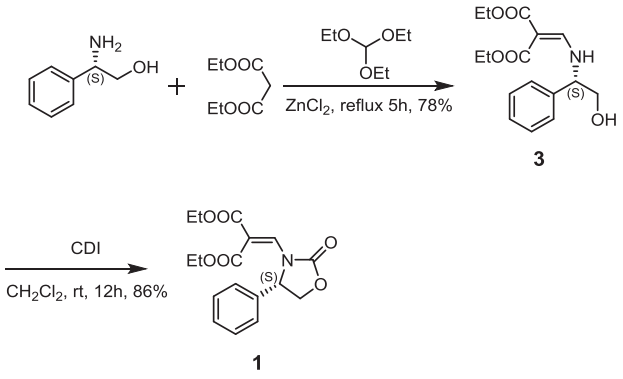
The asymmetric Michael reaction under the control of a chiral ligand is generally regarded as one of the most effective transformations for asymmetric syntheses of β-amino acids. And Evans' chiral auxiliaries are frequently used for enantioselectivity control[24-26]. However, to our best knowledge, the approach for the preparation of β^3-amino acids by asymmetric Michael addition under the control of Evans' chiral auxiliary is unexploited. Herein we reported α, β-unsaturated diethyl malonate incorporated with an oxazolidone chiral auxiliary as diastereoselective Michael addition substrates and their asymmetric adducts by Grignard reagents with up to 98% yield and 99% diastereomeric ratio (d.r.). (Scheme 1).

Although the substrate of this asymmetric Michael addition had never been reported before, we designed a relatively reliable path (Scheme 2) to synthesize it. We commenced the synthesis with starting material (S)-2-phenylglycinol. It was pretreated with ethyl orthoformate at 135-130°C for 2 hours, and then diethyl malonate and zinc chloride were added. The mixture was stirred and refluxed for 5 hours according to the method described in the literature[27]. The obtained compound was then subjected to carbonyldiimidazole for condensation and gave out final product diethyl (S)-2-((2-oxo-4-phenyloxazolidin-3-yl) methylene)malonate with good yield.

Alkylidene malonate is a good Michael addition receptor. We used the Grignard reagent phenyl magnesium bromide, which was an effectively-used nucleophilic

Scheme 1. Proposed substrate-controlled asymmetric Michael addition by organometallic reagents.



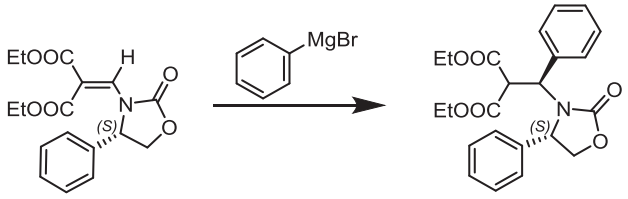
Scheme 2. Preparation of the substrate.

reagent at attacking groups, to search for optimal reaction condition. The chiral oxazolidinone, substituted at the C-5 position with a phenyl group (stereo: S), was proposed to induce the direction of the bulky Grignard nucleophiles through steric hindrance. Grignard reagent PhMgBr was prepared *in situ* with PhBr and Mg in anhydrous tetrahydrofuran, using iodine as the initiator of the reaction. 2 equivalents of freshly prepared PhMgBr was added dropwise to the anhydrous tetrahydrofuran solution of the substrate under an inert (N_2) atmosphere at –40°C. The reaction was stirred at the temperature for another 2 hours and monitored with thin layer chromatography (TLC). The reaction produced a new compound (yields 61%) which was validated as the adduct of the supposed Michael addition with NMR and HR-MS (Supplementary data). Compared with products of the same R_f value on TLC plate at different temperatures (0°C and reflux), the diastereomeric ratio (d.r.) of the product at –40°C was 97:3, as determined with NMR[28]. Though the accurate absolute configuration of the excessive isoform is unclear for the moment, we carried on to optimize the reaction condition.

