COMMUNICATION

Efficient 1,8- to 1,12-asymmetric induction in Grignard reactions of ω-keto esters by using BINOL or its 2′-oligoether derivatives as the chiral auxiliary

Yasufumi Tamai,*† Tetsutaro Hattori,* Masamitsu Date, Hideki Takayama, Yoshinori Kamikubo, Yuji Minato and Sotaro Miyano

Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8579, Japan

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Efficient diastereoselective alkylation of δ- and ε-keto acids with Grignard reagents was achieved in up to 97% de by conversion into the 2′-[3-(2-methoxyethoxy)propoxy]-(1,1′-binaphthyl)-2-ol esters, while the corresponding alkylation of ζ- to θ-keto acids could effectively be carried out in up to 88% de by simply using BINOL as the chiral auxiliary.

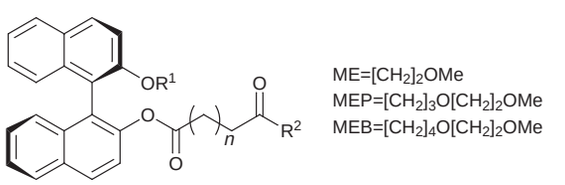
Remote asymmetric induction is a challenging subject in the field of asymmetric synthesis,[1] because it has a potential for shortening the synthetic routes to complex chiral molecules. Although several methodologies to enable highly efficient remote asymmetric induction up to a 1,7-relationship have been developed,[2–4] little is known concerning asymmetric induction beyond a 1,7-relationship.[1,5] Previously, we reported a methodology to realize highly efficient 1,7-asymmetric inductive reduction[3] and Grignard reaction[4] of γ-keto esters. This methodology was based on the idea that the γ-keto esters of (1,1′-binaphthyl)-2-ol having a properly designed oligoether tether as the 2′-substituent (*e.g.* compound **1**) can function as a podand and will construct a stable pseudo-macrocyclic chelate with the aid of an appropriate Lewis acid (*e.g.* complex **21**). Consequently, the orientation of the keto carbonyl group will be fixed and the attack of the nucleophile will occur preferentially from the outside of the pseudo-macrocycle to give high diastereoselectivity. Herein, we report an extension of this methodology to 1,8- to 1,12-asymmetric inductive Grignard reactions of ω-keto esters (Scheme 1).

The Grignard reaction was performed by addition of an ethereal solution of Grignard reagent **15** (1.0 mol dm^{-3}) to a dichloromethane solution of an ω-keto ester **2**–**9** (0.02 mol dm^{-3}) at −78 °C in the presence of $MgBr_2{\cdot}OEt_2$ (3.0 equiv.) until the ω-keto ester had disappeared by monitoring on TLC (silica gel).[4] In the reactions of δ-keto esters **2**–**5**, the initially produced δ-hydroxy esters spontaneously cyclized during usual work-up to afford δ-lactones **16** in good yields after purification by preparative TLC. On the other hand, reactions of the ε- and ζ-keto esters **6**–**9** with Grignard reagent **15a** gave the corresponding diastereomeric ε- and ζ-hydroxy esters. Therefore, to avoid the enrichment of one diastereomer over another during the purification procedure, the hydroxy esters were methylated to diols **17**,**18** before the work-up by addition of another aliquot of the Grignard reagent **15a** to the reaction mixture at −78 °C, followed by allowing the mixture to warm to room temperature. The ees of the isolated products **16**–**18** were determined by chiral GLC or HPLC analyses.‡§

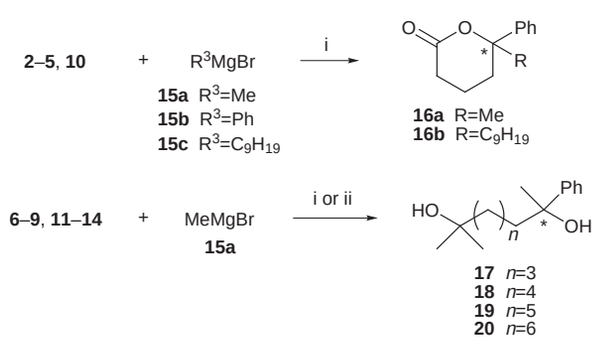
Table 1 lists the results of the Grignard reactions. Treatment of δ-keto esters **2**, **3** and **5** with the methyl Grignard reagent **15a** gave lactone **16a**, the enantiomeric purity of which varied depending on the structure of the 2′-substituent of the chiral auxiliary (entries 1, 2 and 5): ester **3** bearing a 3-(2-methoxyethoxy)propoxy (MEP-O) group gave lactone **16a** with the highest ee (entry 2), while ester **2** bearing a 2-methoxyethoxy (ME-O) group showed lower diastereomeric selectivity and the opposite diastereofacial selectivity compared with the other δ-keto esters (entry 1) in spite of the chiral auxiliary of ester **2** giving the highest de in the corresponding Grignard reaction of γ-keto ester **1**.[4] These results indicate that the optimal chelating group for highly efficient remote asymmetric induction varies with the distance between the keto and ester carbonyl groups. The lactone **16a** was also obtained in the reaction of ω-acetyl ester **4** with the phenyl Grignard reagent **15b** with almost equal diastereoselectivity but opposite diastereofacial selectivity to that obtained from the reaction of the ω-benzoyl ester **3** with

