β,γ-trans-selective γ-butyrolactone formation via homoenolate cross-annulation of enals and aldehydes catalyzed by sterically hindered N-heterocyclic carbene

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Graphical Abstract

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β,γ-*trans*-Selective γ-butyrolactone formation *via* homoenolate cross-annulation of enals and aldehydes catalyzed by sterically hindered N-heterocyclic carbene

Ryuji Kyan [a], Yuya Kitagawa [b], Ryuji Ide [b], Kohei Sato [a,b,c], Nobuyuki Mase [a,b,c,d] and Tetsuo Narumi [a,b,c,d] *

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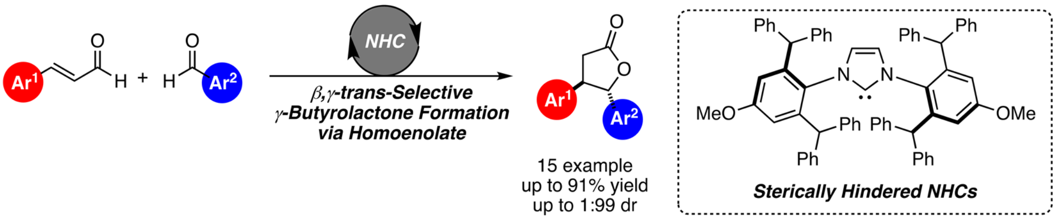

15 example
up to 91% yield
up to 1:99 dr

ELSEVIER

Tetrahedron

β,γ-*trans*-Selective γ-butyrolactone formation *via* homoenolate cross-annulation of enals and aldehydes catalyzed by sterically hindered N-heterocyclic carbene

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ABSTRACT

Highly sterically hindered N-heterocyclic carbenes (NHCs), can be readily prepared from the corresponding anilines, and serve as organocatalysts in NHC-catalyzed homoenolate cross-annulation of α,β-enals and aryl aldehydes. This catalysis enables the convergent construction of β,γ-*trans*-disubstituted γ-butyrolactones that are an important class of molecules in synthetic and medicinal chemistry. The steric features of N-aryl substituents contribute to the selectivity and electronic ones affected the efficiency of this reaction, which proceeds with high diastereoselectivity and affords a variety of β,γ-diaryl-γ-butyrolactones in up to 91% yield with up to 1:99 dr.

1. Introduction

The γ-butyrolactone is a key structural motif found widely in a variety of natural products, biologically active compounds, and pharmaceutical compounds (Figure 1) [1]. Such compounds have versatile pharmacological properties including potent antibiotic, anthelmintic, antifungal, antitumor, antiviral, anti-inflammatory and cytostatic properties, which makes them an important structure in drug development [2], and the γ-butyrolactone therefore serves as an important and robust building block in synthetic organic chemistry [3]. In view of these features, significant efforts have been devoted to the development of stoichiometric or catalytic methods for the stereoselective synthesis of γ-butyrolactones [4]. Despite the many synthetic methods for the γ-butyrolactone scaffold, stereoselective synthesis of β,γ-disubstituted γ-butyrolactones remains a significant challenge.

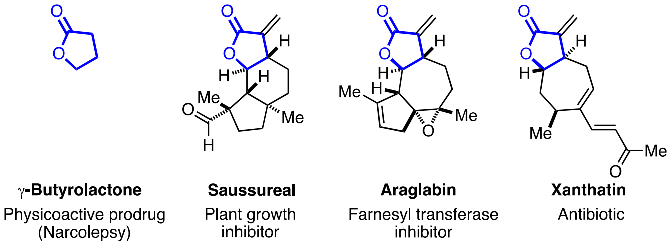

Figure 1. Biologically relevant molecules and natural products containing the β,γ-*trans*-γ-butyrolactone scaffold.

In the past decades, N-heterocyclic carbenes (NHCs) have emerged as efficient organocatalysts for various reactions involving asymmetric C-C bond formation, particularly annulation reactions [5]. The conjugated Breslow intermediate, which can be catalytically generated by NHCs from α,β-unsaturated aldehydes, can serve as a homoenolate equivalent and react with various electrophiles, affording 4 to 7-membered heterocyclic compounds such as the lactone [6,7], the lactam [8] and 5-membered carbocyclic compounds such as cyclopentene [9]. Currently, the

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NHC-catalyzed γ-butyrolactone formation has been achieved with aromatic aldehydes [10], α,β-enals [11], and highly activated ketones such as trifluoromethyl ketones [12], acyl phosphonates [13], α-ketoesters [14] and isatins [15] to give the functionalized β,γ-di- or trisubstituted γ-butyrolactones shown in Figure 2a with low to high β,γ-*cis*-selectivity. Although impressive advances have been made since the first NHC-catalyzed homoenolate annulation reported in 2004, the developed vast majority of NHC-catalyzed γ-butyrolactone formation offer β,γ-*cis*-selective synthetic methods. To the best of our knowledge, there are only a few reports concerning β,γ-*trans*-selective γ-butyrolactone formation by NHC catalysis, and in these cases, the electrophiles are restricted to highly activated ketones such as 2,2,2-trifluoromethylacetophenone [10a, 16], 1,2-diketones [17], and β-halo-α-ketoesters [18] (Figure 2b). A major challenge in this area is the formation of NHC-catalyzed β,γ-*trans*-selective γ-butyrolactone, particularly from simple aldehydes.

Herein, we report a diastereoselective synthesis of β,γ-*trans*-disubstituted γ-butyrolactones *via* cross-annulation of α,β-enal and aryl aldehydes using imidazolylidene catalysts bearing 2,6-dibenzhydrylphenyl groups (Figure 2c). The high steric hindrance of 2,6-dibenzhydrylphenyl groups is critical to controlling the β,γ-*trans* selectivity which provides β,γ-diaryl-γ-butyrolactones in high yields with high diastereoselectivity.

