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ARTICLE TYPE

# Diastereoselection during 1,2-addition of 3-bromomethyl-5H-furan-2-one to α- chiral aldehydes mediated by indium in aqueous and organic solvent systems: Direct route to obtain optically α-methylene-γ-butyrolactones

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**The stereochemical course of indium-promoted allylations to α-chiral aldehydes with 3-bromomethyl-5H-furan-2-one was investigated in anhydrous THF and pure $H_2O$. High levels of 3,4-syn;4,5-syn diastereomers were produced with free hydroxyl derivatives whether in THF or pure $H_2O$, reflecting the promising synthetic potential of this chemistry. This stereo-differentiation was attributed to the strong geometric bias exercised by our allylindium reagent and adherence to a chelation control transition-state alignment. Meanwhile, heightened levels of 3,4-anti; 4,5-anti diastereomers were obtained with rigid aldehydes 1h and 1i.**

The Cram rule[1], which was put forward about six decades ago as a predictor of the stereochemical course of nucleophilic additions to acyclic aldehydes and ketones, has incited organic chemists into thinking systematically about diastereomeric transition states. As a consequence of complications introduced by the dynamic conformational nature of substrates bearing stereogenic centers proximal to the carbonyl group, other researchers have presented paradigms in which the interplay of steric and stereoelectronic effects has been somewhat modified[2–4]. However, all Cram and Felkin–Anh paradigms have been founded in anhydrous conditions because of the sensitivity of organometallic reagents to moisture before indium metal was found to be capable of promoting carbon–carbon bond-forming reactions in water. Subsequently, Paquette and his co-workers established the levels of stereocontrol attainable in aqueous environments when a neighboring heteroatom is present, clarifying competitive intramolecular/intermolecular chelation options[5]. When chelation operates, the reaction diastereoselection is controlled by intramolecular delivery from the sterically less hindered π-face of the preformed complex. In substrates lacking the potential for chelate organization, the interplay of steric and electronic forces summed up in the Felkin–Ahn model[3] provides a useful stereoinduction paradigm. Studies in these laboratories have addressed the applicability of the above criteria to indium-mediated coupling reactions in water.

Optically α-methylene-γ-butyrolactones are an interesting class of compounds because of their intrinsic reactivity, as shown in their use as chiral building blocks for the synthesis of natural products, such as alkaloids, macrocyclic antibiotics, lignan lactones and pheromones[6], as well as their occurrence in a large variety of natural products and biologically active compounds (Fig. 1)[7,8]. The physiological activity of these α-methylene-γ-butyrolactones often depends on enantiomeric purity and absolute configurations[9]. Therefore, many methods have been developed for the synthesis of functionalized α-methylene-γ-butyrolactone derivatives in optically active form[10].

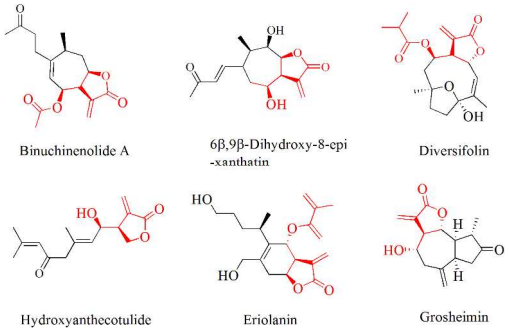
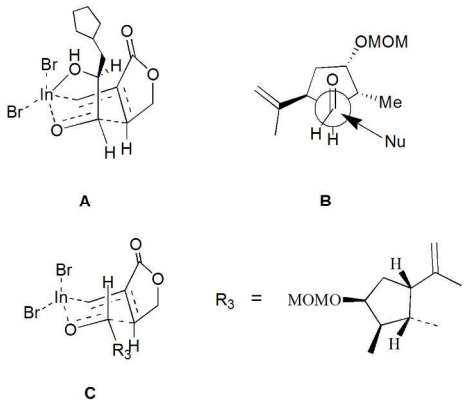
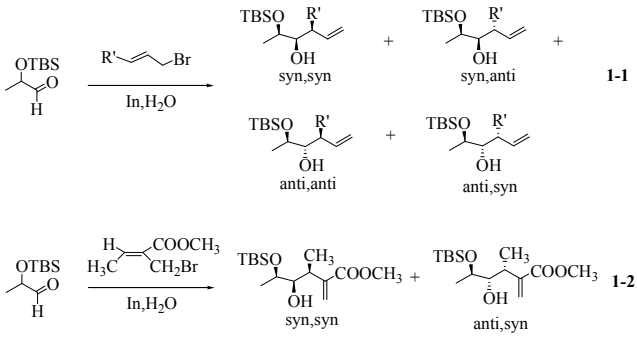



