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A New Entry to Asymmetric Synthesis of Optically Active α,γ-Substituted γ-Butyrolactones, Using a Carbohydrate Derived Amide as Both a Chiral Auxiliary and a Proton Source

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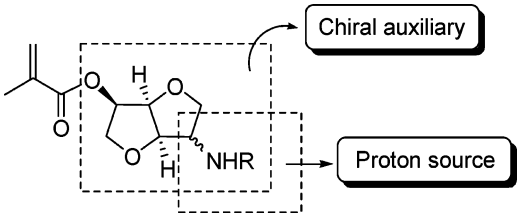
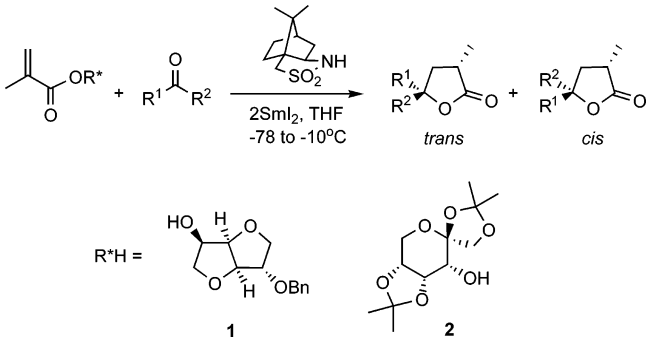


A new entry for the asymmetric synthesis of optically active α,γ-substituted γ-butyrolactones was developed by using a carbohydrate-derived amide as both a chiral auxiliary and a proton source. Unlike the previously reported examples, the chiral auxiliary employed in this reaction also successfully functioned as a protonating agent. Excellent asymmetric induction could be achieved by this dual stereoselective control in the reaction process.

Introduction

The SmI_2-mediated reductive coupling reaction of aldehydes or ketones with chiral α,β-unsaturated esters is very efficient for the synthesis of chiral γ-butyrolactones that are important intermediates and building blocks for fine chemicals and pharmaceuticals.[1,2] This approach, pioneered by Fukuzawa et al.,[3] has a wide applicability. We recently reported a useful reaction system for the asymmetric synthesis of optically active α,γ-substituted γ-butyrolactones by the reaction of ketones with 2-alkyl acrylates derived from various chiral auxiliaries in the presence of protonating agents.[4] Among the chiral auxiliaries developed, we found that inexpensive and easily accessible carbohydrate derivatives were

SCHEME 1



especially useful (Scheme 1).[4] In this strategy, however, both chiral auxiliary and bulky protonating agents such as camphorsultam are essential for the observed excellent enantioselectivites. To simplify the reaction system further, we envisioned a more direct access between ketone and chiral α,β-unsaturated ester if the employed chiral auxiliary itself could also serve as a proton source in the reaction. Furthermore, the chiral auxiliary that also

(1) For review articles on the application of SmI_2 in organic synthesis, see: (a) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (b) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (c) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (d) Skrydstrup, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345. (e) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745. (f) Steel, P. G. *J. Chem. Soc., Perkin Trans.1* **2001**, 2727. (g) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351.

(2) For γ-butyrolactones, see: (a) Depre, D.; Chen, L.-Y.; Ghosez, L. *Tetrahedron* **2003**, *59*, 6797. (b) McMahon, L. R.; Coop, A.; France, C. P.; Winger, G.; Woolverton, W. L. *Eur. J. Pharmacol*. **2003**, *466*, 113. (c) Katoh, T.; Nishide, K.; Node, M.; Hiroo, O. *Heterocycles* **1999**, *50*, 833. (d) Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem*. **1998**, *63*, 2385.

(3) Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482.

(4) (a) Xu, M.-H.; Lin, G.-Q.; Xia, L.-J. *Chin. J. Chem.* **1998**, *16*, 561. (b) Xu, M.-H.; Wang, W.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 2229. (c) Wang, W.; Xu, M.-H.; Lei, X.-S.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 3773. (d) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953. (e) Wang, W.; Zhong, Y.-W.; Lin, G.-Q. *Tetrahedron Lett.* **2003**, *44*, 4613.