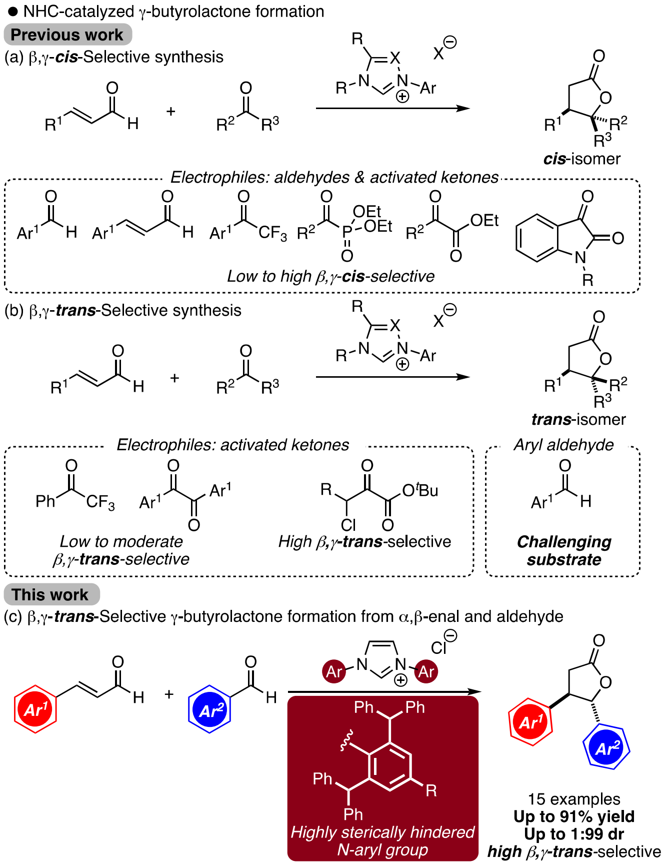
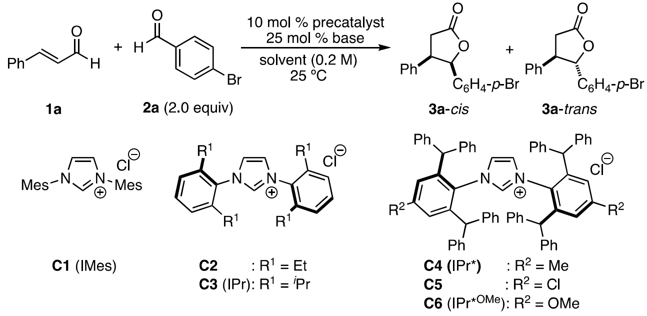


Figure 2. (a) (b) NHC-catalyzed γ-butyrolactone formation. (c) β,γ-*trans*-Selective γ-butyrolactone formation from an α,β-enal and aldehyde.

Table 1. Screening of reaction conditions for the reaction of **1a** with **2a**.[a]



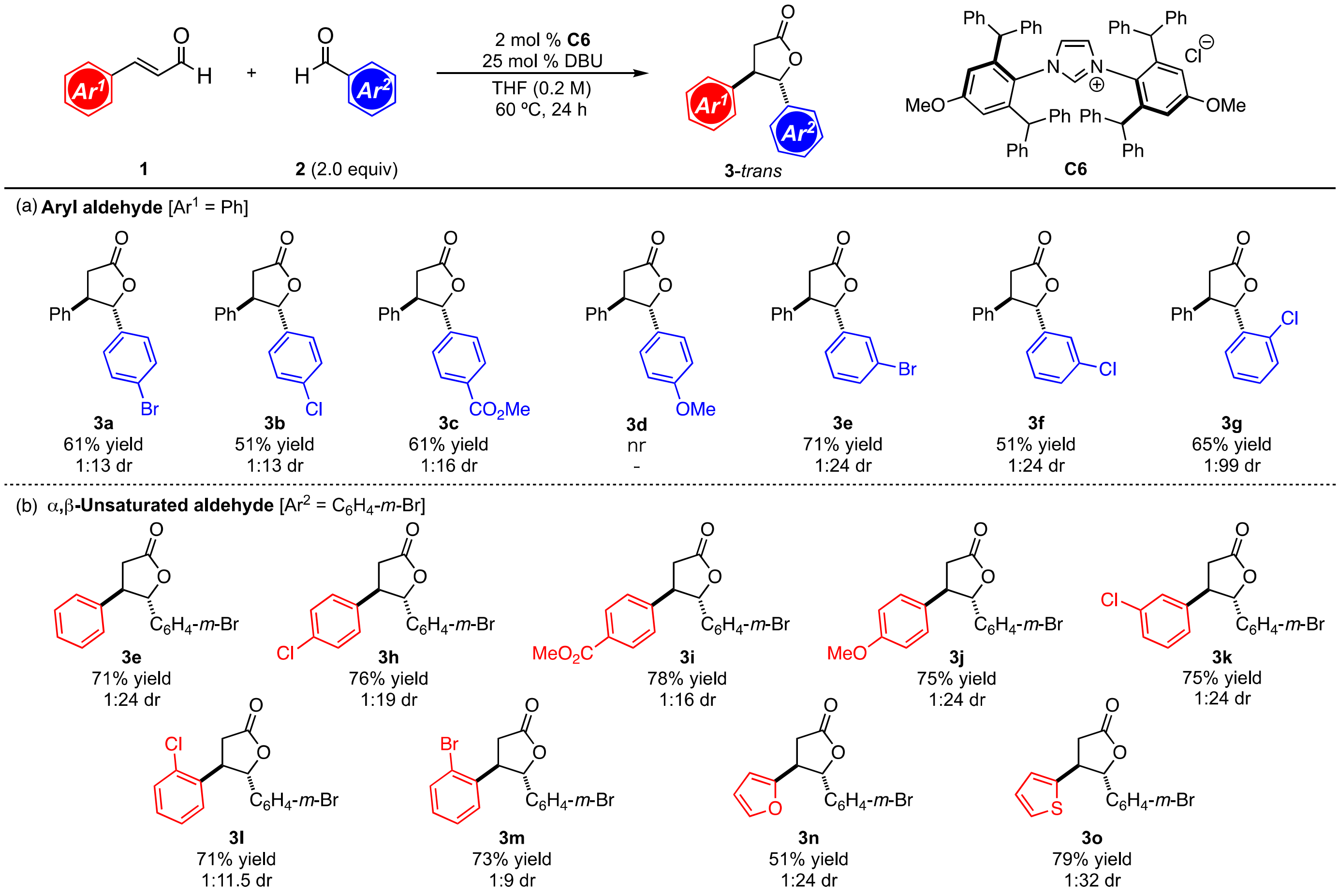
entry	precatalyst	base	solvent	yield [b] (%)	dr [c] (*cis*:*trans*)
1[d]	**C1**	DBU	THF	80	4:1[e]
2[d]	**C2**	DBU	THF	83	3:1[e]
3[d]	**C3**	DBU	THF	90	1:1[e]
4	**C4**	DBU	THF	79	1:16
5	**C4**	KO^{t}Bu	THF	56	1:16
6	**C4**	Et_3N	THF	40	1:16
7	**C4**	TMEDA	THF	48	1:16
8	**C4**	DBU	1,4-DOX	24	1:13
9	**C4**	DBU	toluene	51	1:13
10	**C4**	DBU	$CHCl_3$	36	1:10
11	**C5**	DBU	THF	71	1:16
12	**C6**	DBU	THF	87	1:16
13[f]	**C6**	DBU	THF	91	1:13
14[g]	**C6**	DBU	THF	71	1:13
15[h]	**C6**	DBU	THF	66	1:13

[a]Reaction conditions: α.β-enal (0.30 mmol), aryl aldehyde (0.60 mmol), 10 mol % precatalyst, 25 mol % DBU, and 0.2 M THF at 25 ºC for 24 h. [b]The yield is a combined yield of both diastereomers, determined by ^{1}H NMR analysis of the crude mixture utilizing *p*-*tert*-butylanisole as an internal standard. [c]dr was determined by HPLC analysis of the crude mixture. [d]Reaction was performed for 5 h. [e]dr was determined by ^{1}H NMR analysis of the crude mixture. [f]Reaction was performed at 60 ºC. [g]Reaction was performed with 5 mol % precatalyst at 60 ºC. [h]Reaction was performed with 2 mol % precatalyst at 60 ºC. Mes = mesityl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMEDA = *N*,*N*,*N*',*N*'-tetramethylethylenediamine.

