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Titanium tetraiodide-mediated diastereoselective iodo-aldol and Mannich reactions of γ-alkoxy-α,β-alkynyl ketone derivatives

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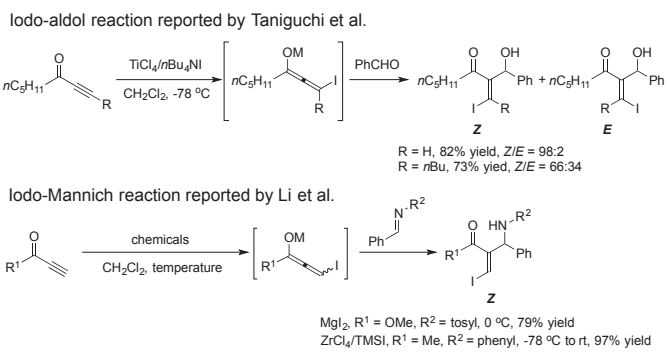
ABSTRACT

The development of the stereoselective synthesis of vinyl halides plays an important role in organic chemistry. The multi-functionalized vinyl iodide is one of the most important intermediates in functional organic compounds. We investigated stereoselective iodo-aldol and iodo-Mannich reactions using γ-alkoxy-α,β-alkynyl ketones. Characteristic features of titanium tetraiodide involve iodination ability and moderate Lewis acidity, which are successfully used for the present stereoselective synthesis of multi-functionalized vinyl iodides. Furthermore, we have succeeded in the synthesis of a useful tetra-substituted furan, via a Sonogashira coupling of the vinyl iodide moiety. The factors to control diastereoselectivity of the iodo-aldol reactions are explained in terms of theoretical calculations. Consequently, the obtained activation free energy and reaction energy indicate the experimentally observed *E*/*Z*-selectivity.

1. Introduction

The development of the stereoselective synthesis of vinyl halides plays an important role in organic chemistry. The synthesized vinyl iodides in a stereoselective manner are important intermediates. In particular, multi-functionalized vinyl iodides have diversity in synthetic organic chemistry due to their convertibility and applicability such as the metal-catalyzed cross-coupling and Nozaki–Hiyama–Kishi reaction as substrates.[1]

Many studies over the last three decades have shown the formation of vinyl iodides from alkynyl ketones. In 1986, Taniguchi et al. reported that the stereoselective iodo-aldol reaction of ethynyl ketones as terminal alkynyl ketones with aldehydes was promoted by $TiCl_4$/nBu_4NI, $TiCl_4$/TMSI (TMS=trimethylsilyl), nBu_4NF/TMSI, $BF_3{\cdot}OEt_2$/nBu_4NI, Et_2AlI, or TiI_4.[2] Among them, the $TiCl_4$/nBu_4NI combined system was the most effective (Scheme 1). The vinyl iodide product by coupling of α,β-acetylenic ketone with aldehyde using a $TiCl_4$/nBu_4NI system has been documented to generate the *E*-isomer as the major product at 0 °C.[2b] However, the iodo-aldol reaction of hexynyl ketone as an internal alkynyl ketone gave the iodo-aldol product with moderate stereoselectivity. In contrast, Li et al. reported that the diastereoselective iodo-Mannich reaction of terminal α,β-acetylenic esters and ketones with imine was promoted by MgI_2[3] or $ZrCl_4$/TMSI[4] (Scheme 1). Although good diastereoselectivity was shown, it reported only terminal alkynes. As is evident from the above reports, several iodo-aldol reactions have been reported via β-iodoallenoate intermediates from alkynyl ketones and esters with $ZrCl_4$/nBu_4NI,[5] Et_2AlI,[6] TMSI,[7] $BF_3{\cdot}OEt_2$/TMSI,[8] $CeCl_3{\cdot}7H_2O$/NaI,[9] or GaI_3.[10] The iodo-aldol reactions using the above promoters with aldehydes gave *Z*-isomers under the almost identical conditions. As previous asymmetric synthesis studies, enantioselective iodo-aldol reactions have been developed using chiral catalyst.[11] Asymmetric synthesis of iodo-aldol reactions using a chiral auxiliary such as a menthyl group has also been reported.[12] However, to our knowledge, the diastereoselective iodo-



Scheme 1. Previous works on the subject of iodo-aldol and iodo-Mannich reaction.

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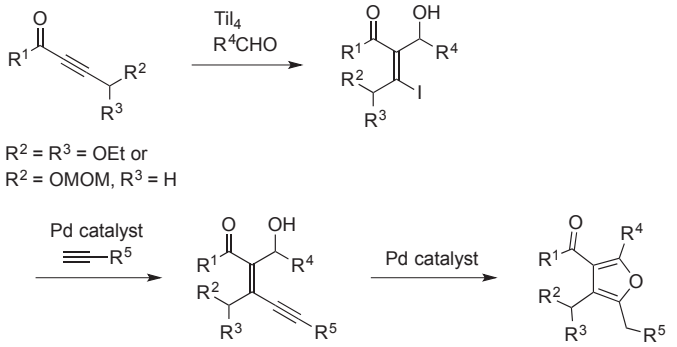
aldol reaction of internal alkynyl ketones has been limited to an intramolecular cyclization.[13]

In an effort to use the iodination ability of titanium tetraiodide more effectively, we have already reported the hydroiodination reaction of alkenes and alkynes,[14] the aza-Prins reaction of *p*-tosylimine derived from ethyl glyoxylate,[15] the synthesis of 2-iodopyridines,[16] and a tandem Prins reaction of alkynes.[17] Titanium tetraiodide has excellent iodination ability and superior reducing ability. In addition, it has a mild Lewis acidity not usually found in other metal iodides. Thus, by using titanium tetraiodide, alkynyl ketone can be diastereoselectively transformed into the vinyl iodide obtained via aldol and Mannich reactions. If cyclization procedure of our method can be used, it is possible to synthesize heterocyclic rings having a variety of substituents from multi-functionalized vinyl iodides (Scheme 2). In this paper, we would like to report the stereoselective synthesis of the multi-substituted vinyl iodide with titanium tetraiodide and the computational analysis of the reaction mechanism using a DFT calculation. Also described is the synthesis of tetra-substituted furan from vinyl iodide via the Sonogashira coupling reaction and iodo-Mannich reaction with imino ester.[18]



Scheme 2. Diastereoselective iodo-aldol reaction of γ-alkoxy-α,β-alkynyl ketone derivatives promoted by titanium tetraiodide.

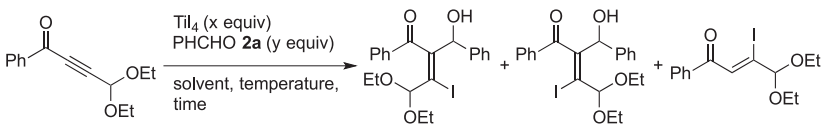
2. Results and discussion

2.1. The iodo-aldol reactions

Initially, reactivity and selectivity were examined in the iodo-aldol reaction of the γ-diethoxyalkynyl ketone **1a** with titanium tetraiodide and benzaldehyde (**2a**). The aim of this study was to obtain the best conditions for the iodo-aldol reaction. As shown in Table 1, several solvents were effective on the yields and the diastereoselectivity (Entries 1–4). When propionitrile (EtCN) was used, the desired iodo-aldol product **3a** was obtained in 45% yield with a moderate diastereoselectivity (Entry 1). However, in other solvents such as toluene, THF, and dichloromethane, the iodo-aldol product **3a** was obtained in lower yields (Entries 2–4). The best solvent obtained from the above examinations was dichloromethane, because in dichloromethane the reaction proceeded most cleanly. Therefore, the reaction temperature in dichloromethane was next examined in detail (Entries 5–9). The reaction at −50 °C gave the iodo-aldol product **3a** in moderate yield with better material balance (Entry 7). The yields of **3a** at −78 and −60 °C were much lower than that at −50 °C (Entries 5–7). However, the yield of the iodoalkenone **4** and material balance at lower temperature were good. These results suggest the importance of the reaction temperature at the initial step for the generation of the coordinated enolate with titanium tetraiodide. Higher temperatures at −40 and −20 °C (Entries 8 and 9) led to formation of the undesired by-products due to decomposition. We next investigated amounts of titanium tetraiodide and benzaldehyde (**2a**) at −50 °C. When the reaction was conducted using 1.2–1.5 equiv of titanium tetraiodide with 1.0 equiv of benzaldehyde (Entries 10–12), the iodo-aldol product **3a** was obtained in good yield with good *E*-selectivity. In addition, we found that the use of an excess TiI_4 remarkably reduced the yield of the iodoalkenone **4**. From the above results, we found the optimized conditions for γ-diethoxyalkynyl ketone.