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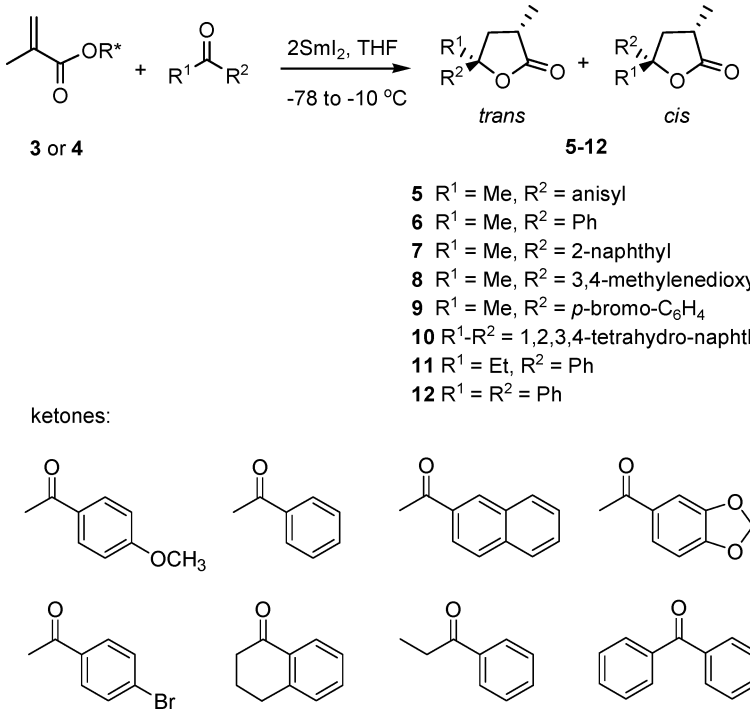
SCHEME 2



functions as a protonating agent might favor stereocontrol in the reaction process and thus potentially improve the stereoselection of the reaction.

Results and Discussion

In our previous studies, the wedge-shaped isosorbide skeleton showed good performance on the induction of high enantioselectivites, so it might be anticipated that the same skeleton, if bearing an appropriately active proton, as indicated in Figure 1, would also afford the

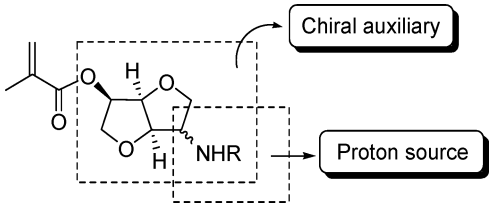
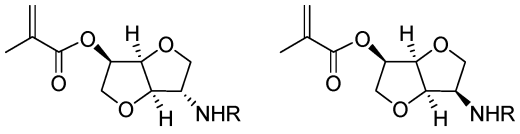


FIGURE 1. Proposed chiral template.



3a R = Ts
3b R = Boc
3c R = Cbz

4a R = Ts
4b R = Boc
4c R = Cbz
4d R = Mts
4e R = Tris

FIGURE 2. New chiral methacrylates for reductive coupling reaction.

products with high enantiomeric purities without adding other protonating agents. Besides, it would be very interesting if the diastereoselectivity and enantioselectivity of the reaction could be readily tuned by choosing the NHR group oriented *exo* or *endo* in the molecule.

TABLE 1. Enantioselective Synthesis of α-Methyl-γ-methyl-γ-anisyl-γ-butyrolactone by Reductive Coupling of Novel Chiral Methacrylates to 4′-Methoxyacetophenone

entry	ester	trans/cis[a]	trans ee (%)[b]	cis ee (%)[b]	yield (%)[c]
1	**3a**	72/28	95 (+)	29 (−)	57
2	**3b**	65/35	94 (+)	20 (−)	60
3	**3c**	71/29	96 (+)	>99 (−)	44
4	**4a**	**31/69**	77 (+)	87 (+)	91
5	**4b**	67/33	99 (+)	81 (+)	36
6	**4c**	75/25	71 (+)	79 (+)	82
7	**4d**	**25/75**	90 (+)	>99 (+)	59
8	**4e**	**33/67**	85 (+)	99 (+)	57

[a] Trans and cis isomers were separated by column chromatography and confirmed by ^{1}H−^{1}H NOESY in light of their NOE effect; the ratio of trans/cis was determined by HPLC or GC. [b] The ee values were determined by HPLC analysis on a Chiralcel column. The sign of $[\alpha]_D$ is given in parentheses. [c] Total isolated yield of trans and cis products.