Adding orders of the substrate and the Grignard reagent was first to be explored. In the reverse order compared with the initial attempt, precooled substrate alkylidene malonate was added dropwise into freshly prepared PhMgBr. It gave a higher yield of the product (81%, entry **2** in Table 1), without a change in d.r. value. The difference of the reaction yields in different adding orders of the two reactants was probably due to possible contact of freshly prepared Grignard reagent with air during the transition. Alkylidene malonate solution directly added dropwise into THF solution of *in situ* prepared Grignard reagent reduced the risk of air invasion. Then we investigated different reacting conditions to explore the optimal solvent, reaction temperature, reacting time and equivalence. The data of yields and d.r. values is shown in Table 1.

When screening for solvents, it was found that solvents dramatically affected the outcome of the reaction (entries **2**-**5**, Table 1). Results of solvent screening revealed that tetrahydrofuran was the best choice of reaction medium to promote the transformation in modest diastereoselectivity, whereas other solvents, such as ether, toluene and dichloromethane (entries **3**-**5**, Table 1), offered no better results than tetrahydrofuran, neither yields nor diastereomeric ratio of products. As expected, reaction temperature affected not only regioselectivity but also stereoselectivity. Higher temperatures resulted in lower yields of the products. But only when the reaction was carried out at room temperature or above, the d.r. of adducts began to decrease. Next, we investigated the reaction time and reactant ratio. Extension of reacting time or

Table 1 Screening of reaction conditions.



1 4

Entry	Solvent[a]	Temperature °C	Equivalence[b]	Time h	Adding order[d]	Yield[c] %	d.r.[e] S:R[f]
1	THF	−40	1:2.0	2	A	68	97:3
2	THF	−40	1:2.0	2	B	81	97:3
3	Et_2O	−40	1:2.0	2	B	72	97:3
4	toluene	−40	1:2.0	2	B	13	97:3
5	DCM	−40	1:2.0	2	B	66	97:3
6	THF	−20	1:2.0	2	B	68	96:4
7	THF	0	1:2.0	2	B	66	96:4
8	THF	rt	1:2.0	2	B	66	96:4
9	THF	60	1:2.0	2	B	44	87:13
10	THF	−40	1:2.0	1	B	63	97:3
11	THF	−40	1:2.0	4	B	78	97:3
12	THF	−40	1:2.0	8	B	80	97:3
13	THF	−40	1:1.2	2	B	65	97:3
14	THF	−40	1:3.0	2	B	79	97:3
15	THF	−40	1:4.0	2	B	80	97:3

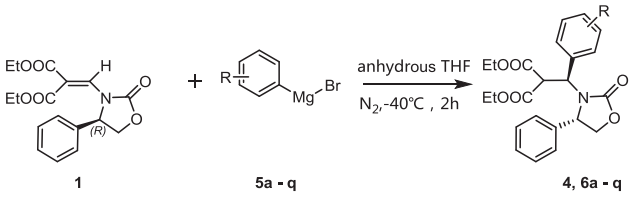
[a] Fresh anhydrous solvent. [b] Equivalence of phenylmagnesium bromide. [c] Isolated yields. [d] Adding order: A, alkylidene malonate into PhMgBr; B, PhMgBr into substrate. [e] d.r.: diastereomeric ratio were determined using ^{1}H NMR. [f] S:R: stereo configuration of the newly formed chiral center.

increased ratio of the Grignard regent retained the excellent diastereoselectivity and improved yields slightly, albeit longer time needed. Therefore, we discovered the proper condition for the asymmetric Michael addition: anhydrous THF solution of substrate alkylidene malonate added dropwise to 2 equivalents of Grignard reagent THF solution at −40°C under N_2 protection for 2 hours offered the best yield and diastereomeric ratio.