In order to understand the scope and limitations of aldehyde, we investigated use of several aldehydes under the optimized reaction conditions (Table 2). Diastereoselectivity of all iodo-aldol products were, in general, *E*-isomers as major products. Several characteristics of this reaction are noteworthy. The reaction of *p*-chlorobenzaldehyde (**2b**), which has an electron-withdrawing group, gave the product ***E*-3b** in 52% yield (Entry 2). The reaction of *p*-methoxybenzaldehyde (**2c**), which has an electron-donating group, also afforded only the product ***E*-3c** in 61% yield (Entry 3). The use of *p*-tolualdehyde (**2d**) gave the product **3d** in 64% yield with high diastereoselectivity (Entry 4). When the reaction of 1-naphthaldehyde (**2e**) was carried out, the iodinated product ***E*-3e** was obtained in 34% yield (Entry 5). The reaction of 2-thiophenecarboxaldehyde (**2f**) as a heteroaromatic aldehyde gave the product ***E*-3f** in 52% yield (Entry 6). When the reactions of

Table 1
Optimization of reaction conditions[a]



1a ***E*-3a** ***Z*-3a** **4**

Entry	TiI_4 (equiv)	**2a** (equiv)	Solvent	Temperature (°C)	Time	Yield of **3a** (%)[b]	*E*/*Z*	Yield of **4** (%)[b]	Yield of **1a** (%)[b]
1	1.0	1.0	EtCN	−78 to −60	85 min	45	72:28	39	1
2	1.0	1.0	Toluene	−78 to −60	110 min	17	84:16	19	42
3	1.0	1.0	THF	−78 to −60	110 min	11	86:14	15	55
4	1.0	1.0	CH_2Cl_2	−78 to −60	80 min	13	79:21	25	47
5	1.0	1.0	CH_2Cl_2	−78	2 h	4	100:0	45	37
6	1.0	1.0	CH_2Cl_2	−60	2 h	9	100:0	38	26
7	1.0	1.0	CH_2Cl_2	−50	2 h	55	90:10	14	20
8	1.0	1.0	CH_2Cl_2	−40	2 h	64	89:11	3	0
9	1.0	1.0	CH_2Cl_2	−20	2 h	28	100:0	0	3
10	1.2	1.0	CH_2Cl_2	−50	2 h	67	89:11	6	18
11	1.3	1.0	CH_2Cl_2	−50	2 h	65	97:3	0	25
12	1.5	1.0	CH_2Cl_2	−50	2 h	56	97:3	4	11
13	1.3	1.2	CH_2Cl_2	−50	2 h	36	83:17	29	3

[a] Reactions were carried out with 0.15 mmol of **1a**, several equivalents of TiI_4 and **2a**, in a solvent (3 mL) under an argon atmosphere (1 atm).
[b] Isolated yield.

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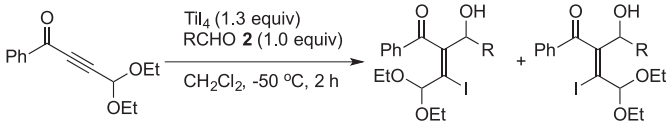
Table 2
Iodo-aldol reaction with several aldehydes[a]



1a E-3 Z-3

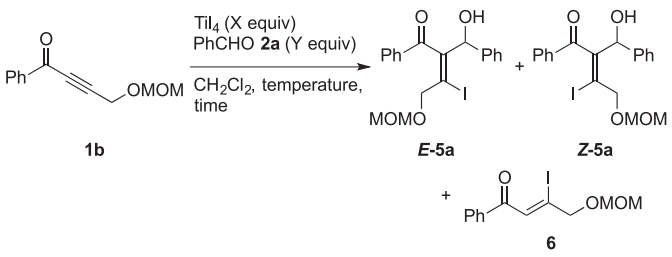
Entry	2	R	3	Yield of 3 (%)[b]	E/Z
1	**2a**	Ph	**3a**	65	97:3
2	**2b**	*p*-ClC_6H_4	**3b**	52	100:0
3	**2c**	*p*-$MeOC_6H_4$	**3c**	61	100:0
4	**2d**	*p*-MeC_6H_4	**3d**	64	89:11
5	**2e**	1-Naphthyl	**3e**	34	100:0
6	**2f**	2-Thienyl	**3f**	52	100:0
7	**2g**	Cl_3C	**3g**	41	100:0
8	**2h**	*n*-Pentyl	**3h**	35	100:0

[a] Reactions were carried out with 0.15 mmol of **1a** and **2**, 0.195 mmol of TiI_4, in dichloromethane (3 mL) under an argon atmosphere (1 atm).
[b] Isolated yield.

chloral (**2g**) and hexanal (**2h**) as aliphatic aldehydes were carried out, the products ***E*-3g** and ***E*-3h** were obtained in moderate yields (Entries 7 and 8).

We next investigated the iodo-aldol reaction of alkynyl ketone **1b** as a γ-monoalkoxyalkynyl ketone **1b** instead of γ-diethoxyalkynyl ketone **1a** with titanium tetraiodide and benzaldehyde (**2a**). The results are summarized in Table 3. At first, we examined γ-methoxymethoxyalkynyl ketone **1b** under the above optimized reaction conditions of γ-diethoxyalkynyl ketone **1a** (Entry 1). The desired iodo-aldol product **5a** was obtained in 65% yield with a moderate *E*-selectivity. To improve both the yield and the diastereoselectivity, several reaction conditions were examined. When the temperature was lower than −50 °C with each 1.0 equiv of titanium tetraiodide and benzaldehyde (Entries 2–7), it was found that the yield and the diastereoselectivity of **5a** were improved. The yield in the case of Entry 6 was slightly reduced to 67%. However, the material balance increased by lowering the temperature. From the above temperature investigation, the best conditions were at −78 °C and for 3.0 h with titanium tetraiodide

Table 3
Optimization of reaction conditions[a]



1b E-5a Z-5a 6

Entry	TiI_4 (equiv)	2a (equiv)	Temperature (°C)	Time (h)	Yield of 5a (%)[b]	E/Z	Yield of 6 (%)[b]
1[c]	1.3	1.0	−50	1.5	65	72:28	5
2[c]	1.0	1.0	−50	1.5	66	73:27	9
3	1.0	1.0	−60	1.5	69	77:23	3
4	1.0	1.0	−60	0.5	72	77:23	2
5	1.0	1.0	−70	1.5	75	78:22	5
6	1.0	1.0	−78	1.5	67	80:20	12
7	1.0	1.0	−78	3.0	76	79:21	8
8	1.1	1.0	−78	3.0	75	78:22	13
9	1.1	1.2	−78	3.0	75	77:23	8
10	1.2	1.2	−78	3.0	82	77:23	12
11	1.2	1.5	−78	3.0	78	75:25	11

[a] Reactions were carried out with 0.15 mmol of **1b**, several equivalents of TiI_4 and **2a**, in a solvent (3 mL) under an oxygen atmosphere (1 atm).
[b] Isolated yield.
[c] Under an argon atmosphere (1 atm).

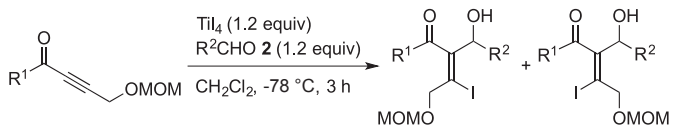
(1.0 equiv) and benzaldehyde (1.0 equiv) (Entry 7). Amounts of titanium tetraiodide and benzaldehyde, under the optimized conditions of Entry 7, were further examined (Entries 8–11). When the reaction was carried out using 1.2 equiv of titanium tetraiodide and benzaldehyde at −78 °C for 3 h (Entry 10), the product **5a** was obtained in the best yield (82%) with good diastereoselectivity. The diastereoselectivities of all the products from γ-methoxymethoxyalkynyl ketone **1b** were slightly lower than those with γ-diethoxyalkynyl ketone **1a**. Although no significant differences in the yields were observed, *E*-selectivity of the γ-methoxymethoxyalkynyl ketone **1b** decreased. The present study shows that *E*-selectivity of the product from γ-methoxymethoxyalkynyl ketone **1b** is influenced by the substituents of the alkynyl ketone.

Under the optimum reaction conditions for γ-methoxy methoxyalkynyl ketone **1b**, we examined several aldehydes to clarify the scope and limitations (Table 4). The reactions with *p*-chlorobenzaldehydes (**2b**) and *p*-methylbenzaldehydes (**2d**) gave the iodo-aldol products **5b** and **5d** in good yields with good diastereoselectivity (Entries 2 and 4). The reaction with *p*-methoxybenzaldehyde (**2c**), as with an electron-donating group, and hexanal (**2g**), as an aliphatic aldehyde, gave respectively the products **5c** and **5g** in moderate yields with moderate diastereoselectivity (Entries 3 and 7). Unfortunately, 1-naphthaldehyde (**2e**) gave the product **5e** in a low yield with no diastereoselectivity (Entry 5). We next examined the alkyl group R^1 of alkynyl ketones. Use of γ-methoxymethoxyalkynyl 2-thienyl ketone **1c** gave the iodo-aldol products **5h** in 74% yield with good diastereoselectivity (Entry 8). When the reaction of γ-methoxymethoxyalkynyl methyl ketone **1d** was carried out, the iodo-aldol product **5i** was obtained in a low yield with low diastereoselectivity (Entry 9). We found that the substituents of the alkynyl ketones and aldehydes varied the yields and selectivity. Regarding the diastereoselectivity, the *E*-isomer predominated in all the cases. A detailed examination into the reaction mechanisms may lead to a better understanding of the diastereoselectivity.

2.2. Computational analysis

Our proposed mechanism of the iodo-aldol reaction between γ-alkoxy-α,β-alkynyl ketone and benzaldehyde is shown in Scheme 3. First, 1,4-addition of titanium tetraiodide to the alkynyl ketone (**React.-1**) provides the titanium allenolate **I-1** via the transition

Table 4
Iodo-aldol reaction of ketone **1b** with several aldehydes[a]



1b-d E-5 Z-5

Entry	1	R^1	2	R^2	5	Yield of 5 (%)[b]	E/Z
1	**1b**	Ph	**2a**	Ph	**5a**	82	77:23
2	**1b**	Ph	**2b**	*p*-ClC_6H_4	**5b**	72	72:25
3	**1b**	Ph	**2c**	*p*-$MeOC_6H_4$	**5c**	56	88:12
4	**1b**	Ph	**2d**	*p*-MeC_6H_4	**5d**	73	79:21
5	**1b**	Ph	**2e**	1-Naphthyl	**5e**	31	56:44
6	**1b**	Ph	**2f**	2-Thienyl	**5f**	33	85:15
7	**1b**	Ph	**2g**	*n*-Pentyl	**5g**	48	70:30
8[c]	**1c**	2-Thienyl	**2a**	Ph	**5h**	74	75:25
9[c]	**1d**	Me	**2a**	Ph	**5i**	32	56:44

[a] Reactions were carried out with 0.15 mmol of **1b**, several equivalents of TiI_4 and **2a**, in a solvent (3 mL) under an oxygen atmosphere (1 atm).
[b] Isolated yield.
[c] Under an argon atmosphere (1 atm).