2. Results and Discussion

According to the reaction conditions reported by us previously, [19], we first carried out the cross-annulation of cinnamaldehyde (**1a**) and *para*-bromobenzaldehyde (**2a**) in the presence of an imidazolium salt (10 mol %) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (25 mol %) in THF at 25 ºC (Table 1). The reaction, catalyzed by the commonly used imidazolium salt **C1** (IMes) bearing mesityl groups proceeded to give the annulation product (**3a**) in 80% yield and 4:1 dr favoring the *cis*-isomer (Table 1, entry 1). The precatalyst **C2**-derived NHC bearing 2,6-diethylphenyl groups furnished **3a** in 83% yield with diastereoselectivity similar to that produced by **C1** (3:1 dr, entry 2). The 2,6-diisopropyl-substituted N-aryl precatalyst **C3** (IPr) provided **3a** in 90% yield with the *trans*-isomer being favored more than with the precatalysts **C1** or **C2** (1:1 dr, entry 3). On the basis of the encouraging results of the steric effects of *ortho*-substituents on the diastereoselectivity, we tested highly sterically hindered imidazolium salts than **C3**. The NHC catalyst derived from the imidazolylidene salt **C4** (IPr*) [20] bearing 2,6-dibenzhydrylphenyl groups gave the desired lactone (**3a**) in 79% yield with a high β,γ-*trans* selectivity of 1:16 dr (entry 4). Although the diastereoselectivity was not sensitive to the change of base, other bases such as potassium *tert*-butoxide, triethylamine, and TMEDA furnished the desired products in reduced yields (40%−56%, entries 5−7) [21]. Use of solvents other than THF resulted in a decrease of the yield to 24%−51% (entries 8−10) [22]. Further optimization of the structure of the imidazolium salt (**C4**) led to a slight increase in the yield. Although the introduction of electron-withdrawing chlorine atoms at the *para*-position led to the recovery of the yield (71%) and similar diastereoselectivity (entry 11), the precatalyst **C6** (IPr^{*OMe}) [23] with electron-donating para-methoxy substitutions was effective, giving the lactone (**3a**) in 87% yield (entry 12). A slightly higher yield of 91% can be obtained by increasing the reaction temperature from 25 ºC to 60 ºC (entry 13). Decreasing the catalyst loading to 1 mol % had little effect, but the reaction with 5 mol % or 2 mol % catalyst loading at 60 ºC gave the products in 71% and 66% yields respectively with comparable β,γ-*trans* selectivities (entries 14−15). Overall, the optimal conditions for the β,γ-*trans*-selective synthesis of γ-butyrolactones involved a combination of the precatalyst (**C6**) and DBU in THF at 60 °C.

Scheme 1. Substrate scope.^{a}

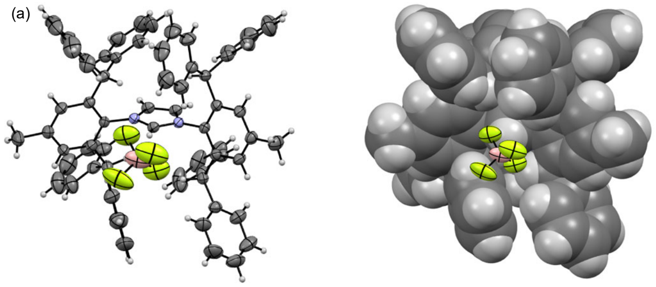


^{a}Reaction conditions: α,β-enal (0.30 mmol), aryl aldehyde (0.60 mmol), 2 mol % precatalyst, 25 mol % DBU, and 0.2 M THF at 60 ºC for 24 h. The yield is an isolated yield of *trans*-isomer after column chromatography. dr was determined by HPLC analysis of the crude mixture.

Having established the optimal conditions, we sought to evaluate the scope and limitations of this transformation with 2 mol % of the precatalyst (**C6**). Substrates with a series of aryl aldehydes were examined (Scheme 1a). The electron-withdrawing groups (Cl, CO_2Me) on the *para*-position in the aromatic ring were tolerated to afford the desired lactone (**3b-3c**) in moderate yields with moderate to high diastereoselectivies, but *para*-methoxy substituted aldehydes proved to be unsuitable substrates, no annulation products being observed. Aryl aldehydes with a *meta*-substituent (*m*-Br, *m*-Cl) and an *ortho*-substituent (*o*-Cl) afforded the corresponding lactone (**3e-3g**) in moderate to good yields with the excellent β,γ-*trans* selectivity of 1:24 to 1:99 dr. In the case of recover from 2 mol % to 10 mol % of a catalyst loading using the *m*-Br or *o*-Cl benzaldehyde as substrate, the desired lactone was obtained in the same yield as at 2 mol %.

Next, we examined the substrate scope of substituted enals (Scheme 1b). Substituents such as chloro, methoxycarbonyl and methoxy group at the *para*-position of cinnamaldehyde provided the corresponding lactone products (**3h-3j**) in high yields with a high β,γ-*trans* selectivity of 1:16 − 1:19 dr. A *meta*-chloro substitution led to the slightly increased yield and diastereoselectivity to give **3k**. On the other hand, *ortho*-substituted substrates (*o*-Cl, *o*-Br) reacted as well to give the corresponding lactone (**3l-3m**) in high yields but with decreased diastereoselectivity. Additionally, γ-butyrolactones with a heteroaromatic ring (**3n-3o**) were obtained in moderate to high yields with excellent β,γ-*trans* selectivity.

To gain structural information concerning the precatalysts bearing the bulky 2,6-dibenzhydrylphenyl groups, the molecular structure of IPr*•HBF_4 [24], the corresponding BF_4 salt of the precatalyst (**C4**) was confirmed by X-ray diffraction of a single crystal, obtained by diffusion of *n*-hexane into a concentrated CH_2Cl_2 solution of the compound. As illustrated in Figure 3a, the IPr*•HBF_4 exhibits a C_2 symmetric structure and the BF_4 anion unit is located in a hydrophobic pocket surrounded by phenyl groups. A structure of the conjugated Breslow intermediate bearing 2,6-dibenzhydrylphenyl groups was generated from the X-ray crystal structure of IPr*•HBF_4 and optimized by density functional theory (DFT) calculation at the B3LYP/6-31G* level of theory in the gas phase (Figure 3b). In line with results obtained by Berkessel [25], the diene moiety in the computed optimized structure of the conjugated Breslow intermediate is almost planar, with the dihedral angle C2-C6-C47-C48 of -177.6º. In addition, a plot was examined of the noncovalent interactions (NCIs) [26] using the DFT-optimized geometry of the conjugated Breslow intermediate bearing 2,6-dibenzhydrylphenyl groups. (Figure 3c). A plot of the NCIs revealed the van der Waals interactions on a large green surface, such as π-π interaction between the C=C double bond of the diene moiety in the conjugated Breslow intermediate and the benzhydryl group of the *ortho*-substituent on the N-aryl group. A blue surface of the strong attractive interaction was found that reflected the OH-π interaction between the hydroxy and benzhydryl groups of the enol, as well as the CH-π interaction between the C47-H and the N-aryl moiety [27]. These results indicated that an array of noncovalent interactions including van der Waals, OH-π, and CH-π interactions can stabilize the structure of the conjugated Breslow intermediate bearing 2,6-dibenzhydrylphenyl groups, forming a reaction site suitable for β,γ-*trans*-selective γ-butyrolactone formation.