**Fig. 1** Representative α-methylene-γ-butyrolactones

**Fig. 2** Transition state model analysis



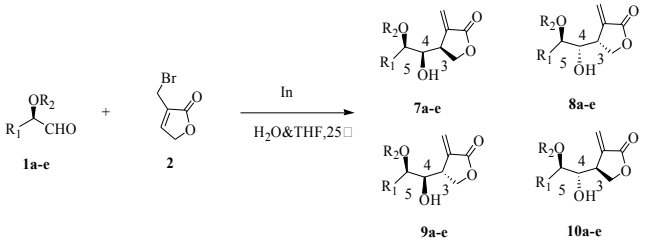

The continuation of our investigation of Barbier coupling reaction attended by 3-bromomethyl-5H-furan-2-one (**2**)[11–14] and the desirability of producing α-methylene-γ-butyrolactone




**Scheme 1** Indium-mediated coulings of allylic bromide to α-oxygenated aldehydes in water

derivatives in optically active form prompted us to extensively examine the condensation of α-chiral aldehydes (**1a-i**) with 3-bromomethyl-5H-furan-2-one (**2**). In the illustrated example[15] where R' was methyl (Scheme 1, 1–1), no anti,syn product was generated; instead, syn,syn; syn,anti and anti,anti diastereomers were afforded rather indiscriminately. Further erosion of stereo control occurred when R' was bromine. In this instance, all four possible alcohols resulted. The lack of stereo control in these circumstances was attributed to facile E/Z equilibration within the relevant indium reagents, as established previously for the related Grignard, potassium, and lithium derivatives. However, very excellent stereocontrol (only syn) was obtained for methyl (Z)-2-(bromomethyl)-2-butenoate, which possesses greater thermodynamic stability than the E alternative (Scheme 1, 1–2)[16]. In this report, we further confirmed the feasibility of setting three contiguous stereogenic centers in highly controlled fashion under aqueous conditions with α-hydroxyaldehydes or rigid aldehydes,

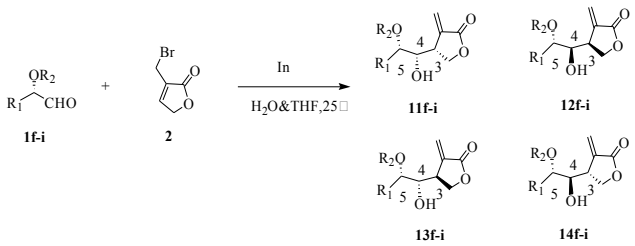
**Table 1** Indium-mediated couplings of **2** to α-oxygenated aldehydes **1a-e** in $H_2O$ or THF, 25 °C[a]




| Entry | Aldehyde | Solvents | Time (h) | Yields[b](%) | 7:8:9:10[c] |
|---|---|---|---|---|---|
| 1 | OTBS, CHO **1a** | $H_2O$ | 12 | 75.6 | 1.2:1:0:0 |
| 2 | | THF | 30 | 77.0 | 0.8:1:0:0 |
| 3 | OTBS, Ph, CHO **1b** | $H_2O$ | 12 | 80.0 | 4.0:1:0:0 |
| 4 | | THF | 30 | 75.0 | 2.5:1:0:0 |
| 5 | OTBDPS, CHO **1c** | $H_2O$ | 12 | 79 | 2.0:1:0:0 |
| 6 | | THF | 30 | 75.4 | 1.5:1:0:0 |
| 7 | OTBDPS, Ph, CHO **1d** | $H_2O$ | 12 | 78.2 | 1:1.2:0:0 |
| 8 | | THF | 30 | 76.0 | 1:2.0:0:0 |
| 9 | OBn, CHO **1e** | $H_2O$ | 8 | 80.5 | 0.55:1:0:0.4 |
| 10 | | THF | 24 | 71.0 | 0.7:1:0:0.75 |

[a] All of the reaction were conducted minimally in duplicate with at a concentration of 0.1M with vigorous stirring for the indicated time span.[b] Isolated yields by flash column chromatography. [c] The product proportions in all cases were determined by 1H NMR integration at 400 MHz.