Table 1 Grignard reactions of keto esters **2**–**9**

Entry	Substrate	Nucleophile	Product	Yield (%)	Ee (%) Abs. config.
1	**2**	**15a**	**16a**	73	59 (*S*)-(−)
2	**3**	**15a**	**16a**	80	93 (*R*)-(+)
3	**3**	**15c**	**16b**	82	97 (*R*)-(+)
4	**4**	**15b**	**16a**	70	92 (*S*)-(−)
5	**5**	**15a**	**16a**	79	74 (*R*)-(+)
6	**6**	**15a**	**17**	90	82 (*S*)-(−)
7	**7**	**15a**	**17**	83	41 (*S*)-(−)
8	**8**	**15a**	**18**	89	4
9	**9**	**15a**	**18**	96	7



1 *n*=1, R^1=ME, R^2=Ph
2 *n*=2, R^1=ME, R^2=Ph
3 *n*=2, R^1=MEP, R^2=Ph
4 *n*=2, R^1=MEP, R^2=Me
5 *n*=2, R^1=MEB, R^2=Ph
6 *n*=3, R^1=MEP, R^2=Ph
7 *n*=3, R^1=MEB, R^2=Ph
8 *n*=4, R^1=MEP, R^2=Ph
9 *n*=4, R^1=MEB, R^2=Ph
10 *n*=2, R^1=H, R^2=Ph
11 *n*=3, R^1=H, R^2=Ph
12 *n*=4, R^1=H, R^2=Ph
13 *n*=5, R^1=H, R^2=Ph
14 *n*=6, R^1=H, R^2=Ph



Scheme 1 *Reagents*: i, $MgBr_2{\cdot}Et_2O$ (3.0 equiv.), Et_2O–CH_2Cl_2; ii, Et_2O–CH_2Cl_2.

† Present address: Department of Industrial Chemistry, College of Engineering, Nihon University, Koriyama 963-8642, Japan.

Table 2 Reactions of keto esters **10**–**14** with methylmagnesium bromide **15a**

Entry	Substrate	Additive	Product	Yield (%)	Ee (%) Abs. config.
1	**10**	None	**16a**	75	5
2	**10**	$MgBr_2{\cdot}Et_2O$	**16a**	85	1
3	**11**	None	**17**	92	44 (*R*)-(+)
4	**11**	$MgBr_2{\cdot}Et_2O$	**17**	91	61 (*R*)-(+)
5	**12**	None	**18**	93	74 (*R*)-(+)
6	**12**	$MgBr_2{\cdot}Et_2O$	**18**	92	88 (*R*)-(+)
7	**13**	None	**19**	91	51 (*R*)-(+)
8	**13**	$MgBr_2{\cdot}Et_2O$	**19**	86	85 (*R*)-(+)
9	**14**	None	**20**	89	48 (*R*)-(+)
10	**14**	$MgBr_2{\cdot}Et_2O$	**20**	88	81 (*R*)-(+)

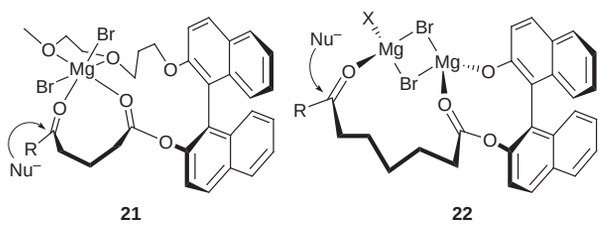


Fig. 1 Schematic views of chelated complexes **21** and **22**.

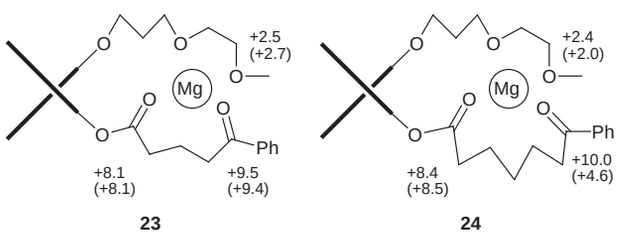


Fig. 2 Downfield shifts in ppm of the ^{13}C signals for esters **3** and **8** upon complexation with $MgBr_2$ (complexes **23** and **24**, respectively). The downfield shifts of the chelates after the addition of 7 vol% of diethyl ether are shown in parentheses.