To check the potential of this hypothesis, we first synthesized novel methacrylate compounds **3a** and **3b** from readily available carbohydrate derivative isomannide (Figure 2).[5] Early experiments were then carried out by using these two methacrylates (Scheme 2). As we anticipated, when a solution of chiral methacrylate **3a** and 4′-methoxyacetophenone in THF at −78 °C was treated with 2 equiv of SmI_2, the reaction proceeded smoothly in the absence of any other proton source, and the diastereomeric *trans*- and *cis*-α-methyl-γ-methyl-γ-anisyl-γ-butyrolactone resulting from this asymmetric coupling were isolated in the ratio of about 72/28 and 57% overall yield (Table 1, entry 1). The trans isomer was obtained with excellent enantioselectivity (95% ee). In contrast, much lower ee (29%) was observed for the *cis* product. Similar results were found when **3b** was reacted (entry 2). To our delight, these results are very close to

that obtained from our previous reaction system with use of chiral auxiliary **1** and bulky protonating agent camphorsultam,[4d] indicating the success of our new strategy.

Encouraged by these results, we further prepared methacrylate substrates **3c** and **4a**−**c** with different R substituents and NHR orientation. When **3c** (R = Cbz) was employed under the same reaction conditions, unlike the cases of **3a** and **3b**, we found that both trans and cis products with very high enantioselectivities were obtained; remarkably, a dramatic enhancement of enantioselectivity of the cis product (from 29% or 20% to >99% ee) was observed (entry 3). Interestingly, when the NHR group *endo*-oriented **4a** was used, we found that the major diastereomer obtained was cis (trans/cis = 31/69), inconsistent with the results obtained from **3a**−**c**. Moreover, the configuation of the cis product resulting from **4a** was also different from that resulting from **3a**−**c** (entry 4). These results led to the suggestion that the diastereoselectivity and enantioselectivity of the reaction may be highly dependent on the orientation of the NHR group. To confirm this consideration, the use of **4b** and **4c** was examined. Surprisingly, when *tert*-butyloxycarbonyl-substituted **4b** was used, the reaction provided the trans isomer as the major product with 99% ee and cis product with 81% ee.[6] The diastereomeric ratio (trans/cis = 67/33) was not identical with those resulting from **4a**, but similar to those with **3b** (entry 5). In comparison with **4b**, using benzyloxycarbonyl-substituted methacrylate **4c** also led to the major trans product (trans/cis = 75:25) but with lower enantioselectivity (71%). The minor cis product was obtained with 79% ee and a same configuration (entry 6). In all cases, the configurations of the trans products were always the same whatever methacrylate, **3** or **4**, was used; however, the configurations of the cis products were found opposite when **3** or **4** was used (entries 1−8). Thus, it can be concluded that only the configuration of the cis product was largely determined by the stereochemistry of the proton source part. It is clear that the transition state model of the reaction is not significantly changed if the NHR group of the proton source is away from the reaction site, namely *exo* oriented. Whatever the R group is, products with the same configurations are obtained. However, in the reactions of substrate **4**, the NHR group is on the same side of the reaction site, and the formation of the transition state was strongly affected by the nature of the R group due to either steric or chelating effects, thus leading to different enantiomers. In the case of **4a**, we assumed that the chelation of the samarium ion and the oxygen of the sulfonyl group in the substrate may be an important factor for the observed diastereoselectivity. The exact transition-state model and precise mechanistic explanation still remain unclear at this moment.[7]

To investigate the steric effect of the sulfonyl group, two other substrates, **4d** and **4e,** were prepared. Gratifyingly, the use of both 2-mesitylenesulfonyl (Mts) and 2,4,6-triisopropylbenzenesulfonyl (Tris) substituent, rather than a tosyl (Ts) substituent, under the same conditions afforded much better results (entries 7 and 8). A substantial improvement in both the diastereoselectivity (trans/cis = 25:75) and enantioselectivity (90% ee for trans, >99% ee for cis) were realized when **4d** was employed (entry 7). The increased selectivity when an Mts or a Tris group was used instead of a Ts group is undoubtedly due to the steric effect. These results also clearly indicate that the structure of the R group in molecule **4** has a major influence on the product distribution: cis diastereomers are favored when R is a sulfonyl group. Thus, either enantiomer of the cis product with extremely high ee (>99%) can be obtained by choosing the appropriate chiral substrate (entry 3 and 7).