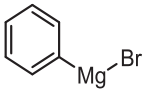
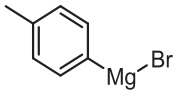
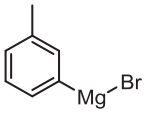
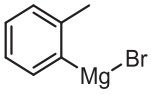
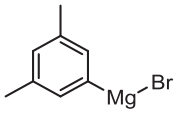
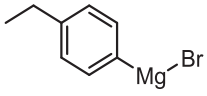
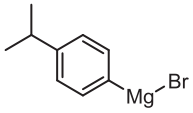
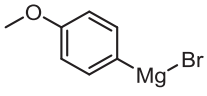
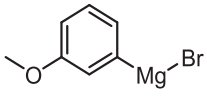
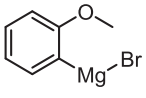
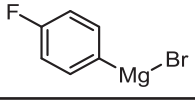
Having established that the Evans' chiral auxiliary incorporated alkylidene malonate could be π-facial preferentially attacked by PhMgBr, we then moved on to explore the scope of the reaction with respect to other Grignard reagents. The results were summarized in Table 2. As shown in the table, the yields were mainly affected, but not the diastereomeric ratio of reactions with differentially-substituted PhMgBr. Compared with PhMgBr, alkyl substitutions on the phenyl group in different positions, prepared *in situ*, decreased yields of adducts, these substitutions including single methyl (**6a**, 4-Me 74%; **6b**, 3-Me 70%; **6c**, 2-Me 60%), double methyl (**6d**, 3,5-dimethyl 66%), ethyl (**6e**, 4-Et 70%) or isopropyl (**6f**, 4-iPr 66%). Methoxy group substituted PhMgBr also resulted in slightly lower yield (**6g**-**i**, 54-61%). Some other Grignard reagents with electron-withdrawing group substitutions were favored in the reaction (**6j**, 4-F 92%; **6k**, 3-F 87%; **6l**, 3-CF_3 78%; **6m**, 4-Cl 87%; **6n**, 3-Cl 84%). The variation of reaction yield was possibly due to stability of Grignard reagents: electron-withdrawing substitutions that reduced the electron density in aromatic ring of the nucleophiles resulted in stable Grignard reagents which led to high yields of products.

Considering the results obtained, this methodology was a very convenient method for preparing adducts of alkyl magnesium bromide. But both yield and stereoselectivity were affected when alkyl magnesium bromides were used as nucleophilic reagents. Although

Table 2 Effect of different substitutents on phenyl ring of Grignard reagents to the reaction

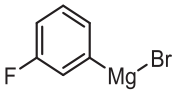
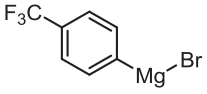
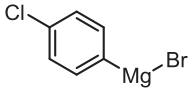
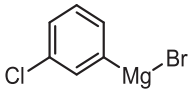
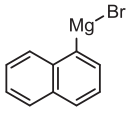
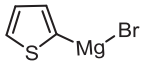


1 5a - q 4, 6a - q

Entry	Compound No. of adducts	Grignard reagents	Yield[a] %	d.r.[b] S:R[c]
1	**4**		81	97:3
2	**6a**		74	97:3
3	**6b**		70	97:3
4	**6c**		60	97:3
5	**6d**		66	97:3
6	**6e**		70	97:3
7	**6f**		66	96:4
8	**6g**		61	97:3
9	**6h**		57	98:2
10	**6i**		54	97:3
11	**6j**		92	97:3

(*Continued*)

Table 2 Continued

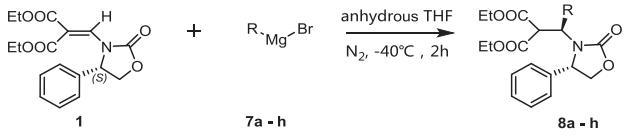
Entry	Compound No. of adducts	Grignard reagents	Yield[a] %	d.r.[b] S:R[c]
12	**6k**		87	97:3
13	**6l**		78	97:3
14	**6m**		87	97:3
15	**6n**		84	97:3
16	**6o**		63	98:2
17	**6p**		72	99:1

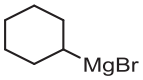
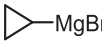
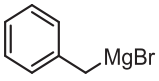
[a] Isolated yields. [b] d.r.: diastereomeric ratio were determined using ^{1}H NMR. [c] S:R: stereo configuration of the newly formed chiral center.