X-ray crystal structure of IPr*• HBF$_4$

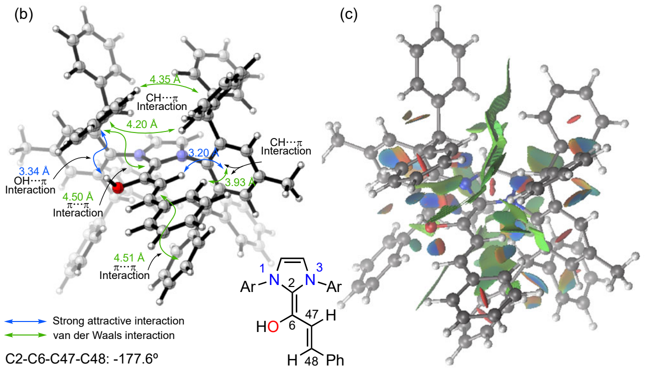


Figure 3. (a) ORTEP plot of IPr*•HBF$_4$ X-ray crystal structure. Thermal ellipsoids are shown at 50% probability (left). Combined ellipsoid/space-filling representation (right). CCDC:836611. (b) The DFT-optimized structure of the conjugated Breslow intermediate. (c) Color-coded NCIs surfaces (attractive decreasing from blue to green, repulsive increasing from yellow to red) for conjugated Breslow intermediate.

Based on the stereochemical outcome and the steric effects of the *ortho*-substituents of the NHC catalysts, Newman projections of the stereochemical model for the homoenolate addition step are depicted in Figure 4. As a possible explanation for the differences of diastereoselectivity on the catalysts **C1** and **C6**, the direction of the nucleophilic attack to the aryl aldehyde could be restricted due to the steric hindrance of the N-aryl groups [12b]. In the case of **C6** bearing bulky 2,6-dibenzhydrylphenyl groups, the homoenolate addition step could involve two conformations. The conformation that generates the *cis*-lactone (**A**) can be disfavored due to the steric and/or electrostatic repulsion between the *ortho*-substituent on the N-aryl group and the carbonyl oxygen atom of the aryl aldehyde. On the other hand, even though highly sterically hindered, the aryl aldehyde has closed the reaction site of homoenolate addition by the hydrogen bonding between the enol and the carbonyl oxygen. As a result, the conformation that generates the *trans*-isomer (**B**) is favored over the conformation that produces the *cis*-isomer (**A**). The differences of the steric effects of N-aryl group on conformations (**C**) and (**D**) should be less pronounced in the case of **C1** with the mesityl groups. Even with the possible formation of the similar hydrogen bonding (**D**), the conjugated Breslow intermediate derived from **C1** would react with aryl aldehyde in such a way that minimizes the dipole–dipole interaction with the carbonyl group and enol moiety (**C**), resulting in a moderate level of β,γ-*cis* selectivity.

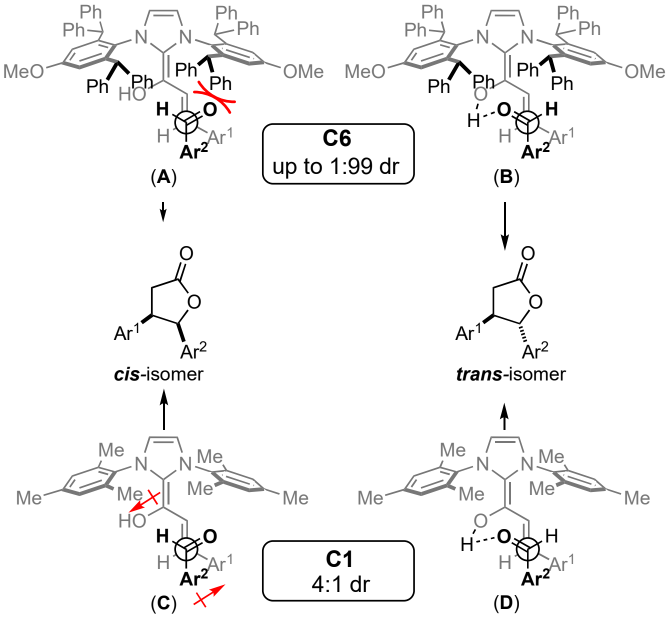


Figure 4. Possible diastereocontrol models of **C1** and **C6**.

3. Conclusion

In conclusion, a highly β,γ-*trans*-selective cross-annulation reaction of α,β-enals and aryl aldehyde is reported. The NHC generated from the imidazolium salt (**C6**) which bears bulky 2,6-dibenzhydrylphenyl groups was found to be a highly efficient catalyst, providing β,γ-diaryl-γ-butyrolactones in high yields with high diastereoselectivity. This catalysis tolerates the low catalyst loading of 2 mol % at high temperatures without any decrease of diastereoselectivity. Structural and computational analysis revealed that bulky 2,6-dibenzhydrylphenyl groups can play a key role in the conjugated Breslow intermediate, forming various noncovalent interactions including van der Waals, OH-π, and CH-π interactions and providing the suitable reaction site for β,γ-*trans*-selective γ-butyrolactone formation. A mechanistic study for this transformation and the observed β,γ-*trans* selectivity is currently underway in our laboratory.

4. Experimental Section

4.1 General Methods

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under a nitrogen atmosphere, using commercially supplied solvents and reagents unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck 60F$_{254}$ precoated silica gel plates and was visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid, *para*-anisaldehyde, or ninhydrin. Flash column chromatography was carried out silica gel 60 N (Kanto Chemical Co., Inc.).

4.2 Characterization Data

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker Biospin AVANCE III HD. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$) as an internal standard. Infrared (IR) spectra were recorded on a JASCO FT/IR 6300, and are reported in wavenumbers (cm^{-1}). Low- and high-resolution mass spectra were recorded on a Bruker Daltonics compact (ESI-MS) spectrometers and JEOL JMS-T100GCV (EI-MS) spectrometers in the positive and negative detection mode.