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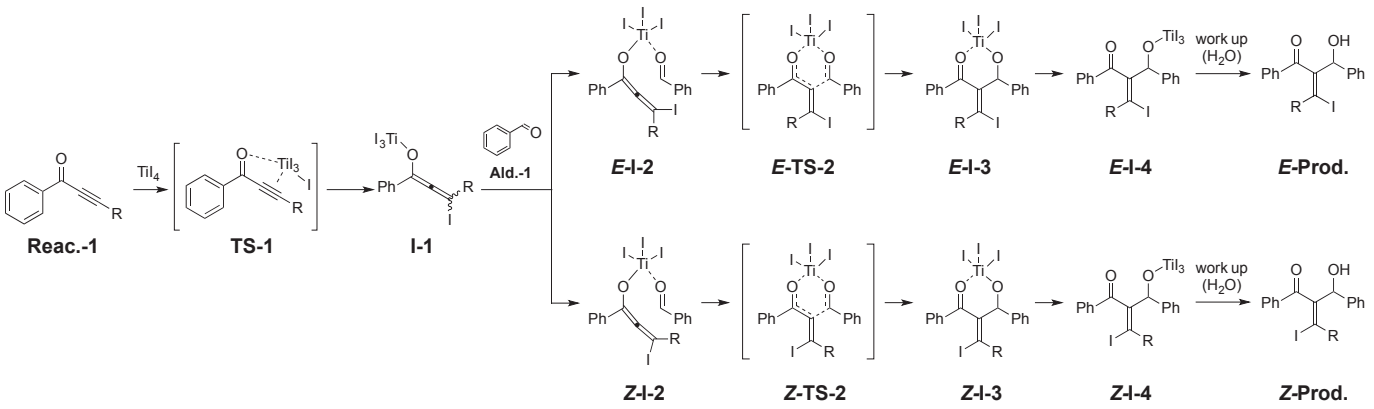


Scheme 3. Full mechanism for the titanium tetraiodine promoted iodo-aldol reaction.

state structure **TS-1**. Subsequently, the allenolate **I-1** undergoes the intramolecular coordination with the aldehyde to generate a penta-coordinate titanium aldlate **I-2**. The C—C bond formation occurs from the aldlate **I-2** through a six-membered transition state ***E*-TS-2** and/or ***Z*-TS-2** to give the aldlate **I-3**, in which the generation of a penta-coordinate enolate and a six-membered ring containing titanium was reported by Patel et al.[19,20] Diastereoselectivity of the resulting vinyl iodide is likely to be determined at the initial C—C bond formation stage between the allenolate (**I-1**) and aldehyde (**Ald.-1**). Finally the protonation of the intermediate **I-4** affords the product ***E*/*Z*-Prod.**

To clarify the exact reaction mechanism and an origin of the selectivity of the products of the iodo-aldol reaction between γ-alkoxy-α,β-alkynyl ketone and aldehyde with the titanium tetraiodide, we calculated the transition state of the reaction for both substrates **1a** and **1b** using the Gaussian 09 program.[21,22] Structures were fully optimized followed by frequency calculation on the stationary point performed with 6-31G(d) basis set for all atoms except for the iodine, which was employed the B3LYP density functional theory[23] in combination with a pseudo-potential LANL2DZ basis set.[24,25] In order to confirm the transition state structures, the intrinsic reaction coordinate (IRC) calculations were carried out at the same level of theory.

The results of the optimized structures of **TS-2** and the relative energy diagrams in each stage are shown in Figs. 1 and 2. As for the distance between the aldehyde carbon and the α-carbon of the substrates, ***Z*-TS-2** had a shorter distance than that of ***E*-TS-2** (**TS-2a**: *E*/*Z*=2.29 vs 2.20, **TS-2b**: *E*/*Z*=2.30 vs 2.26) (Fig. 1). This result indicates that a tighter ***Z*-TS-2** is more stable than the ***E*-TS-2**.[26] Furthermore, in terms of the relative energy analysis for each step **TS-2** or **I-3** in a diastereoselective manner, the reaction of the *Z*-isomer is kinetically more favored than that of the *E*-isomer, while regarding the reaction intermediate **I-4**, the *E*-isomer is more stable (Fig. 2). As comparison of the reaction diagram of **1b** with **1a**, the activation energy of the transition state **TS-2** is lower than that of **1a**. Energy differences between *E*- and *Z*-isomers at each state **I-3** or **I-4** is larger in the case of **1a**. Since the present iodo-aldol reaction using TiI_4 appears to proceed under the equilibrium conditions, a retro-aldol reaction may be involved. The small energy difference between the intermediates **I-3** and **I-4** in the case of **1b** may promote a retro-aldol reaction to lead a decrease in diastereoselectivity. From these results, we suggest that when the substrate **1a** is used for the reaction, the reactivity would decrease with a better diastereoselectivity, while when the substrate **1b** is used, the reactivity would increase with a decreased diastereoselectivity. These predictions support the experimental results.

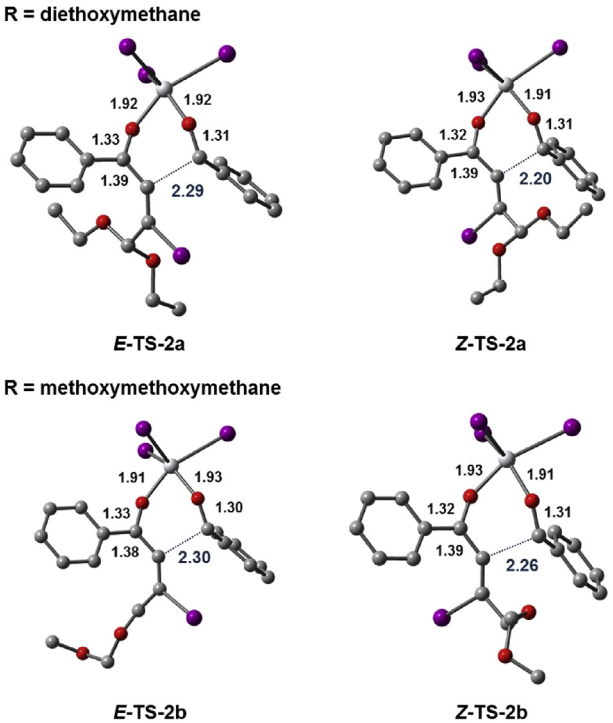


Fig. 1. Optimized geometries of diastereomeric transition state structure TS-2s for the concerted titanium enolate to benzaldehyde. The distances are shown in Å. The indicated color refer to Gray-Carbon, Red-Oxygen, White-Titanium, Purple-Iodine (Hydrogen is not shown).

2.3. The iodo-Mannich reactions

We next examined the iodo-Mannich reaction of γ-alkoxy-α,β-alkynyl ketones with imino ester instead of aldehydes. γ-Diethoxyalkynyl ketone **1a** was treated with the *p*-methoxyphenyl imino ester **7** (1.2 equiv) in the presence of titanium tetraiodide (1.2 equiv) at −40 °C for 1.5 h (Scheme 4). The reaction gave the iodo-Mannich product ***E*-8** as a single *E*-diastereomer in 41% yield. We next examined iodo-Mannich reaction of γ-methoxymethoxyalkynyl ketone **1b** instead of γ-diethoxyalkynyl ketone **1a**. The reaction was carried out with 1.2 equiv of alkynyl ketone and TiI_4 at −50 °C for 1.5 h (Scheme 4). Compared with γ-