**Table 2** Indium-Mediated Couplings of **2** to α-Oxyenated Aldehydes **1f-i** in $H_2O$ or THF, 25 °C[a]




| Entry | Aldehyde | Solvents | Time (h) | Yields[b](%) | 11:12:13:14[c] |
|---|---|---|---|---|---|
| 11 | OH, CHO **1f** | $H_2O$ | 6 | 79.2 | 0.08:0.07:1:0.02 |
| 12 | | THF | 18 | 72.0 | 0.06:0:1:0.02 |
| 13 | OH, CHO **1g** | $H_2O$ | 6 | 85 | 0.05:0.03:1:0.01 |
| 14 | | THF | 18 | 72 | 0.04:0.06:1:0.01 |
| 15 | O, CHO **1h** | $H_2O$ | 16 | 87.4 | 0:13:1:1.3 |
| 16 | H, MOMO, H, CHO **1i** | $H_2O$ | 12 | 70.0 | only 12i |

[a] All of the reaction were conducted minimally in duplicate with at a concentration of 0.1M with vigorous stirring for the indicated time span.[b] Isolated yields by flash column chromatography. [c] The product proportions in all cases were determined by 1H NMR integration at 400 MHz.

through which we can obtain functionalized α-methylene-γ-butyrolactone derivatives in high diastereoselectivity. This finding is not only ascribed to Felkin–Ahn or chelation-control transition states, but also to the persistence of a single (E)-geometry organoindium intermediate of 3-bromomethyl-5H-furan-2-one (**2**).

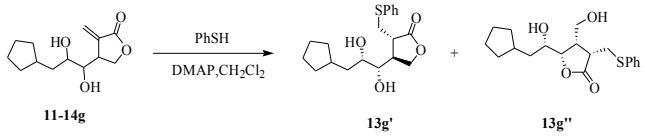
In an effort to vary the basicity of the α-oxy substituent and its steric environment to reasonable levels, the five substrates **1a–e** were examined (Table 1). The preparation of **1a–e** was adapted from the existing literature. 3-Bromomethyl-5H-furan-2-one (**2**) was prepared according to the method developed in our laboratory[12]. The allylation of **1a–e** was conducted at room temperature in pure $H_2O$ and anhydrous THF. Consistent with our previous report[13], the quantities of the reagents were regulated to conform to an aldehyde/indium powder/allyl bromide ratio of 1.0:2.0:1.5. The results were not as good as those obtained from the condensation of methyl (Z)-2-(bromomethyl)-2-butenoate with **1a**[16]. Hardly any π-facial discrimination was observed in Felkin–Ahn transition state when the allylation of **1a** with (**2**) was conducted (Table 1, entries 1 and 2). The product distributions were quantified by comparison with the literature[16] and analysis of coupling constant (for **7a**, $J_{3-4}$=10.6, $J_{4-5}$=2.4). The considerably more extended reaction time required for the allylation performed with THF constituted a trend that was observed throughout this study. 3,4-Anti;4,5-syn diastereomers **7b** improved as the size of $R_1$ in aldehydes **1a** was amplified from methyl to phenyl (Table 1, entries 3 and 4). When the substituent was OTBDPS, the preferred diastereofacile selectivity of the reaction was reversed to 4,5-anti (Table 1, entries 7 and 8). The results indicate that larger groups ($R_2$), such as tert-butyldimethylsilyl and tert-butyldiphenylsilyl, effectively deterred transient binding of the attached oxygen to the indium, at

least in water, and promoted alternative conversion to product via Felkin–Ahn transition state. Thus, steric effects appeared to exert a significant influence on the outcome of these single asymmetric induction processes. The diastereoselectivity between C-3 and C-4 can be explained by six-membered cyclic transition state **C** (Fig. 2). However, when $R_2$ was benzyl, which possesses some chelating abilities, the product distribution became more complicated and a relatively low level of both simple (anti/syn) diastereoselectivity and distereofacial selectivity was obtained (Table 1, entries 9–10).

The next series of experiments was performed with the unprotected α-hydroxyaldehydes and two rigid aldehydes (Table 2). Heavy predominance of the 3,4-syn;4,5-syn diastereomers **13f** and **13g** occurred when the series of experiments was performed with α-hydroxy aldehydes **1f** and **1g** whether in THF or in pure $H_2O$ (Table 1, entries 11–14). This result indicated high chelation control transition state preference in the carbonyl reagent[17,18]. However, the diastereoselectivity was decreased to 1.26:1(**7:8,** Table 1) when the hydroxy of **1f** was protected with tert-butyldimethylsilyl chloride. It was established that the α-hydroxy was fundamental for the selectivity.