4.3 HPLC Conditions

For HPLC separations, a Cosmosil 5C18-AR-II analytical column (Nacalai Tesque, 4.6 × 250 mm, flow rate 1.0 mL min^{-1}), YMC-Triart C18 analytical column (YMC, 4.6 × 250 mm, flow rate 1.0 mL min^{-1}) was employed, and eluted products were detected by UV at 230 nm. A solvent system consisting of 0.1% TFA aqueous solution (v/v, solvent A) and 0.1% TFA in MeCN (v/v, solvent B) was used for HPLC elution.

*4.4 Experimental Procedure of Precatalysts **C4-C6***

4.4.1 (1E,2E)-N^1,N^2-Bis(2,6-bis(diphenylmethyl)-4-methylphenyl)ethane-1,2-diimine

To a suspension of 2,6-dibenzhydryl-4-methylaniline [20] (4.57 g, 10.4 mmol) in MeCN (104 mL) was added 39% aqueous of glyoxal (8.8 M, 0.59 mL, 5.20 mmol) and a catalytic amount of formic acid at room temperature. After being stirred at 60 ºC for 7 day, concentration under reduced pressure followed by recrystallization with $CHCl_3$-Et_2O gave the title compound (2.00 g, 43% yield) as a yellow solid. The solid compound was used immediately in next step.

*4.4.2 1,3-Bis(2,6-bis(diphenylmethyl)-4-methylphenyl)-1H-imidazole-2-ium chloride (IPr*Cl, **C4**) [20]*

To a solution of (1*E*,2*E*)-N^1,N^2-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)ethane-1,2-diimine (6.14 g, 6.81 mmol) in THF (235 mL) was added paraformaldehyde (204 mg, 6.81 mmol), anhydrous zinc chloride (928 mg, 6.81 mmol) at 70 ºC, and HCl in dioxane (4 M, 2.56 mL, 10.2 mmol) was added dropwise. After being stirred at 70 ºC for 5 h, concentration under reduced pressure followed by flash column chromatography over silica gel with CH_2Cl_2-MeOH (9:1) to give the pale pink solid, which was further purified recrystallization (CH_2Cl_2-*n*-hexane) gave the title compound **C4** (2.11 g, 33% yield) as a white solid: IR (ATR) ν 3283, 3060, 3026, 2918, 1683, 1601, 1494, 1448, 1240, 1175, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 6H), 5.39 (s, 2H), 5.51 (s, 4H), 6.70 (s, 4H), 6.77 (d, J = 7.4 Hz, 8H), 7.05 (t, J = 7.4 Hz, 8H), 7.09 (d, J = 7.6 Hz, 4H), 7.11 (d, J = 7.4 Hz, 4H), 7.17 (t, J = 7.6 Hz, 8H), 7.30 (d, J = 7.6 Hz, 8H),11.90 (s, 1H); ^{13}C NMR (100 MHz) δ 21.8 (2C), 51.0 (4C), 122.8 (2C), 126.4 (4C), 126.6 (4C), 128.4 (16C), 129.3 (10C), 130.6 (8C), 131.1 (4C), 140.4 (4C), 140.6 (2C), 142.2, 142.5 (4C), 143.1 (4C); HRMS (ESI), *m/z* calcd for $C_{69}H_{57}N_2$ $[M-Cl]^+$ 913.4516, found 913.4520.

4.4.3 (1E,2E)-N^1,N^2-Bis(2,6-bis(diphenylmethyl)-4-chlorophenyl)-ethane-1,2-diimine

To a suspension of 2,6-dibenzhydryl-4-chloroaniline [28] (11.3 g, 24.5 mmol) in MeCN (245 mL) was added 39% aqueous of glyoxal (8.8 M, 1.39 mL, 12.3 mmol) and a catalytic amount of formic acid at room temperature. After being stirred at 60 ºC for 10 day, concentration under reduced pressure followed by recrystallization with $CHCl_3$-Et_2O gave the title compound (8.74 g, 76% yield) as a yellow solid. The solid compound was used immediately in next step.

*4.4.4 1,3-Bis(2,6-bis(diphenylmethyl)-4-chlorophenyl)-1H-imidazole-2-ium chloride (**C5**)*

To a solution of (1*E*,2*E*)-N^1,N^2-bis(2,6-bis(diphenylmethyl)-4-chlorophenyl)ethane-1,2-diimine (8.71 g, 9.24 mmol) in THF (80.0 mL) was added paraformaldehyde (277 mg, 9.24 mmol), anhydrous zinc chloride (1.26 g, 9.24 mmol) at 70 ºC, and HCl in dioxane (4 M, 3.47 mL, 13.9 mmol) was added dropwise. After being stirred at 70 ºC for 4 h, concentration under reduced pressure followed by flash column chromatography over silica gel with CH_2Cl_2-MeOH (9:1) to give the pale pink solid, which was further purified recrystallization (CH_2Cl_2-*n*-hexane) gave the title compound **C5** (924 mg, 10% yield) as a white solid: IR (ATR) ν 3062, 2921, 2369, 1681, 1575, 1435, 1218 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 4H), 5.47 (s, 2H), 6.71－6.80 (m, 8H), 6.97 (s, 4H), 7.10－7.25 (m, 25H), 7.25－7.33 (m, 7H), 13.41 (s, 1H); ^{13}C NMR (100 MHz) δ 51.4 (4C), 123.2 (2C), 127.3 (8C), 128.8 (8C), 128.9 (8C), 129.0 (8C), 129.9 (8C), 130.4 (4C), 130.8 (2C), 137.8 (2C), 141.0 (4C), 141.7 (4C), 143.1 (4C), 143.2; HRMS (ESI), *m/z* calcd for $C_{67}H_{51}Cl_2O_2$ $[M-Cl]^+$ 953.3424, found 953.3422.

4.4.5 (1E,2E)-N^1,N^2-Bis(2,6-bis(diphenylmethyl)-4-methoxyphenyl)ethane-1,2-diimine

To a suspension of 2,6-dibenzhydryl-4-methoxyaniline [23] (4.29 g, 9.40 mmol) in MeCN (94.0 mL) was added 39% aqueous of glyoxal (8.8 M, 0.53 mL, 4.70 mmol) and a catalytic amount of formic acid at room temperature. After being stirred at 60 ºC for 7 day, concentration under reduced pressure followed by recrystallization with $CHCl_3$-Et_2O gave the title compound (3.02 g, 69% yield) as a yellow solid. The solid compound was used immediately in next step.