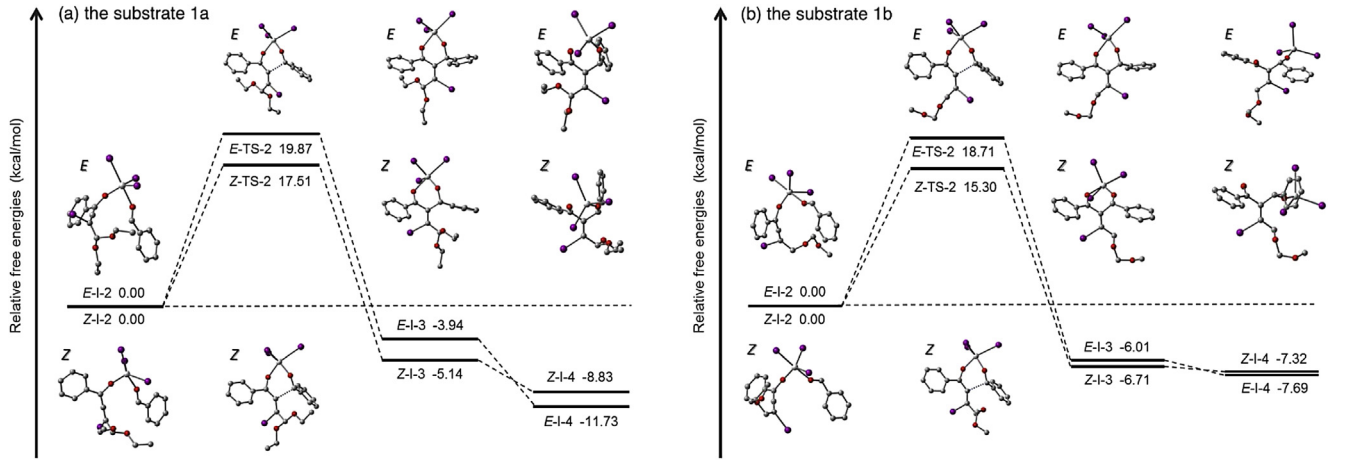
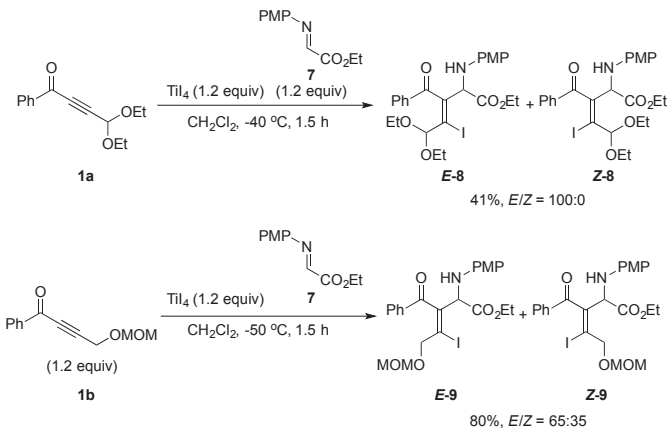
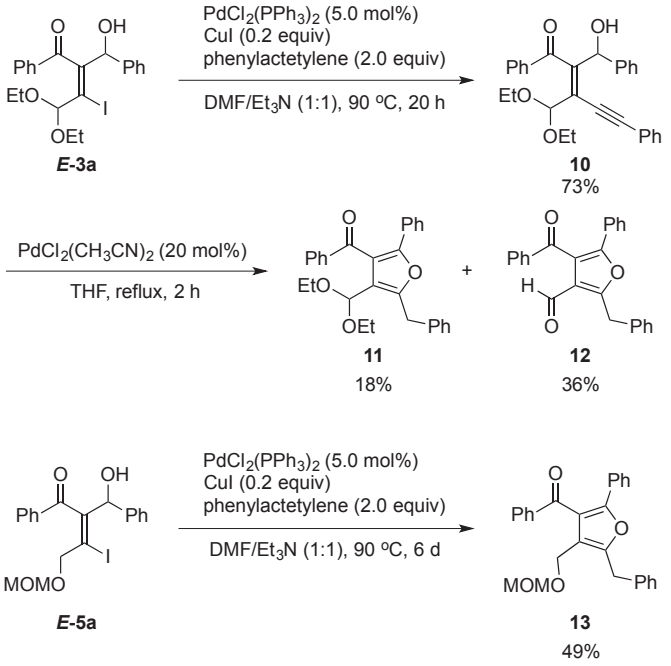


Fig. 2. The relative energy diagram of the iodo-aldol reaction intermediates at 223.15 K, 1.0 atm. The left figure shows the use of γ-diethoxyphenyl ketone and the right figure shows the use of γ-methoxymethoxyphenyl ketone.

diethoxyalkynyl ketone **1a**, the use of γ-methoxymethoxyalkynyl ketone **1b** gave the desired product **9** in good yield. As in the cases with iodo-aldol reaction, it was found that the γ-alkoxy group of alkynyl ketone showed a significant influence on the yield and the diastereoselectivity. The use of γ-diethoxyalkynyl ketone **1a** gave a high diastereoselectivity and moderate yield. In contrast, the use of the γ-methoxymethoxy alkynyl ketone **1b** gave the products (***E***- and ***Z*-9**) in satisfactory yields with a moderate diastereoselectivity.



Scheme 4. The examination of the iodo-Mannich reaction under the previous iodo-aldol reaction conditions. PMP=*p*-methoxyphenyl.



Scheme 5. Synthesis of tetra-substituted furans derived from iodo-aldol adducts. DMF=*N*,*N*-dimethylformamide.

2.4. Cyclization of the iodo-aldol product

We next examined the transformation of the iodo-aldol product into tetra-substituted furans via the enynol intermediate. Initially, we tried the Sonogashira coupling of the iodo-aldol product ***E*-3a** with phenylacetylene in the presence of $PdCl_2(PPh_3)_2$ and CuI to give the enynol **10** in 73% yield.[27] The cyclization reaction of the enynol **10** with $PdCl_2(CH_3CN)_2$ in THF at reflux afforded the furans **11** and **12** in 18% and 36% yields, respectively (Scheme 5).[28] Under similar enynol synthesis conditions for ***E*-3a**, we carried out a one-pot synthesis of the iodo-aldol product ***E*-5a**. Although it took a long reaction time, the transformation of the iodo product ***E*-5a** directly afforded the furan **13** in 49% yield.

3. Conclusion

In conclusion, we have developed the diastereoselective iodo-aldol and iodo-Mannich reactions promoted by titanium tetraiodide. These reactions are attractive synthetic methods for producing multi-functionalized alkenes. One of the notable features of iodo-aldol reaction is a high diastereoselectivity by using suitable alkynyl ketones and reaction conditions. Furthermore, the iodo-aldol products can be transformed into tetra-substituted furans by palladium-catalyzed Sonogashira coupling and subsequent cyclization.

The computational analysis was also carried out to find factors to control the diastereoselectivity of iodo-aldol reactions. From the results of the relative energy analysis and energy differences between *E*- and *Z*-isomers, we found that the substrate **1a** had a decreased reactivity with a better diastereoselectivity, while the substrate **1b** had increased reactivity with a decreased diastereoselectivity, which supported the experimental results.

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We also examined multi-functional iodo-Mannich reaction. The results demonstrate for the first time, that diastereoselective iodo-Mannich reaction of an internal alkyne using titanium tetraiodide gives multi-functionalized vinyl iodides with nitrogen functional groups. Iodo-Mannich reaction appears to have a high potential with a good diastereoselectivity.

4. Experimental section

Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrometer. ^{1}H NMR spectra were recorded on a JEOL ECX-400 spectrometer (400 MHz) or a JEOL JNM *a*-500 spectrometer (500 MHz) with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a JEOL ECX-400 spectrometer (100 MHz) or a JEOL JNM *a*-500 spectrometer (126 MHz). Chemical sifts are reported in d units, parts per million from the central peak of $CDCl_3$ (d 77.0) as an internal reference. High resolution mass spectra (EI or ESI) were recorded on a JEOL JMS-700D mass spectrometer or a Thermo Orbitrap Velos ETD Ultimate 3000 system. Propionitrile (EtCN) was distilled from phosphorus pentaoxide and then from calcium hydride, and stored over molecular sieves 4 Å. Toluene was pre-dried with $CaCl_2$, distilled, and stored over molecular sieves 4 Å. Tetrahydrofuran (THF) was distilled from benzophenone ketyl immediately before use. Dichloromethane (CH_2Cl_2) was pre-dried with P_2O_5, distilled from CaH_2, and stored over molecular sieves 4 Å. Purification of products was performed by column chromatography on silica gel (Kanto Chemical Co. Inc., Silica Gel 60 N (spherical, neutral)) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254). All reactions were carried out under an argon or an oxygen atmosphere.

4.1. Synthesis of alkynyl ketone

γ-Alkoxy-α,β-alkynyl ketone **1a** was prepared according to the literature method.[29]

*4.1.1. 4-(Methoxymethoxy)-1-phenylbut-2-yn-1-one (**1b**).*[18a] To a solution of 4-hydroxy-1-phenylbut-2-yn-1-one[30] (0.845 g, 5.27 mmol) in CH_2Cl_2 (30.0 mL) was added *N*-ethyldiisopropylamine (2.04 g, 15.8 mmol) at room temperature under an argon atmosphere. The mixture was cooled to −15 °C. Chloromethylmethylether (0.64 g, 7.91 mmol) was added to the mixture. The reaction mixture was gradually warmed to room temperature during 18 h. Water (30 mL) was added to quench the reaction. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with 1.5 M HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), water (20 mL), brine (20 mL), and dried over Na_2SO_4. The solvents were evaporated in vacuo and then the residue was purified by chromatography on silica gel (*n*-hexane/EtOAc=4/1 as an eluent) to give 4-(methoxymethoxy)-1-phenylbut-2-yn-1-one (0.23 g, 21%); Red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 3H), 4.51 (s, 2H), 4.79 (s, 2H), 7.48–7.51 (m, 2H), 7.60–7.65 (m, 1H), 8.13–8.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.2, 55.8, 83.7, 89.8, 95.3, 128.6, 129.6, 134.3, 136.3, 177.4; IR (neat): 2948, 2230, 1652, 1599, 1451, 1312, 1264, 1149, 1106, 1047, 921, 699 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{12}O_3$ $(M)^+$ 204.0786, found 204.0783.

4.1.2. 4-(Methoxymethoxy)-1-(thiophen-2-yl)but-2-yn-1-ol.[18a] To a solution of 3-(methoxymethoxy)prop-1-yne (0.401 g, 4.01 mmol) in THF (7.0 mL) was added *n*BuLi (2.44 mL, 1.64 M in *n*-hexane, 4.00 mmol) at −78 °C under an argon atmosphere. After stirring for 30 min, thiophene-2-carbaldehyde (0.448 g, 3.99 mmol) was added to the solution and the mixture was stirred at −78 °C for 30 min. The reaction mixture was warmed to room temperature and stirred for 30 min. Saturated aqueous NH_4Cl (10 mL), ice, and diethyl ether (10 mL) were added to quench the reaction. The phases were separated and the aqueous phase was extracted with diethyl ether (10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvents were evaporated in vacuo and then the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=4/1 as an eluent) to give 4-(methoxymethoxy)-1-(thiophen-2-yl)but-2-yn-1-ol (0.726 g, 86%); Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16–3.25 (m, 1H), 3.35 (s, 3H), 4.28 (d, *J*=1.8 Hz, 2H), 4.69 (s, 2H), 5.64–5.68 (m, 1H), 6.93–6.96 (m, 1H), 7.12–7.14 (m, 1H), 7.25–7.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.2, 55.4, 59.8, 81.2, 85.5, 94.5, 125.3, 125.8, 126.6, 144.3; IR (neat): 3397, 3104, 2948, 2891, 1442, 1360, 1269, 1210, 1148, 1101, 1045, 989, 923, 857, 754, 710 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{12}O_3S$ $(M)^+$ 212.0507, found 212.0517.