As may be anticipated, directly determining the relative stereochemistry of the four diastereomers from $^1H$ and $^{13}C$ NMR spectra was not possible. Fortunately, the major derivatives **13g'**, which was crystalline, can be isolated by column chromatography (Scheme 2). Consequently, single-crystal X-ray analyses revealed its absolute configurations (See supporting information). This result was attributed to the chelation control transition-state alignment **A** (Fig. 2). The distribution of **11g**, **12g** and **14g** was determined by a comparison with the literature[15] and our experiment observations. In addition, during the Michael addition reaction, we isolated a small amount transesterification product **13g''**, whose absolute configuration was also determined by single-crystal X-ray analyses (See supporting information).

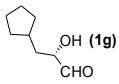
**Scheme 2** Michael addition reaction of **11-14g** obtained from entry 13




**11-14g** **13g'** **13g''**

Given their shorter reaction time in water, aldehydes **1h** and **1i** were examined only under aqueous conditions (entries 15 and 16). Heavy predominance of the 3,4-anti;4,5- anti diastereomers **12h** was received with aldehydes **1h** according to Felkin–Ahn transition state. Flash chromatography on silica gel resulted in separation of a 10:1 mixture of **12h** and **14h** from the 3,4-syn;4,5-syn diastereomer **13h**. The absolute configuration of major product **12h** was determined by single-crystal X-ray analyses of **12h'** (See supporting information) which was obtained the same as Scheme 2 so that we could define the absolute configurations of **13h** and **14h** through a comparison of coupling constants of $J_{3-4}$ and $J_{4-5}$ with **12h**(for **12h**, $J_{4-5}$=11.2, $J_{3-4}$=13.6; for **13h**, $J_{4-5}$=6.8, $J_{3-4}$=8.4; for **14h**, $J_{4-5}$=11.2). To our surprise, only 3,4-anti;4,5-anti diastereomers **12i** was obtained with rigid aldehydes **1i**. These results can be ascribed to the six-membered cyclic transition state **B** and Felkin–Ahn transition state **C** (Fig. 2).

**Table 3** Salt effects on indium-promoted allylation in water at 25 $^oC$[a]

| Entry | Aldehydes | Added salt ( no of equiv ) | Time(h) | Yield(%)[b] | 11g:12g:13g:14g |
|---|---|---|---|---|---|
| 17 |  | LiBr(1.0) | 6 | 78.7 | 0.08:0.04:1.0:0.02 |
| 18 | | $MgCl_2$(1.0) | 6 | 79.2 | 0.08:0.03:1.0:0.03 |
| 19 | | $Et_4NBr$(1.0) | 6 | 76.2 | 0.08:0.13:1.0:0.02 |
| 20 | | $(n\text{-}Bu)_4NI$(1.0) | 6 | 88.6 | 0.2:0.03:1.0:0.03 |
| 21 | | $(n\text{-}Bu)_4NBr$(1.0) | 6 | 80.5 | 0.18:0.03:1.0:0.03 |



[a] All of the reactions were performed at least in duplicate with vigorous stirring.
[b] Isolated yields by flash columnn chromatography.

Subsequently, we studied salt effects in the allylation reaction of hydroxyaldehydes **1g** with (2) (Table 3). For Diels–Alder cycloadditions performed in water, the presence of salts increases the amount of endo products because of an increase in the internal pressure of the system[19]. Were the reaction volumes for formation of the syn and anti homoallylic alcohols to differ comparably, the possibility exists that product ratios can be conveniently manipulated to synthetic advantage in this manner. When **1g** was admixed with 1.0mol equivalent of LiBr or $MgCl_2$ and subjected to conventional allylation in $H_2O$, the diastereofacial selectivities (syn/anti) declined somewhat to 18:1 in both cases (Table 3, entries 17 and 18). Moreover, the use of tetraethylammonium bromide resulted in a substantial decrease to a record level of 7.2:1 (entry 19). Although the proportion of **11g** increased to some extent (Table 3, entries 20 and 21), it affected the average selectivities. In fact, the lithium and magnesium halides performed less well than the quaternary salt.

## Conclusions

We further confirmed that highly functionalized acyclic molecules containing three contiguous stereogenic centers can be assembled with high stereoselectivity from simple building blocks in water as the reaction medium. As the geometry inherent in the allylindium reagent of (**2**) was biased strongly in E sense, control of product stereochemistry as in **12** or **13** can be expected to operate at synthetically practical levels with α-hydroxyaldehydes or α-rigid aldehydes, respectively. Meanwhile, we provided a highly efficient and convenient method to establish functionalized α-methylene-γ-butyrolactone derivatives in optically active form. Further application in total synthesis of optically natural products with this type of substitution is currently under investigation.

## Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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