4.4.6 1,3-Bis(2,6-bis(diphenylmethyl)-4-methoxyphenyl)-1H-imidazole-2-ium chloride (IPr^{OMe}Cl, **C6**) [23]*

To a solution of (1*E*,2*E*)-N^1,N^2-bis(2,6-bis(diphenylmethyl)-4-methoxyphenyl)ethane-1,2-diimine (1.07 g, 1.15 mmol) in THF (39.7 mL) was added paraformaldehyde (34.5 mg, 1.15 mmol), anhydrous zinc chloride (156 mg, 1.15 mmol) at 70 ºC, and HCl in dioxane (4 M, 0.43 mL, 1.73 mmol) was added dropwise. After being stirred at 70 ºC for 3 h, concentration under reduced pressure followed by flash column chromatography over silica gel with CH_2Cl_2-MeOH (9:1) to give the pale pink solid, which was further purified recrystallization (CH_2Cl_2-*n*-hexane) gave the title compound **C6** (495 mg, 44% yield) as a white solid: IR (ATR) ν 3289, 3060, 2905, 1682, 1599, 1240, 1175, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 6H), 5.30 (s, 4H), 5.43 (s, 2H), 6.46 (s, 4H), 6.76－6.88 (m, 8H), 7.08－7.21 (m, 16H), 7.21－7.30 (m, 16H), 12.82 (s, 1H); ^{13}C NMR (100 MHz) δ 51.5 (4C), 55.2 (2C), 115.6 (4C), 123.4 (2C), 125.3 (2C), 126.9 (4C), 127.0 (4C), 128.6 (8C), 128.7 (8C), 129.1 (8C), 130.0 (8C), 141.7 (4C), 142.4 (4C), 142.7 (4C), 143.2, 160.8 (2C); HRMS (ESI), *m/z* calcd for $C_{69}H_{57}N_2O_2$ $[M-Cl]^+$ 945.4415, found 945.4417.

4.5 Experimental Procedures of γ-butyrolactone

4.5.1 General procedure for catalytic annulations of enals and aldehydes with excess DBU as a base

To a suspension of precatalyst **C6** (0.006 mmol, 0.02 equiv.) and arylaldehyde **2** (0.600 mmol, 2.0 equiv.) in THF (1.5 mL, 0.2 M) was added α,β-unsaturated aldehyde **1** (0.300 mmol, 1.0 equiv.) at room temperature under N_2 atmosphere. To the above mixture was added DBU (11.3 μL, 0.075 mmol, 0.25 equiv.) to start the reaction at 60 ºC. After being stirred at 60 ºC for 24 h, the solution was filtered through a small pad of SiO$_2$, concentration under reduced pressure followed by flash column chromatography over silica with *n*-hexane-EtOAc (8:1 to 5:1) gave a lactone **3**-*trans*. The diastereomer ratio was determined by HPLC analysis of the crude reaction mixture by comparison of the area ratio.

*4.5.2 trans-5-(4-Bromophenyl)-4-phenyldihydrofuran-2(3H)-one (**3a**-trans)*

By use of the general procedure, *p*-bromobenzaldehyde (111.0 mg, 0.60 mmol) was converted into the title compound **3a** in 66% NMR yield. The diastereomeric ratio (1:13 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3a**-*trans* (58.0 mg, 61% yield) as a yellow oil: IR (ATR) ν 1783 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.93 (dd, *J* = 17.6, 11.1 Hz, 1H), 3.05 (dd, *J* = 17.6, 8.5 Hz, 1H), 3.51 (ddd, *J* = 11.1, 8.8, 8.5 Hz, 1H), 5.36 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 2H), 7.12－7.21 (m, 2H), 7.29－7.40 (m, 3H), 7.46 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 37.1, 50.8, 86.7, 122.6, 127.2 (2C), 127.4 (2C), 128.1 129.2 (2C), 131.8 (2C), 136.7, 137.2, 174.9; HRMS (EI), *m*/*z* calcd for $C_{16}H_{13}BrO_2$ [M]$^+$ 316.0099, found 316.0092; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 11.7 min, $t_{R(trans)}$ = 13.3 min.

*4.5.3 trans-5-(4-Chlorophenyl)-4-phenyldihydrofuran-2(3H)-one (**3b**-trans)*

By use of the general procedure, *p*-chlorobenzaldehyde (84.3 mg, 0.60 mmol) was converted into the title compound **3b** in 56% NMR yield. The diastereomeric ratio (1:13 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3b**-*trans* (41.3 mg, 51% yield) as a colorless oil: IR (ATR) ν 1783 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.93 (dd, *J* = 17.6, 11.1 Hz, 1H), 3.05 (dd, *J* = 17.6, 8.5 Hz, 1H), 3.52 (ddd, *J* = 11.1, 8.8, 8.5 Hz, 1H), 5.38 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.13－7.20 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.31－7.38 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 37.1, 50.8, 86.6, 127.0 (2C), 127.4 (2C), 128.0, 128.8 (2C), 129.2 (2C), 134.5, 136.2, 137.3, 174.9; HRMS (EI), *m*/*z* calcd for $C_{16}H_{13}ClO_4$ [M]$^+$ 272.0604, found 272.0610; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 10.8 min, $t_{R(trans)}$ = 12.1 min.

*4.5.4 trans-Methyl 4-(5-oxo-3-phenyltetrahydrofuran-2-yl)benzoate (**3c**-trans)*

By use of the general procedure, methyl terephthalaldehydate (98.5 mg, 0.60 mmol) was converted into the title compound **3c** in 65% NMR yield. The diastereomeric ratio (1:16 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (5:1) gave the title compound **3c**-*trans* (54.2 mg, 61% yield) as a white solid: IR (ATR) ν 1788 (CO), 1721 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.95 (dd, *J* = 17.6, 11.0 Hz, 1H), 3.07 (dd, *J* = 17.6, 8.5 Hz, 1H), 3.54 (ddd, *J* = 11.0, 8.7, 8.5 Hz, 1H), 3.90 (s, 3H), 5.46 (d, *J* = 8.7 Hz, 1H), 7.14－7.20 (m, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.31－7.39 (m, 3H), 7.99 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 37.1, 50.8, 52.2, 86.7, 125.4 (2C), 127.4 (2C), 128.1, 129.2 (2C), 129.9 (2C), 130.4, 137.3, 142.7, 166.5, 174.9; HRMS (EI), *m*/*z* calcd for $C_{18}H_{16}O_4$ [M]$^+$ 296.1049, found 296.1044; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 50:50, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 14.1 min, $t_{R(trans)}$ = 16.8 min.

*4.5.5 trans-5-(3-Bromophenyl)-4-phenyldihydrofuran-2(3H)-one (**3e**-trans)*

By use of the general procedure, *m*-bromobenzaldehyde (70.3 μL, 0.60 mmol) was converted into the title compound **3e** in 74% NMR yield. The diastereomeric ratio (1:24 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3e**-*trans* (67.8 mg, 71% yield) as a yellow oil: IR (ATR) ν 1783 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.92 (dd, *J* = 17.6, 10.8 Hz, 1H), 3.06 (dd, *J* = 17.6, 8.5 Hz, 1H), 3.55 (ddd, *J* = 10.8, 8.5, 8.5 Hz, 1H), 5.37 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 7.14－7.21 (m, 3H), 7.30－7.41 (m, 4H), 7.45 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 37.1, 50.6, 86.4, 122.8, 124.3, 127.4 (2C), 128.1, 128.6, 129.3 (2C), 130.2, 131.8, 137.5, 140.1, 174.9; HRMS (EI), *m*/*z* calcd for $C_{16}H_{13}BrO_2$ [M]$^+$ 316.0099, found 316.0095; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 11.1 min, $t_{R(trans)}$ = 12.4 min.