*4.1.3. 4-(Methoxymethoxy)-1-(thiophen-2-yl)but-2-yn-1-one (**1c**).*[18a] To a suspension of MnO_2 (2.97 g, 34.2 mmol) in CH_2Cl_2 (7.0 mL) was added a solution of 4-(methoxymethoxy)-1-(thiophen-2-yl)but-2-yn-1-ol (0.726 g, 3.42 mmol) in CH_2Cl_2 (3.0 mL) at 0 °C. The mixture was stirred for 1 h and warmed to room temperature. After stirring at room temperature for 1 h, the reaction mixture was filtered through a Celite pad. The solvents were removed in vacuo and then the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=4/1 as an eluent) to give 4-(methoxymethoxy)-1-(thiophen-2-yl)but-2-yn-1-one (**1c**) (0.672 g, 93%); Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H), 4.44 (s, 2H), 4.73 (s, 2H), 7.11–7.16 (m, 1H), 7.68–7.71 (m, 1H), 7.87–7.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.9, 55.6, 83.1, 88.2, 95.1, 128.3, 135.4, 144.2, 169.0; IR (neat) 3100, 2950, 2229, 1625, 1516, 1411, 1359, 1280, 1231, 1208, 1152, 1105, 1047, 988, 922, 837, 729 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{10}O_3S$ $(M)^+$ 210.0351, found 210.0353.

*4.1.4. 5-(Methoxymethoxy)pent-3-yn-2-one (**1d**).*[18a] To a solution of 3-(methoxymethoxy)prop-1-yne (0.501 g, 5.00 mmol) in THF (7.0 mL) was added *n*BuLi (3.05 mL, 1.64 M in *n*-hexane, 5.00 mmol) at −78 °C under argon. After stirring for 30 min, acetaldehyde (0.315 g, 7.15 mmol) was added to the solution and the mixture was stirred at −78 °C for 62 h. Saturated aqueous NH_4Cl (10 mL), ice, and diethyl ether (10 mL) were added to quench the reaction. The phases were separated and the aqueous phase was extracted with diethyl ether (10 mL). The combined organic extracts were dried over Na_2SO_4 and filtered. The solvents were removed in vacuo to give the crude 5-(methoxymethoxy)pent-3-yn-2-ol (0.650 g); To a suspension of MnO_2 (3.97 g, 45.7 mmol) in CH_2Cl_2 (7.0 mL) was added a solution of the crude 5-(methoxymethoxy)pent-3-yn-2-ol (0.650 g) in CH_2Cl_2 (3.0 mL) at 0 °C. The mixture was stirred at 0 °C for 10 h and warmed up to room temperature. After stirring at room temperature for 30 min, the reaction mixture was filtered through a Celite pad. The solvents were removed in vacuo and then the residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=4/1 as an eluent) to give 5-(methoxymethoxy)pent-3-yn-2-one (0.400 g, 56%); Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.36 (s, 3H), 4.33 (s, 2H), 4.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.3, 53.7, 55.5, 85.1, 87.0, 95.0, 183.7; IR (neat) 2951, 2891, 2212, 1679, 1423, 1359, 1227, 1151, 1106, 1049, 964, 923 cm^{-1}; HRMS (EI) calcd for $C_7H_{10}O_3$ $(M)^+$ 142.0630, found 142.0631.

4.2. The iodo-aldol reaction

To a suspension of TiI_4 (0.195 mmol) in CH_2Cl_2 (1.0 mL) was added a mixture of γ-diethoxyalkynyl ketone **1a** (0.15 mmol) and aldehyde **2** (0.15 mmol) in CH_2Cl_2 (2.0 mL) at −50 °C under an argon atmosphere. The mixture was stirred at −50 °C for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and EtOAc and saturated aqueous $NaHSO_3$ were added successively. The

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mixture was filtered through a Celite pad, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative silica gel TLC (*n*-hexane/EtOAc=4/1 as an eluent, developed four times) to give the iodo-aldol product **3** and the iodoalkenone **4**.

*4.2.1. (E)-4,4-Diethoxy-2-[hydroxy(phenyl)methyl]-3-iodo-1-phenylbut-2-en-1-one (**E-3a**).*[18a] White semisolid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J=7.1 Hz, 3H), 1.04 (t, J=7.1 Hz, 3H), 3.06–3.14 (m, 2H), 3.20–3.28 (m, 1H), 3.33–3.46 (m, 2H), 4.13 (s, 1H), 6.03 (d, J=5.7 Hz, 1H), 7.12–7.25 (m, 3H), 7.31–7.35 (m, 2H), 7.46–7.51 (m, 3H), 7.71–7.73 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.6, 14.6, 62.4, 62.4, 80.7, 100.5, 111.7, 126.3, 128.0, 128.3, 128.3, 129.7, 133.8, 136.2, 140.1, 148.1, 195.9; IR (neat) 3466, 2975, 2880, 1653, 1493, 1449, 1407, 1374, 1349, 1243, 1058, 951, 848, 760, 703 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{23}IO_4$ $(M)^+$ 466.0641, found 466.0653.

*4.2.2. (Z)-4,4-Diethoxy-2-[hydroxy(phenyl)methyl]-3-iodo-1-phenylbut-2-en-1-one (**Z-3a**).*[18a] Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J=7.1 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 3.39 (br s, 1H), 3.52–3.63 (m, 2H), 3.64–3.73 (m, 2H), 4.95 (s, 1H), 6.07 (d, J=5.3 Hz, 1H), 7.16–7.24 (m, 3H), 7.33–7.43 (m, 4H), 7.49–7.53 (m, 1H), 7.80–7.82 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 15.1, 62.8, 62.8, 73.2, 99.6, 106.6, 126.5, 128.0, 128.4, 128.6, 129.9, 133.6, 134.1, 140.2, 151.0, 197.1; IR (neat) 3424, 2924, 1665, 1595, 1449, 1257, 1145, 1059, 769, 697 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{23}IO_4$ $(M)^+$ 466.0641, found 466.0660.

*4.2.3. (Z)-4,4-Diethoxy-3-iodo-1-phenylbut-2-en-1-one (**4**).*[18a] Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, J=7.1 Hz, 6H), 3.62 (dq, J=7.1, 9.4 Hz, 2H), 3.70 (dq, J=7.1, 9.4 Hz, 2H), 4.97 (d, J=1.2 Hz, 1H), 7.48–7.51 (m, 2H), 7.58–7.62 (m, 1H), 7.76 (d, J=1.2 Hz, 1H), 7.95–7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 62.0, 104.1, 112.8, 128.7, 128.8, 132.6, 133.6, 136.2, 191.4; IR (neat) 3422, 2975, 2882, 1668, 1598, 1448, 1314, 1263, 1222, 1177, 1121, 1061, 1023, 855, 769, 694 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}IO_3$–C_2H_5 $(M)^+$ 330.9831, found 330.9845.

*4.2.4. (E)-2-[(4-Chlorophenyl)(hydroxy)methyl]-4,4-diethoxy-3-iodo-1-phenylbut-2-en-1-one (**E-3b**).*[18a] Yellow semisolid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J=7.1 Hz, 3H), 1.03 (t, J=7.1 Hz, 3H), 3.06–3.14 (m, 2H), 3.19–3.26 (m, 1H), 3.33–3.45 (m, 2H), 4.14 (s, 1H), 5.99 (d, J=5.5 Hz, 1H), 7.18–7.22 (m, 2H), 7.34–7.43 (m, 4H), 7.50–7.55 (m, 1H), 7.72–7.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 62.4, 80.1, 100.5, 112.1, 127.8, 128.4, 128.5, 129.6, 133.8, 134.0, 136.1, 138.6, 147.6, 195.6; IR (neat) 3440, 2979, 2925, 1650, 1594, 1492, 1448, 1405, 1350, 1249, 1056, 858, 814, 736, 687 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{22}ClIO_4$ $(M)^+$ 500.0251, found 500.0232.

*4.2.5. (E)-4,4-Diethoxy-2-[hydroxy(4-methoxyphenyl)methyl]-3-iodo-1-phenylbut-2-en-1-one (**E-3c**).*[18a] Orange oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J=7.1 Hz, 3H), 1.02 (t, J=7.1 Hz, 3H), 2.91 (br s, 1H), 3.07–3.15 (m, 1H), 3.18–3.26 (m, 1H), 3.33–3.44 (m, 2H), 3.74 (s, 3H), 4.12 (s, 1H), 5.93 (d, J=3.5 Hz, 1H), 6.75–6.78 (m, 2H), 7.34–7.42 (m, 4H), 7.49–7.53 (m, 1H), 7.76–7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 55.2, 62.3, 80.3, 100.4, 111.0, 113.7, 127.9, 128.3, 129.7, 132.4, 133.7, 136.3, 148.5, 159.3, 195.9; IR (neat) 3475, 2977, 1668, 1610, 1510, 1449, 1249, 1175, 1061, 821, 755 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{25}IO_5$ $(M)^+$ 496.0747, found 496.0739.