the methyl Grignard reagent **15a**. This suggests that the orientation of the keto carbonyl group in the chelated complex **21** (Fig. 1) is identical in these two reactions (compare entry 4 with entry 2). Highly efficient asymmetric induction was also achieved in the reaction of ester **3** with the nonyl Grignard reagent **15c** to give lactone **16b**, which is a useful intermediate for the synthesis of the antibiotic malyngolide (entry 3).[6] The Grignard reaction of ε-keto ester **6** bearing a MEP-O chelating group showed a surprisingly high level of diastereoselectivity for a 1,9-asymmetric induction (entry 6). However, the reactions of ζ-keto esters **8**,**9** resulted in low diastereoselectivities even after changing the chelating group from MEP-O to a longer oligoether tether (entries 8 and 9).

To investigate the cause of the serious decrease in diastereoselectivity in the reactions of ζ-keto esters, complexation experiments of the δ- and ζ-keto ester **3** and **8** with an excess of $MgBr_2$ in CD_2Cl_2 were carried out (Fig. 2). The ^{13}C NMR spectra of the $MgBr_2$ chelates of esters **3** and **8** (complexes **23** and **24**, respectively) showed considerable downfield shifts of both carbonyl carbons and the terminal carbon of the oligoether tether. The chemical shift values of the complex **23** were only slightly changed by addition of a 7 vol% of diethyl ether (the amount used in the Grignard reaction). However, complex **24** showed a considerable decrease in the downfield shifts after the same treatment. These observations suggest that the stability of the magnesium chelates in the presence of diethyl ether changes according to the length of the carbon chain of the keto acid component. Therefore, it may be concluded that the more stable the pseudo-macrocyclic complex is, the higher diastereoselectivity will be attained by fixing the orientation of the keto carbonyl group and that the carbon chain of the ζ-keto acid moiety in ester **8** is too long to construct a stable pseudo-macrocyclic chelate with $MgBr_2$.

It occurred to us to use BINOL itself as a chiral auxiliary (Scheme 1).[7] Mono ω-benzoylcarboxylic esters of (*R*)-BINOL **10**–**14** (0.02 mol dm^{-3} in dichloromethane) were preorganized with 1.0 equiv. of the methyl Grignard reagent **15a** (1.0 mol dm^{-3} in diethyl ether) at −78 °C for 30 min in the presence or absence of $MgBr_2{\cdot}OEt_2$ (3.0 equiv.) and the resulting alkoxide complex was subjected to the Grignard reaction, according to the above-mentioned procedure (Table 2).‡§ In the case of reactions of the δ-keto ester **10**, lactone **16a** was obtained in almost completely racemic form (entries 1 and 2). To our pleasure, however, the reactions of the keto esters linked by longer carbon chains **11**–**14** proceeded diastereoselectively to give the corresponding diols **17**–**20** with moderate to good optical purities (entries 3, 5, 7 and 9). The diastereoselectivities were improved to practical des by addition of $MgBr_2{\cdot}OEt_2$ except in the case of ε-keto ester **11** (entries 4, 6, 8 and 10).

Although the mechanism of asymmetric induction in this system is not clear at this stage, the substrates **12**–**14**, when treated with the Grignard reagent **15a**, might form a binuclear alkoxide complex with the aid of $MgBr_2$ as schematically visualized by stereostructure **22** (Fig. 1). In this complex, the ester carbonyl oxygen should ligate to a metal cation to form a firm nine-membered chelate containing a binaphthyl unit. Accordingly, ligation of the keto carbonyl oxygen to the other magnesium center of the Lewis acid requires a relatively long carbon chain between the two carbonyl groups, which would explain the higher diastereoselectivities in the reactions of ζ- to θ-keto esters **12**–**14** than those in the reactions of δ- and ε-keto esters **10**,**11**. Further efforts to elucidate the chiral discrimination mechanisms and extend the scope and utility of these methodologies are in progress.

Acknowledgements

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Notes and references

‡ The ee of compound **16a** was determined by GLC analysis using an ASTEC Chiraldex G-TA column (0.25 mm i.d. × 20 m). The ee values of compounds **16b**,**17**–**20** were determined by HPLC analyses using a Daicel Chiralpak AD (for **16b**, **17**, **18** and **20**; eluent, 3–10% propan-2-ol in hexane) or Chiralcel OD-H (for **19**; eluent, 10% propan-2-ol in hexane) column (4.6 mm i.d. × 25 cm).

§ The absolute configurations of compounds **16a**,**17**–**20** were determined by chemical correlation to (*R*)-(+)-5-methyl-5-phenyl-4,5-dihydrofuran-2(3*H*)-one.[8] The absolute configuration of compound **16b** was determined by chemical correlation to (*R*)-(+)-6-hydroxymethyl-6-nonyl-3,4,5,6-tetrahydro-2*H*-pyran-2-one.[9]

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