*4.5.6 trans-5-(3-Chlorophenyl)-4-phenyldihydrofuran-2(3H)-one (**3f**-trans)*

By use of the general procedure, *m*-chlorobenzaldehyde (68.0 μL, 0.60 mmol) was converted into the title compound **3f** in 53% NMR yield. The diastereomeric ratio (1:24 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3f**-*trans* (41.9 mg, 51% yield) as a yellow oil: IR (ATR) ν 1782 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.92 (dd, *J* = 17.6, 10.8 Hz, 1H), 3.06 (dd, *J* = 17.6, 8.5 Hz, 1H), 3.55 (ddd, *J* = 10.8, 8.5, 8.5 Hz, 1H), 5.39 (d, *J* = 8.5 Hz, 1H), 6.98－7.04 (m, 1H), 7.16－7.21 (m, 2H), 7.21－7.27(m, 2H), 7.27－7.40 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 37.0, 50.6, 86.4, 123.8, 125.6, 127.3 (2C), 128.1, 128.8, 129.2 (2C), 129.9, 134.7, 137.5, 139.8, 174.8; HRMS (EI), *m*/*z* calcd for $C_{16}H_{13}ClO_2$ [M]$^+$ 272.0604, found 272.0603; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 10.2 min, $t_{R(trans)}$ = 11.5 min.

4.5.7 *trans-5-(2-Chlorophenyl)-4-phenyldihydrofuran-2(3H)-one (**3g**-trans)*

By use of the general procedure, *o*-chlorobenzaldehyde (67.6 μL, 0.60 mmol) was converted into the title compound **3g** in 69% NMR yield. The diastereomeric ratio (1:99 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3g**-*trans* (53.2 mg, 65% yield) as a yellow oil: IR (ATR) ν 1784 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.78 (dd, *J* = 17.8, 6.5 Hz, 1H), 3.04 (dd, *J* = 17.8, 8.8 Hz, 1H), 3.66 (ddd, *J* = 8.8, 6.5, 5.3 Hz, 1H), 5.85 (d, *J* = 5.3 Hz, 1H), 7.21-7.48 (m, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 35.8, 48.7, 84.3, 126.5, 126.9 (2C), 127.3, 127.8, 129.1 (2C), 129.7, 130.0, 132.3, 136.2, 139.8, 176.2, 174.9; HRMS (EI), *m*/*z* calcd for $C_{16}H_{13}ClO_2$ [M]$^+$ 272.0604, found 272.0600; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 17.9 min, $t_{R(trans)}$ = 10.6 min.

*4.5.8 trans-5-(3-Bromophenyl)-4-(4-chlorophenyl)dihydrofuran-2(3H)-one (**3h**-trans)*

By use of the general procedure, (*E*)-3-(4-chlorophenyl)acrylaldehyde (49.9 mg, 0.30 mmol) was converted into the title compound **3h** in 80% NMR yield. The diastereomeric ratio (1:19 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3h**-*trans* (80.1 mg, 76% yield) as a yellow oil: IR (ATR) ν 1786 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.88 (dd, *J* = 17.6, 10.8 Hz, 1H), 3.07 (dd, *J* = 17.6, 8.6 Hz, 1H), 3.53 (ddd, *J* = 10.8, 8.6, 8.6 Hz, 1H), 5.32 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 7.12 (d, *J* = 8.4, 2H), 7.20 (t, *J* = 7.9, Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.40 (s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 36.9, 50.1, 86.2, 123.0, 124.3, 128.5, 128.7 (2C), 129.5 (2C), 130.3, 132.0, 134.1, 135.8, 139.7, 174.4; HRMS (EI), *m*/*z* calcd for $C_{16}H_{12}BrClO_2$ [M]$^{+}$ 349.9709, found 349.9710; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 14.4 min, $t_{R(trans)}$ = 17.2 min.

*4.5.9 trans-Methyl 4-(2-(3-bromophenyl)-5-oxotetrahydrofuran-3-yl)benzoate (**3i**-trans)*

By use of the general procedure, (*E*)-4-(3-oxoprop-1-en-1-yl)benzoate (57.1 mg, 0.30 mmol) was converted into the title compound **3i** in 83% NMR yield. The diastereomeric ratio (1:16 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (5:1) gave the title compound **3i**-*trans* (87.5 mg, 78% yield) as a white solid: IR (ATR) ν 1784 (CO), 1720 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.94 (dd, *J* = 17.6, 10.8 Hz, 1H), 3.10 (dd, *J* = 17.6, 8.5 Hz, 1H), 3.62 (ddd, *J* = 10.8, 8.5, 8.5 Hz, 1H), 3.93 (s, 3H), 5.38 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.39 (s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 36.8, 50.6, 52.3, 86.0, 123.0, 124.2, 127.5 (2C), 128.5, 130.1, 130.3, 130.5 (2C), 132.0, 139.7, 142.5, 166.4, 174.3; HRMS (EI), *m*/*z* calcd for $C_{18}H_{15}BrO_4$ [M]$^{+}$ 374.0154, found 374.0152; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 50:50, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 21.7 min, $t_{R(trans)}$ = 25.1 min.

*4.5.10 trans-5-(3-Bromophenyl)-4-(4-methoxyphenyl)dihydrofuran-2(3H)-one (**3j**-trans)*

By use of the general procedure, (*E*)-3-(4-methoxyphenyl)acrylaldehyde (48.7 mg, 0.30 mmol) was converted into the title compound **3j** in 79% NMR yield. The diastereomeric ratio (1:24 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (5:1) gave the title compound **3j**-*trans* (78.3 mg, 75% yield) as a white solid: IR (ATR) ν 1785 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.88 (dd, *J* = 17.6, 11.0 Hz, 1H), 3.03 (dd, *J* = 17.6, 8.6 Hz, 1H), 3.49 (ddd, *J* = 11.0, 8.6, 8.6 Hz, 1H), 3.81 (s, 3H), 5.32 (d, *J* = 8.6 Hz,1H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.39 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 37.2, 50.0, 55.3, 86.6, 114.6 (2C), 122.8, 124.3, 128.4 (2C), 128.5, 129.1, 130.2, 131.7, 140.1, 159.3, 174.9; HRMS (EI), *m*/*z* calcd for $C_{17}H_{15}BrO_3$ [M]$^{+}$ 346.0205, found 346.0211; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 10.7 min, $t_{R(trans)}$ = 12.3 min.