TABLE 2. Reductive Coupling of Novel Chiral Methacrylate 3 or 4 to Ketones for the Preparation of α,γ-Substituted γ-Butyrolactones

entry	S[a]	P[b]	trans/cis[c]	trans ee (%)[d]	cis ee (%)[d]	yield (%)[e]
1	**3a**	**6**	>99/1	97 (+)	15 (−)	74
2	**3c**	**6**	60/40	83 (+)	21 (−)	89
3	**4d**	**6**	15/85	97 (+)	23 (+)	78
4	**3a**	**7**	77/22	93 (−)	23 (−)	77
5	**3c**	**7**	84/16	>99 (+)	54 (−)	75
6	**4d**	**7**	23/77	96 (−)	22 (+)	76
7	**3a**	**8**	75/25	96 (+)	21 (−)	53
8	**3c**	**8**	73/27	96 (+)	32 (−)	59
9	**4d**	**8**	23/77	90 (+)	31 (−)	60
10	**3a**	**9**	60/40	93 (+)	6 (−)	53
11	**3c**	**9**	73/27	96 (+)	49 (−)	60
12	**4d**	**9**	16/84	94 (+)	24 (−)	58
13	**3a**	**10**	78/22	78 (+)	90 (+)	61
14	**3c**	**10**	67/33	80 (−)	84 (+)	42
15	**4d**	**10**	20/80	70 (−)	73 (+)	56
16	**3a**	**11**	87/13	78 (−)	54 (−)	90
17	**3c**	**11**	77/23	92 (−)	9 (−)	78
18	**3a**	**12**		75 (+)		41
19	**3c**	**12**		86 (+)		40

[a] Chiral methacrylate substrate. [b] Product. [c] Trans and cis isomers were separated by column chromatography and confirmed by ^{1}H−^{1}H NOESY in light of their NOE effect; the ratio of trans/cis was determined by HPLC or GC. [d] The ee values were determined by HPLC analysis on a Chiralcel column. The sign of $[\alpha]_D$ is given in parentheses. [e] Total isolated yield of trans and cis products.

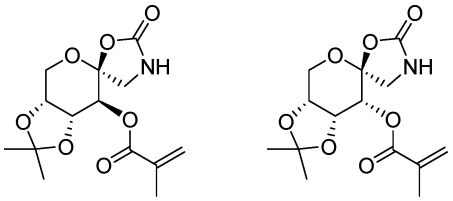
On the basis of the above results, methacrylates **3a**, **3c**, and **4d** appear to be the most favorable substrates and give excellent stereoselectivities. Reactions of these substrates with a series of ketones were also successfully tested to afford the corresponding γ-butyrolactones (**6**−**12**) (Scheme 2). Table 2 summarizes the results obtained from this procedure. As indicated in Table 2, the trans products were attained with generally high ee values in all cases; extremely high enantioselectivity (>99%) was achieved with 2-acetonaphthone (entry 5). In contrast, for the cis product, lower enantioselectivities were obtained, the ee values were found to be largely dependent on the structure of the ketones, and the highest (90% ee) was obtained when 1-tetralone was used (entry 13). The reaction of symmetric benzophenone was also examined, and 86% ee was found when **3c** was used (entry 19). Notably, an extremely high degree of diastereofacial selectivity (>99/1) was observed in the reaction of **3a** with acetophenone (entry 1).

We previously demonstrated that the reaction of chiral auxiliary **2**-derived methacrylate with ketones in the

(5) Isomannide and isosorbide are easily obtained by dehydration of mannitol and sorbitol, respectively. (a) Wiggins, L. F. *J. Chem. Soc.* **1945**, 4. (b) Montgomery, R.; Wiggins, L. F. *J. Chem. Soc.* **1946**, 390.

(6) The recovery of the chiral auxiliary was examined in this case, and 86% of the employed auxiliary was recovered by column chromatography.

(7) Proposed working models are included in the Supporting Information.



11 12

FIGURE 3. Chiral methacrylates derived from D-glucose.

TABLE 3. Reductive Coupling of Novel Chiral Methacrylate 11 or 12 to Ketones for the Preparation of γ-Butyrolactones

entry	S[a]	P[b]	trans/cis[c]	trans ee (%)[d]	cis ee (%)[d]	yield (%)[e]
1	**11**	**5**	60/40	21 (+)	61 (+)	74
2	**11**	**7**	50/50	25 (−)	17 (−)	32
3	**12**	**5**	50/50	**99 (+)**	**99 (+)**	94
4[f]	**12**	**5**	45/55	64 (+)	56 (+)	52
5[f,g]	**12**	**5**	30/70	**98 (+)**	**99 (+)**	73
6	**12**	**7**	18/72	77 (−)	80 (+)	70
7	**12**	**8**	15/85	72 (+)	88 (+)	94
8	**12**	**9**	10/90	90 (+)	82 (+)	68