*4.2.6. (E)-4,4-Diethoxy-2-[hydroxy(p-tolyl)methyl]-3-iodo-1-phenylbut-2-en-1-one (**E-3d**).*[18a] White semisolid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (t, J=7.1 Hz, 3H), 1.0 (t, J=7.1 Hz, 3H), 2.26 (s, 3H), 2.90 (d, J=5.5 Hz, 1H), 3.07–3.14 (m, 1H), 3.18–3.26 (m, 1H), 3.33–3.44 (m, 2H), 4.12 (s, 1H), 5.96 (d, J=6.2 Hz, 1H), 7.04–7.05 (m, 2H), 7.33–7.38 (m, 4H), 7.48–7.53 (m, 1H), 7.75–7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 21.1, 62.3, 80.6, 100.4, 111.3, 126.4, 128.3, 129.0, 129.7, 133.7, 136.4, 137.2, 137.7, 148.4, 195.9; IR (neat) 3450, 2978, 2920, 1654, 1514, 1447, 1406, 1351, 1244, 1163, 1056, 951, 811, 745, 687 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{25}IO_4$ $(M)^+$ 480.0798, found 480.0795.

*4.2.7. (Z)-4,4-Diethoxy-2-[hydroxy(p-tolyl)methyl]-3-iodo-1-phenylbut-2-en-1-one (**Z-3d**).*[18a] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J=7.1 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 2.26 (s, 3H), 3.23 (d, J=5.5 Hz, 1H), 3.49–3.70 (m, 4H), 4.91 (s, 1H), 6.02 (d, J=6.2 Hz, 1H), 7.04–7.06 (m, 2H), 7.29–7.31 (m, 2H), 7.36–7.40 (m, 2H), 7.50–7.54 (m, 1H), 7.82–7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 15.1, 21.1, 62.8, 73.3, 99.2, 106.4, 126.5, 128.6, 129.1, 129.9, 133.5, 134.2, 137.3, 137.8, 151.2, 197.1; IR (neat) 3449, 2976, 1665, 1511, 1449, 1255, 1146, 1105, 1061, 807 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{25}IO_4$ $(M)^+$ 480.0798, found 480.0821.

*4.2.8. (E)-4,4-Diethoxy-2-[hydroxy(naphthalen-1-yl)methyl]-3-iodo-1-phenylbut-2-en-1-one (**E-3e**).*[18a] Orange semisolid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J=7.3 Hz, 3H), 1.02 (t, J=7.3 Hz, 3H), 3.09–3.30 (m, 3H), 3.37–3.48 (m, 2H), 4.25 (s, 1H), 6.59 (d, J=7.3 Hz, 1H), 7.10–7.18 (m, 2H), 7.27–7.77 (m, 9H), 8.16–8.18 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.6, 14.6, 62.3, 62.3, 78.2, 100.6, 112.4, 123.6, 124.5, 125.2, 125.6, 126.4, 127.9, 128.1, 128.6, 128.8, 129.1, 130.9, 133.4, 133.5, 135.3, 148.6, 196.0; IR (neat) 3497, 3060, 3012, 2979, 2929, 2882, 1668, 1596, 1512, 1449, 1396, 1371, 1345, 1317, 1260, 1236, 1216, 1179, 1155, 1109, 1062, 759 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{26}IO_4$ $(M+H)^+$ 517.0876, found 517.0864.

*4.2.9. (E)-4,4-Diethoxy-2-[hydroxy(thiophen-2-yl)methyl]-3-iodo-1-phenylbut-2-en-1-one (**E-3f**).*[18a] Yellow semisolid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, J=7.3 Hz, 3H) 1.03 (t, J=7.3 Hz, 3H), 3.19–3.24 (m, 3H), 3.36–3.43 (m, 2H), 4.16 (s, 1H), 6.18 (d, J=4.3 Hz, 1H), 6.89–6.91 (m, 1H), 7.17–7.19 (m, 2H), 7.38–7.41 (m, 2H), 7.52–7.55 (m, 1H), 7.82–7.84 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.6, 62.4, 62.4, 77.7, 100.4, 111.6, 125.3, 125.5, 126.7, 128.4, 129.7, 133.8, 136.4, 143.6, 147.7, 198.4; IR (neat) 3467, 3011, 2978, 2928, 2883, 1668, 1616, 1596, 1582, 1449, 1372, 1347, 1316, 1266, 1240, 1158, 1105, 1061, 756 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}IO_4S$ $(M+H)^+$ 473.0284, found 473.0267.

*4.2.10. (E)-4,4-Diethoxy-3-iodo-1-phenyl-2-(2,2,2-trichloro-1-hydroxyethyl)but-2-en-1-one (**E-3g**).*[18a] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J=6.9 Hz, 3H), 1.0 (t, J=6.9 Hz, 3H), 2.77–2.83 (m, 1H), 3.16–3.30 (m, 2H), 3.47–3.54 (m, 1H), 3.96 (S, 1H), 5.51 (d, J=8.2 Hz, 1H), 5.64 (d, J=8.2 Hz, 1H), 7.50–7.54 (m, 2H), 7.65–7.69 (m, 1H), 8.04–8.06 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.6, 14.7, 62.4, 63.1, 92.8, 100.0, 101.3, 126.6, 128.8, 130.0, 134.8, 136.3, 139.5, 196.9; IR (neat) 3434, 3019, 2929, 1641, 1595, 1450, 1415, 1321, 1285, 1257, 1215, 1156, 1110, 1062, 931, 843, 824, 757 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{18}Cl_3IO_4$–I $(M)^+$ 379.0271, found 379.0255.

*4.2.11. (E)-2-(2,2-Diethoxy-1-iodoethylidene)-3-hydroxy-1-phenyloctan-1-one (**E-3h**).*[18a] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J=6.9 Hz, 3H), 1.01 (t, J=7.3 Hz, 3H), 1.04 (t, J=7.3 Hz, 3H), 1.23–1.81 (m, 8H), 2.15 (d, J=5.0 Hz, 1H), 3.16–3.26 (m, 2H), 3.36–3.45 (m, 2H), 4.16 (s, 1H), 4.71–4.75 (m, 1H), 7.46–7.50 (m, 2H), 7.57–7.61 (m, 1H), 7.96–7.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.6, 14.6, 22.5, 25.5, 31.3, 35.5, 62.3, 79.2, 100.4, 108.3, 128.6, 129.7, 133.9, 136.5, 149.9, 195.8; IR (neat) 3504, 2954, 2930,

2867, 1667, 1615, 1595, 1448, 1374, 1315, 1249, 1167, 1115, 1062, 955, 756 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{30}IO_4$ $(M+H)^+$ 461.1189, found 461.1146.

*4.2.12. (E)-2-[Hydroxy(phenyl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**E-5a**).*[18a] Orange oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 3H), 3.23 (br s, 1H), 4.05 (d, J=12.8 Hz, 1H), 4.10 (d, J=12.8 Hz, 1H), 4.35 (d, J=6.8 Hz, 1H), 4.37 (d, J=6.8 Hz, 1H), 5.95 (s, 1H), 7.15–7.25 (m, 3H), 7.30–7.34 (m, 2H), 7.44–7.49 (m, 3H), 7.66–7.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 72.7, 81.2, 95.8, 106.5, 126.2, 128.0, 128.3, 128.4, 129.4, 133.7, 136.3, 140.1, 147.4, 195.5; IR (neat) 3446, 3016, 2930, 1668, 1449, 1253, 1150, 1051, 939, 757, 698 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{19}IO_4$ $(M)^+$ 438.0328, found 438.0348.

*4.2.13. (Z)-2-[Hydroxy(phenyl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**Z-5a**).*[18a] Orange semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 3H), 3.49 (br s, 1H), 4.60 (s, 2H), 4.74 (d, J=6.9 Hz, 1H), 4.77 (d, J=6.9 Hz, 1H), 5.96 (s, 1H), 7.10–7.25 (m, 3H), 7.32–7.37 (m, 4H), 7.47–7.51 (m, 1H), 7.76–7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 70.4, 72.9, 95.4, 101.1, 126.3, 128.0, 128.5, 129.9, 133.6, 134.1, 140.1, 151.3, 197.2; IR (neat) 3521, 3058, 2933, 1660, 1587, 1449, 1387, 1272, 1033, 805, 761, 691 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{19}IO_4$ $(M)^+$ 438.0328, found 438.0324.

*4.2.14. (Z)-3-Iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**6**).*[18a] Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 3H), 4.40 (s, 2H), 4.75 (s, 2H), 7.46–7.50 (m, 2H), 7.56–7.60 (m, 1H), 7.66–7.67 (m, 1H), 7.95–7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 76.2, 95.8, 112.0, 128.4, 128.6, 128.7, 133.4, 136.7, 190.3; IR (neat) 3060, 2991, 2935, 2842, 1670, 1597, 1448, 1260, 1220, 1150, 1111, 1045, 921, 863, 757, 702 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}IO_3$ $(M)^+$ 331.9909, found 331.9896.

*4.2.15. (E)-2-[(4-Chlorophenyl)(hydroxy)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**E-5b**).*[18a] Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 3H), 3.21 (d, J=6.2 Hz, 1H), 4.06 (d, J=13.3 Hz, 1H), 4.11 (d, J=13.3 Hz, 1H), 4.36 (d, J=6.7 Hz, 1H), 4.38 (d, J=6.7 Hz, 1H), 5.92 (d, J=5.9 Hz, 1H), 7.19–7.22 (m, 2H), 7.34–7.41 (m, 4H), 7.50–7.54 (m, 1H), 7.68–7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 72.7, 80.6, 95.8, 107.1, 127.7, 128.5, 128.6, 129.4, 133.8, 134.0, 136.2, 138.7, 146.8, 195.3; IR (neat) 3440, 2990, 2880, 1667, 1489, 1255, 1150, 1012, 812, 688 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{18}ClIO_4$ $(M)^+$ 471.9938, found 471.9919.