some alkyl Grignard reagents were less easily prepared, adducts in the reaction (Table 3), such as **8a** and **8b** with less stereohindered alkyl groups, were more meaningful. From the results shown in Table 3, methyl (**8a**), ethyl (**8b**), isopropyl(**8c**) and *n*-butyl (**8d**) Grignard reagents were tolerated in the reaction, but with lower yields and diastereomeric ratios. Other alkyl groups, such as cyclohexyl (**8e**), cyclopropyl (**8f**), prop-1-en-2-yl (**8g**) and benzyl (**8h**) also could be easily introduced in the substrate with acceptable yields and diastereomeric ratios, which indicated that a variety of alkyl Grignard reagents could function well in the reaction. Stereohindered alkyl groups and isopropyl Grignard reagents were favored in the reaction, which gave out higher yield and stereoselectivity.

Besides Grignard reagents, organolithium agents and organozinc reagents were also probed in the reaction. When using phenyllithium to replace phenylmagnesium bromide, the same adduct **4** was obtained with a yield of 19% and a d.r. of 97:3. But other organolithiums like methyllithium and *n*-butyllithium only afforded trace desired products, even at lower temperature (–80°C) or higher equivalence of organolithiums (4:1). Also, neither did organozinc reagents diethylzinc nor allylzinc bromide

Table 3 Different alkyl Grignard reagents tolerated in the reaction



Entry	Compound No. of adducts	Grignard reagents	Yield[a] %	d.r.[b] S:R[c]
1	**8a**	MeMgBr	58	86:14
2	**8b**	EtMgBr	56	80:20
3	**8c**		53	76:24
4	**8d**	*n*-Bu—MgBr	60	85:15
5	**8e**		75	81:19
6	**8f**		74	86:14
7	**8g**		79	97:3
8	**8h**		52	88:12

[a] Isolated yields. [b] d.r.: diastereomeric ratio were determined using ^{1}H NMR. [f] S:R: stereo configuration of the newly formed chiral center.

function. The most by-products obtained were identified as products of 1,2-Michael addition, which was possibly because organolithium and organozinc reagents were too nucleophilic to afford thermodynamic adducts.

Induced by Evans' chiral auxiliary (stereo: S), a new stereo center was formed in the reaction. We determined the configuration of the stereo center via X-ray crystallography of compound **6m** (Figure 1). We were intrigued to find that the new stereo center formed in the reaction was determined as S.

To rationalize our observation, we carried out calculations with Spartan Model and found that in the most favorable conformation of the substrate (compound **1**), the 2-oxazolidone cycle was not on the geometrical plane composed by double bonds of the alkene and one of carbonyl group of diesters as we imagined. Possibly due to conformational hinderance, the approximate plane of 2-oxazolidone cycle preferred a dihedral angle of 35-75 degree, and the phenyl ring attached to the β carbon atom could shield the bottom face in a synergistic manner. This left a space at the back for the attacking nucleophilic groups, resulting in high diastereoselectivity. The most favorable conformation of the substrate opted to be similar to conformation $\boldsymbol{E_1}$ other than conformation $\boldsymbol{E_2}$ (Scheme 3), with an energy gap of 39.9 kJ/mol (WaveFunction Spartan 14 v1.1.4), although