*4.5.11 trans-5-(3-Bromophenyl)-4-(3-chlorophenyl)dihydrofuran-2(3H)-one (**3k**-trans)*

By use of the general procedure, (*E*)-3-(3-chlorophenyl)acrylaldehyde (50.0 mg, 0.30 mmol) was converted into the title compound **3k** in 78% NMR yield. The diastereomeric ratio (1:24 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3k**-*trans* (78.7 mg, 75% yield) as a yellow oil: IR (ATR) ν 1784 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.88 (dd, *J* = 17.6, 10.6 Hz, 1H), 3.07 (dd, *J* = 17.6, 8.6 Hz, 1H), 3.53 (ddd, *J* = 10.6, 8.6, 8.6 Hz, 1H), 5.36 (d, *J* = 8.6 Hz, 1H), 7.02－7.09 (m, 2H), 7.17－7.24 (m, 2H), 7.29－7.34 (m, 2H), 7.40 (s, 1H), 7.45－7.52 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 36.9, 50.3, 86.0, 123.0, 124.2, 125.6, 127.5, 128.4, 128.5, 130.3, 130.6, 132.0, 135.1, 139.6, 139.7, 174.3; HRMS (EI), *m*/*z* calcd for $C_{16}H_{12}BrClO_2$ [M]$^{+}$ 349.9709, found 349.9713; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 13.7 min, $t_{R(trans)}$ = 16.4 min.

*4.5.12 trans-5-(3-Bromophenyl)-4-(2-chlorophenyl)dihydrofuran-2(3H)-one (**3l**-trans)*

By use of the general procedure, (*E*)-3-(2-chlorophenyl)acrylaldehyde (50.0 mg, 0.30 mmol) was converted into the title compound **3l** in 78% NMR yield. The diastereomeric ratio (1:11.5 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3l**-*trans* (74.9 mg, 71% yield) as a yellow oil: IR (ATR) ν 1784 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.83 (dd, *J* = 17.8, 8.3 Hz, 1H), 3.09 (dd, *J* = 17.8, 8.9 Hz, 1H), 4.13 (ddd, *J* = 8.9, 8.3, 6.8 Hz, 1H), 5.55 (d, *J* = 6.8 Hz, 1H), 7.15－7.51 (m, 8H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 35.4, 46.2, 84.8, 122.9, 123.9, 127.7, 127.8, 128.4, 129.2, 130.4, 130.5, 131.8, 134.0, 136.0, 140.3, 175.0; HRMS (EI), *m*/*z* calcd for $C_{16}H_{12}BrClO_2$ [M]$^{+}$ 349.9709, found 349.9711; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 14.4 min, $t_{R(trans)}$ = 15.6 min.

*4.5.13 trans-4-(2-Bromophenyl)-5-(3-bromophenyl)dihydrofuran-2(3H)-one (**3m**-trans)*

By use of the general procedure, (*E*)-3-(2-bromophenyl)acrylaldehyde (63.3 mg, 0.30 mmol) was converted into the title compound **3m** in 81% NMR yield. The diastereomeric ratio (1:9 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3m**-*trans* (84.4 mg, 73% yield) as a yellow oil: IR (ATR) ν 1785 (CO) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.78 (dd, *J* = 17.8, 8.4 Hz, 1H), 3.11 (dd, *J* = 17.8, 8.8 Hz, 1H), 4.16 (ddd, *J* = 8.8, 8.4, 6.8 Hz, 1H), 5.53 (d, *J* = 6.8 Hz, 1H), 7.15－7.25 (m, 3H), 7.37－7.42 (m, 2H), 7.45－7.50 (m, 2H), 7.57－7.63 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 36.0, 48.4, 85.1, 122.9, 124.0, 124.6, 127.6, 128.5 (2C), 129.5, 130.4, 131.8, 133.8, 137.8, 140.2, 174.9; HRMS (EI), *m*/*z* calcd for $C_{16}H_{12}Br_2O_2$ [M]$^{+}$ 393.9240, found 393.9208; HPLC YMC-Triart C18, H$_2$O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 15.5 min, $t_{R(trans)}$ = 16.5 min.

*4.5.14 trans-5-(3-Bromophenyl)-4-(furan-2-yl)dihydrofuran-2(3H)-one (3**n**-trans)*

By use of the general procedure, (*E*)-3-(furan-2-yl)acrylaldehyde (36.6 mg, 0.30 mmol) was converted into the title compound **3n** in 53% NMR yield. The diastereomeric ratio (1:24 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3n**-*trans* (47.0 mg, 51% yield) as a yellow oil: IR (ATR) ν 1786 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93-3.01 (m, 1H), 2.98-3.07 (m, 1H), 3.57-3.69 (m, 1H), 5.42-5.49 (m, 1H), 6.13 (d, *J* = 3.3 Hz, 1H), 6.35 (dd, *J* = 3.3, 1.9 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.44 (s, 1H), 7.44 (d, *J* = 1.9 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.4, 44.0, 83.3, 107.8, 110.6, 122.9, 124.1, 128.5, 130.3, 131.8, 140.0, 142.8, 150.2, 174.3; HRMS (EI), *m/z* calcd for $C_{14}H_{11}BrO_3$ [M]$^{+}$ 305.9892, found 305.9884; HPLC YMC-Triart C18, H_2O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 8.6 min, $t_{R(trans)}$ = 9.8 min.

*4.5.15 trans-5-(3-Bromophenyl)-4-(thiophen-2-yl)dihydrofuran-2(3H)-one (3**o**-trans)*

By use of the general procedure, (*E*)-3-(thiophen-2-yl)acrylaldehyde (41.5 mg, 0.30 mmol) was converted into the title compound **3o** in 82% NMR yield. The diastereomeric ratio (1:32 dr) was determined by the reverse phase HPLC of the crude reaction mixture by comparison of the area% of each diastereomer. Flash column chromatography with *n*-hexane-EtOAc (8:1) gave the title compound **3o**-*trans* (76.6 mg, 79% yield) as a yellow oil: IR (ATR) ν 1787 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (dd, *J* = 17.4, 11.0 Hz, 1H), 3.14 (dd, *J* = 17.4, 8.6 Hz, 1H), 3.84 (ddd, *J* = 11.0, 8.6, 8.6 Hz, 1H), 5.34 (d, *J* = 8.6 Hz 1H), 6.83 (d, *J* = 3.6 Hz, 1H), 6.98 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 5.1 Hz, 1H), 7.45 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.1, 46.1, 86.5, 122.9, 124.6, 125.0, 125.7, 127.4, 128.9, 130.2, 132.1, 139.4, 140.2, 173.9; HRMS (EI), *m/z* calcd for $C_{14}H_{11}BrO_2S$ [M]$^{+}$ 321.9663, found 321.9659; HPLC YMC-Triart C18, H_2O (containing 0.1% TFA)/MeCN (containing 0.1% TFA) = 40:60, flow rate = 1.0 mL/min, UV: λ = 230 nm, $t_{R(cis)}$ = 10.6 min, $t_{R(trans)}$ = 12.0 min.

Declaration of Competing Interests

The authors declare no conflict of interest.

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Appendix A. Supplementary Information

This section contains the experimental details, and ^{1}H and ^{13}C NMR spectra. Supplementary Information related to this article can be found at XXX.

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