*4.2.16. (Z)-2-[(4-Chlorophenyl)(hydroxy)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**Z-5b**).*[18a] Brown semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3H), 3.60 (d, J=5.8 Hz, 1H), 4.61 (s, 2H), 4.76 (d, J=6.8 Hz, 1H), 4.79 (d, J=6.8 Hz, 1H), 5.94 (d, J=5.8 Hz, 1H), 7.19–7.21 (m, 2H), 7.30–7.32 (m, 2H), 7.36–7.40 (m, 2H), 7.51–7.55 (m, 1H), 7.77–7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 70.6, 72.1, 95.4, 101.5, 127.7, 128.6, 129.9, 133.8, 133.8, 133.9, 138.5, 150.9, 197.1; IR (neat) 3510, 2947, 1661, 1590, 1488, 1445, 1403, 1275, 1147, 1101, 1029, 948, 850, 813, 710 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{18}ClIO_4$ $(M)^+$ 471.9938, found 471.9925.

*4.2.17. (E)-2-[Hydroxy(4-methoxyphenyl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**E-5c**).*[18a] Orange semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 3.02 (d, J=5.9 Hz, 1H), 3.08 (s, 3H), 3.74 (s, 3H), 4.05 (d, J=13.1 Hz, 1H), 4.09 (d, J=13.1 Hz, 1H), 4.36 (d, J=6.9 Hz, 1H), 4.38 (d, J=6.9 Hz, 1H), 5.86 (d, J=5.9 Hz, 1H), 6.76–6.79 (m, 2H), 7.34–7.42 (m, 4H), 7.48–7.52 (m, 1H), 7.72–7.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 55.5, 72.6, 80.9, 95.8, 105.8, 113.7, 127.7, 128.5, 129.4, 132.4, 133.8, 136.4, 147.7, 159.3, 195.6; IR (neat) 3451, 3007, 2938, 1673, 1611, 1510, 1452, 1377, 1247, 1025, 864, 822, 745 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}IO_5$ $(M)^+$ 468.0434, found 468.0438.

*4.2.18. (Z)-2-[Hydroxy(4-methoxyphenyl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**Z-5c**).*[18a] Yellow semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 3.29 (br s, 1H), 3.48 (s, 3H), 3.74 (s, 3H), 4.55 (d, J=12.8 Hz, 1H), 4.59 (d, J=12.8 Hz, 1H), 4.75 (d, J=6.9 Hz, 1H), 4.78 (d, J=6.9 Hz, 1H), 5.93 (d, J=5.7 Hz, 1H), 6.76–6.79 (m, 2H), 7.28–7.31 (m, 2H), 7.36–7.40 (m, 2H), 7.50–7.54 (m, 1H), 7.80–7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 56.2, 70.3, 72.8, 95.4, 100.6, 113.9, 127.7, 128.5, 129.9, 132.3, 133.6, 151.6, 159.3, 197.3; IR (neat) 3520, 2938, 2842, 1662, 1606, 1513, 1444, 1256, 1179, 1143, 1032, 942, 815, 724, 684 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}IO_5$–I $(M)^+$ 341.1389, found 341.1392.

*4.2.19. (E)-2-[Hydroxy(p-tolyl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**E-5d**).*[18a] White semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.06 (d, J=6.2 Hz, 1H), 3.08 (s, 3H), 4.05 (d, J=13.1 Hz, 1H), 4.09 (d, J=13.1 Hz, 1H), 4.36 (d, J=6.7 Hz, 1H), 4.38 (d, J=6.7 Hz, 1H), 5.89 (d, J=6.2 Hz, 1H), 7.04–7.06 (m, 2H), 7.33–7.37 (m, 4H), 7.48–7.52 (m, 1H), 7.71–7.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 55.5, 72.7, 81.1, 95.8, 106.2, 126.3, 128.4, 129.0, 129.5, 133.7, 136.4, 137.2, 137.8, 147.6, 195.5; IR (neat) 3483, 2932, 1659, 1513, 1448, 1402, 1317, 1242, 1063, 928, 802, 760, 692 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}IO_4$–I $(M)^+$ 325.1440, found 325.1429.

*4.2.20. (Z)-2-[Hydroxy(p-tolyl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**Z-5d**).*[18a] White semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.31 (d, J=5.7 Hz, 1H), 3.48 (s, 3H), 4.55 (d, J=13.1 Hz, 1H), 4.59 (d, J=13.1 Hz, 1H), 4.74 (d, J=6.8 Hz, 1H), 4.78 (d, J=6.8 Hz, 1H), 5.93 (d, J=5.7 Hz, 1H), 7.04–7.06 (m, 2H), 7.24–7.26 (m, 2H), 7.35–7.39 (m, 2H), 7.50–7.54 (m, 1H), 7.80–7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 56.1, 70.3, 73.0, 77.2, 95.4, 100.6, 126.3, 128.5, 129.2, 129.9, 133.5, 134.2, 137.2, 137.8, 151.5, 197.2; IR (neat) 3504, 2934, 1652, 1591, 1516, 1445, 1244, 1144, 1044, 923, 806, 686 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}IO_4$ $(M)^+$ 452.0485, found 452.0471.

*4.2.21. (E)-2-[Hydroxy(naphthalen-1-yl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**E-5e**).*[18a] Orange oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.11 (s, 3H), 3.56 (d, J=6.4 Hz, 1H), 4.14 (s, 2H), 4.40 (s, 2H), 6.75 (d, J=6.8 Hz, 1H), 7.13–7.17 (m, 2H), 7.29–7.79 (m, 9H), 8.09–8.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 72.6, 78.6, 95.8, 107.4, 123.6, 124.6, 125.3, 125.6, 126.4, 128.1, 128.5, 128.9, 128.9, 130.8, 133.4, 133.6, 135.2, 135.8, 147.8, 195.7; IR (neat): 3462, 3055, 3017, 2933, 2892, 1668, 1622, 1596, 1449, 1405, 1373, 1315, 1260, 1242, 1216, 1151, 1105, 1061, 993, 936, 799, 755 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{22}IO_4$ $(M+H)^+$ 489.0563, found 489.0530.

*4.2.22. (Z)-2-[Hydroxy(naphthalen-1-yl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**Z-5e**).*[18a] Light yellow semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 3H), 3.56 (br s, 1H), 4.61 (d, J=12.8 Hz, 1H), 4.67 (d, J=12.8 Hz, 1H), 4.77 (d, J=6.9 Hz, 1H), 4.81 (d, J=6.9 Hz, 1H), 6.52 (d, J=7.8 Hz, 1H), 7.11–7.15 (m, 2H), 7.25–7.80 (m, 9H), 8.17–8.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 69.9, 70.4, 95.6, 100.9, 122.7, 125.1, 125.4, 125.7, 126.5, 128.2, 128.8, 129.0, 129.5, 130.3, 133.3, 133.6, 133.8, 135.0, 151.1, 197.1; IR (neat): 3433, 3066, 3012, 2935, 2892, 1667, 1596, 1511, 1449, 1315, 1275, 1241, 1216, 1150, 1104, 1062, 1029, 986, 936, 927, 799, 755 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{22}IO_4$ $(M+H)^+$ 489.0563, found 489.0530.

*4.2.23. (E)-2-[Hydroxy(thiophen-2-yl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**E-5f**).*[18a] Yellow oil. ^1H NMR

(500 MHz, $CDCl_3$) δ 3.10 (s, 3H), 3.39 (br s, 1H), 4.07 (d, *J*=12.8 Hz, 1H), 4.11 (d, *J*=12.8 Hz, 1H), 4.37 (s, 2H), 6.11 (s, 1H), 6.88–6.90 (m, 1H), 7.16–7.17 (m, 2H), 7.37–7.40 (m, 2H), 7.51–7.54 (m, 1H), 7.77–7.79 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.6, 72.6, 78.3, 95.7, 106.7, 125.3, 125.3, 126.7, 128.5, 129.4, 133.9, 136.5, 143.7, 146.8, 195.1; IR (neat): 3450, 3011, 2937, 2885, 1667, 1622, 1595, 1582, 1449, 1375, 1315, 1242, 1216, 1179, 1151, 1105, 1049, 1004, 932, 755 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{17}IO_4S$ $(M)^+$ 443.9892, found 443.9891.

*4.2.24. (Z)-2-[Hydroxy(thiophen-2-yl)methyl]-3-iodo-4-(methoxymethoxy)-1-phenylbut-2-en-1-one (**Z-5f**).*[18a] Yellow semisolid; ^1H NMR (500 MHz, $CDCl_3$) δ 3.47 (s, 3H), 3.65 (d, *J*=6.1 Hz, 1H), 4.58 (d, *J*=12.8 Hz, 1H), 4.61 (d, *J*=12.8 Hz, 1H), 4.74 (d, *J*=6.7 Hz, 1H), 4.77 (d, *J*=6.7 Hz, 1H), 6.14 (d, *J*=6.1 Hz, 1H), 6.87–6.90 (m, 1H), 7.03–7.04 (m, 1H), 7.17–7.19 (m, 1H), 7.40–7.43 (m, 2H), 7.53–7.56 (m, 1H), 7.87–7.89 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.1, 69.5, 70.6, 95.5, 101.6, 125.4, 125.6, 126.9, 128.6, 129.9, 133.7, 134.2, 144.0, 150.5, 196.9; IR (neat) 3411, 2019, 1667, 1596, 1450, 1316, 1260, 1216, 1150, 1103, 1041, 926, 764 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{17}IO_4S$ $(M)^+$ 443.9892, found 443.9873.