[a] Chiral methacrylate substrate. [b] Product. [c] Trans and cis isomers were separated by column chromatography and confirmed by $^1H-^1H$ NOESY in light of their NOE effect; the ratio of trans/cis was determined by HPLC or GC. [d] The ee values were determined by HPLC analysis on a Chiralcel. The sign of $[\alpha]_D$ is given in parentheses. [e] Total isolated yield of trans and cis products. [f] In the presence of 1.0 equiv of ^{t}BuOH. [g] The reaction system was diluted 5 times.

presence of a bulky protonating agent could give satisfactory results in both diastereoselectivities (in favor of cis isomers) and enantioselectivities (up to 99%).[4e] To extend our study, we prepared two new methacrylates **11** and **12** that have similar skeletons to that of **2** and a free amide proton (Figure 3).[8] Studies were carried out with different ketones and the results are summarized in Table 3. As we can see, treatment of **11** or **12** with ketones in THF resulted in successful conversion to the desired γ-butyrolactones. In most cases, cis isomers were indeed obtained as major products and relatively high ee values were attained when **12** was used (entries 3 and 6−8). It is noteworthy that the reaction of **12** with 4′-methoxyacetophenone afforded a 50:50 diastereomeric ratio and extremely high enantiomeric excess (99% ee) for both isomers (entry 3). To gain some insight into the protonation mechanism, we performed the same reaction in the presence of *tert*-butyl alcohol. We wished to see if the observed excellent stereoselection was due to the self-protonation in the reaction process. We first run the reaction under similar reaction conditions with additional protonating agent *tert*-butyl alcohol; although the diastereomeric ratio remained similar (45/55), the ee values of both trans and cis products were found to decrease a lot (64% for trans and 56% for cis) (entry 4). However, when the above reaction was performed in a diluted system, excellent ee values (98% for trans and 99% for cis) were observed again regardless of the presence of *tert*-butyl alcohol (entry 5),[9] indicating a intramolecular protonation process. Thus, these two independent experimental results suggest that self-protonation should be involved in the reaction process.[10]

Conclusions

In summary, we have shown a new entry to the asymmetric synthesis of optically active α,γ-substituted γ-butyrolactones using carbohydrate-derived amide as both a chiral auxiliary and a proton source. Unlike the previously reported examples,[4b,d] the chiral auxiliary employed here also successfully functioned as a protonating agent to afford the reaction with excellent stereoselectivity. This provides a new and interesting example of dual stereoselective control in asymmetric synthesis. In addition, the combination of a chiral auxiliary and a proton source within one molecule has led to the development of a new type of bifunctional chiral template for asymmetric synthesis. It provides useful insight to the design of multifunctional chiral templates. Detailed mechanistic studies of the stereocontrol process in this new reaction system as well as the extension of this method are currently underway.

Experimental Section

General Procedure of the SmI_2-Mediated Asymmetric Reductive Coupling Reaction. To a dry Schlenk flask with samarium metal powder (200 mg, 1.3 mmol) was added a solution of diiodomethane (freshly distilled, 0.081 mL, 1.0 mmol) in THF (5 mL) at room temperature under nitrogen. After being stirred for 1 h, the deep blue solution was cooled to −78 °C, and a mixture of methacrylate (0.5 mmol) and ketone (0.5 mmol) in THF (5 mL) was added. The resulting mixture was stirred for 1 h at the same temperature and then allowed to warm slowly; the reaction was subsequently quenched at −10 °C with 5% aqueous HCl, extracted with ethyl ether, washed with aqueous $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. The solution was concentrated and the resulting residue was purified by flash column chromatography on silica gel to afford the optically active γ-butyrolactones.

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Supporting Information Available: Characterization data of all compounds and supposed working models of the reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Prepared from D-glucose, see: (a) Tian, H.; She, X.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435. (b) Shu, L.; Shen, Y.-M.; Burke, C.; Goeddel, D.; Shi, Y. *J. Org. Chem.* **2003**, *68*, 4963.

(9) The difference between the trans/cis ratio in entry 3 and that in entry 5 might be explained by the conformation change of the reaction transition state in the diluted system. The exact reason is not clear at this time.

(10) Other experimental results that are also supportive: comparing with the results in entry 5 of Table 1, no significant difference was found (trans/cis = 69/31, 99% ee for trans and 79% ee for cis) when substrate **4b** was reacted with 4′-methoxyacetophenone (**5**) in the presence of 1.0 equiv of *tert*-butyl alcohol under diluted (5 times) conditions.