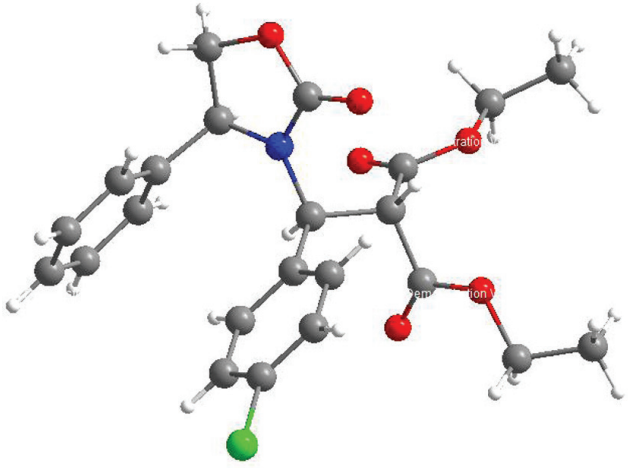
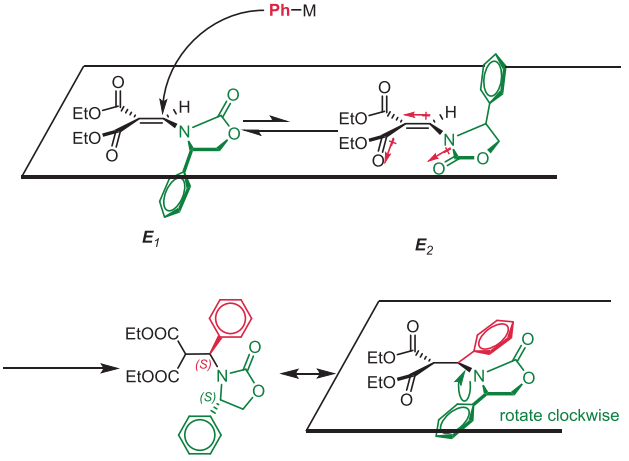


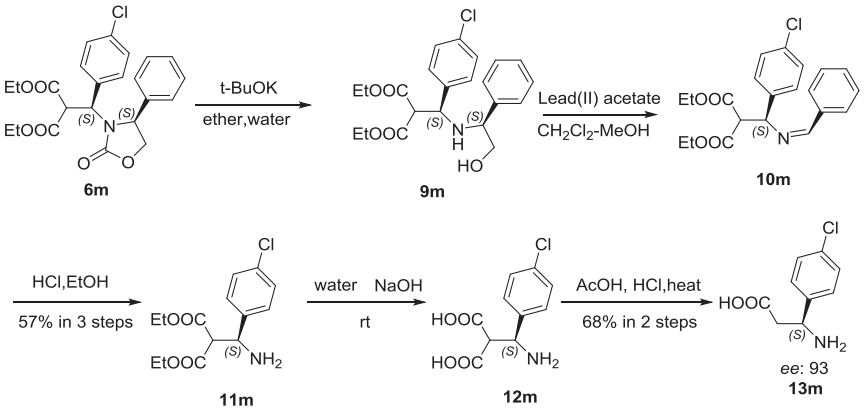
Figure 1. X-ray crystallography of compound **6m** (S,S).



Scheme 3. Possible mechanism of π-facial preference and diastereoselectivity.

in both conformations, the alkene is almost coplanar with the oxazolidinone ring, which allows delocalization of the nitrogen lone pair. $\boldsymbol{E_1}$ is probably favored as a result of the dipole-dipole interaction presented in $\boldsymbol{E_2}$. Consequently, conformation $\boldsymbol{E_1}$ provides the necessary π-facial differentiation for the observed stereochemical outcome. When an attacking nucleophilic group, such as a phenyl group, was added to double bonds of the alkene, substitutents on the newly formed chiral central rotated thermodynamically (Scheme 3) to the orientation exhibited in final actual conformation in the crystallography.

In order to confirm the chirality of newly formed center and to establish a useful synthetic application of the reaction, we developed a synthetic route to transform product compound **6m** to a β-amino acid. The Evans' chiral auxiliary was removed to release the chiral amino group. After hydrolysis of the diester and decarbonylation, a β-phenylalanine was afforded with total yield 38.7% (Scheme 4).



Scheme 4. Synthetic application of the diastereoselective Michael addition.

In conclusion, we described herein a novel diastereoselective Michael addition of α, β-unsaturated diethyl malonate incorporated with a 2-oxazolidone chiral auxiliary attacked by Grignard reagents. This study not only illustrated the potential of enamides as viable chiral templates in organic synthesis, but also provided a solution to synthesize chiral β-amides or amino acids. Further studies on extending this strategy to related α, β-unsaturated carbonyl compounds and nucleophilic donors are currently underway in our laboratory.

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Appendix A. Supplementary data: Supplementary data to this article can be found online.

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