*4.2.25. (E)-3-Hydroxy-2-[1-iodo-2-(methoxymethoxy)-ethylidene]-1-phenyloctan-1-one (**E-5g**).*[18a] Orange oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.9 Hz, 3H), 1.24–1.80 (m, 8H), 2.26 (br s, 1H), 3.11 (s, 3H), 4.05 (d, *J*=13.3 Hz, 1H), 4.09 (d, *J*=13.3 Hz, 1H), 4.40 (s, 2H), 4.63–4.67 (m, 1H), 7.46–7.50 (m, 2H), 7.57–7.61 (m, 1H), 7.94–7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.5, 25.5, 31.3, 35.5, 55.5, 72.6, 79.7, 95.7, 103.4, 128.7, 129.5, 133.9, 136.5, 149.2, 195.4; IR (neat) 3478, 3066, 2954, 2931, 2854, 1667, 1622, 1596, 1581, 1449, 1375, 1315, 1256, 1179, 1151, 1105, 1033, 938, 923, 754 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{26}IO_4$ $(M+H)^+$ 433.0876, found 433.0847.

*4.2.26. (Z)-3-Hydroxy-2-[1-iodo-2-(methoxymethoxy)-ethylidene]-1-phenyloctan-1-one (**Z-5g**).*[18a] Light yellow semisolid; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.9 Hz, 3H), 1.22–1.40 (m, 4H), 1.43–1.53 (m, 1H), 1.57–1.66 (m, 3H), 2.70 (d, *J*=4.6 Hz, 1H), 3.49 (s, 3H), 4.52 (d, *J*=12.9 Hz, 1H), 4.61 (d, *J*=12.9 Hz, 1H), 4.75–4.83 (m, 3H), 7.47–7.51 (m, 2H), 7.59–7.63 (m, 1H), 8.01–8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.5, 25.6, 31.4, 36.4, 56.2, 70.0, 71.4, 95.4, 100.0, 128.8, 130.0, 133.8, 134.4, 152.9, 197.2; IR (neat): 3451, 3060, 3004, 2954, 2932, 2854, 1665, 1596, 1580, 1449, 1314, 1259, 1152, 1103, 1039, 938, 757 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{26}IO_4$ $(M+H)^+$ 433.0876, found 433.0847.

*4.2.27. (E)-2-[Hydroxy(phenyl)methyl]-3-iodo-4-(methoxymethoxy)-1-(thiophen-2-yl)but-2-en-1-one (**E-5h**).*[18a] Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 3H), 3.19 (br s, 1H), 4.16 (d, *J*=13.1 Hz, 1H), 4.21 (d, *J*=13.1 Hz, 1H), 4.45 (d, *J*=6.8 Hz, 1H), 4.48 (d, *J*=6.8 Hz, 1H), 5.94 (d, *J*=6.0 Hz, 1H), 6.93–6.95 (m, 1H), 7.17–7.29 (m, 4H), 7.45–7.47 (m, 2H), 7.61–7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 72.7, 80.8, 95.8, 107.3, 125.8, 127.8, 128.0, 128.1, 135.8, 139.7, 143.4, 147.5, 187.0; IR (neat): 3449, 3016, 2936, 1638, 1516, 1453, 1409, 1355, 1214, 1153, 1108, 1048, 918, 856, 755 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{17}IO_4S$–I $(M)^+$ 317.0848, found 317.0857.

*4.2.28. (Z)-2-[Hydroxy(phenyl)methyl]-3-iodo-4-(methoxymethoxy)-1-(thiophen-2-yl)but-2-en-1-one (**Z-5h**).*[18a] Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 3H), 3.55 (br s, 1H), 4.61 (s, 2H), 4.74 (d, *J*=6.8 Hz, 1H), 4.77 (d, *J*=6.8 Hz, 1H), 5.96 (d, *J*=6.0 Hz, 1H), 6.95–6.99 (m, 1H), 7.17–7.26 (m, 3H), 7.36–7.47 (m, 3H), 7.62–7.63 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 56.2, 70.4, 72.6, 95.3, 101.8, 126.2, 128.0, 128.2, 128.5, 135.5, 135.7, 140.1, 151.9, 189.5; IR (neat) 3444, 3020, 2941, 1642, 1515, 1411, 1354, 1214, 1150, 1051, 922, 759 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{17}IO_4S$–C_2H_5O $(M)^+$ 398.9552, found 398.9536.

*4.2.29. (E)-3-[Hydroxy(phenyl)methyl]-4-iodo-5-(methoxymethoxy)pent-3-en-2-one (**E-5i**).*[18a] Yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.07 (d, *J*=5.5 Hz, 1H), 3.38 (s, 3H), 4.32 (d, *J*=13.4 Hz, 1H), 4.37 (d, *J*=13.4 Hz, 1H), 4.62 (s, 2H), 5.83 (d, *J*=5.5 Hz, 1H), 7.27–7.32 (m, 1H), 7.35–7.38 (m, 2H), 7.41–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2, 56.0, 72.5, 80.2, 95.6, 106.6, 125.7, 128.0, 128.6, 139.7, 151.1, 202.9; IR (neat) 3434, 3060, 3029, 2997, 2946, 2886, 1698, 1605, 1494, 1449, 1352, 1213, 1149, 1104, 1044, 920, 759, 705 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}IO_4$–HO $(M)^+$ 359.0144, found 359.0145.

*4.2.30. (Z)-3-[Hydroxy(phenyl)methyl]-4-iodo-5-(methoxymethoxy)pent-3-en-2-one (**Z-5i**).*[18a] Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H), 3.45 (s, 3H), 3.53 (d, *J*=5.5 Hz, 1H), 4.48 (d, *J*=13.3 Hz, 1H), 4.58 (d, *J*=13.3 Hz, 1H), 4.71 (d, *J*=6.9 Hz, 1H), 4.75 (d, *J*=6.9 Hz, 1H), 5.89 (d, *J*=5.5 Hz, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 30.1, 56.1, 70.0, 71.6, 95.5, 97.9, 125.9, 128.1, 128.7, 139.6, 154.1, 204.9; IR (neat) 3397, 3010, 2932, 2891, 1700, 1626, 1494, 1450, 1350, 1215, 1149, 1109, 1050, 919, 757, 700 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{17}IO_4$–I $(M)^+$ 249.1127, found 249.1126.

4.3. The iodo-Mannich reaction

*4.3.1. Ethyl (E)-3-benzoyl-5,5-diethoxy-4-iodo-2-[(4-methoxyphenyl)amino]pent-3-enoate (**E-8**).* To a suspension of TiI_4 (100 mg, 0.18 mmol) in CH_2Cl_2 (1.0 mL) was added a mixture of γ-diethoxyalkynyl ketone **1a** (34.8 mg, 0.15 mmol) and imino ester **7** (37.3 mg, 0.18 mmol) in CH_2Cl_2 (2.0 mL) at −40 °C under an argon atmosphere. The mixture was stirred at −40 °C for 1.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and EtOAc and 10% aqueous $NaHSO_3$ were added successively. The mixture was filtered through a Celite pad, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by buffered preparative silica gel TLC (*n*-hexane/EtOAc/toluene=3/1/1 as an eluent) to give the iodo-Mannich products ***E*-8** (34.8 mg, 41%). Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (dd, *J*=6.9, 7.3 Hz, 3H) 1.06 (t, *J*=6.9 Hz, 3H), 1.32 (t, *J*=7.1 Hz, 3H), 3.00 (dq, *J*=6.9, 9.7 Hz, 1H), 3.26 (q, *J*=6.9 Hz, 2H), 3.47 (dq, *J*=7.3, 9.7 Hz, 1H), 3.74 (s, 3H), 4.08 (s, 1H), 4.21–4.35 (m, 2H), 4.54 (d, *J*=5.5 Hz, 1H), 5.32 (d, *J*=5.5 Hz, 1H), 6.58–6.62 (m, 2H), 6.73–6.77 (m, 2H), 7.26–7.30 (m, 2H), 7.44–7.48 (m, 1H), 7.72–7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.6, 14.6, 55.7, 61.7, 62.3, 62.4, 67.3, 100.0, 114.8, 115.4, 115.5, 128.3, 129.2, 133.8, 136.2, 140.1, 145.1, 152.8, 169.5, 194.6; IR (neat) 3374, 3065, 2978, 2932, 2907, 2831, 1739, 1661, 1595, 1515, 1449, 1369, 1290, 1238, 1156, 1113, 1063, 1031, 822, 736, 690 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{30}INO_6$–I $(M)^+$ 440.2073, found 440.2068.

*4.3.2. Ethyl (E)-3-benzoyl-4-iodo-5-(methoxymethoxy)-2-[(4-methoxyphenyl)amino]pent-3-enoate (**E-9**).* To a suspension of TiI_4 (100 mg, 0.18 mmol) in CH_2Cl_2 (1.0 mL) was added a mixture of γ-methoxymethoxyalkynyl ketone **1b** (36.8 mg, 0.18 mmol) and imino ester **7** (31.1 mg, 0.15 mmol) in CH_2Cl_2 (2.0 mL) at −50 °C under an argon atmosphere. The mixture was stirred at −50 °C for 1.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and EtOAc and 10% aqueous $NaHSO_3$ were added successively. The mixture was filtered through a Celite pad, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by buffered preparative silica gel TLC (*n*-hexane/EtOAc/CH_2Cl_2=4/1/1 as an eluent) to give the iodo-Mannich products **E-9** (41.9 mg, 52%) and **Z-9**

(22.6 mg, 28%); Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H), 3.12 (s, 3H), 3.75 (s, 3H), 4.08 (s, 2H), 4.25–4.33 (m, 2H), 4.36 (d, J=6.9 Hz, 1H), 4.41 (d, J=6.9 Hz, 1H), 4.56 (d, J=5.5 Hz, 1H), 5.21 (d, J=5.5 Hz, 1H), 6.58–6.62 (m, 2H), 6.74–6.78 (m, 2H), 7.27–7.31 (m, 2H), 7.44–7.49 (m, 1H), 7.69–7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 55.5, 55.7, 62.3, 67.7, 72.2, 95.3, 110.2, 114.8, 115.3, 128.5, 129.0, 133.7, 136.4, 140.2, 144.9, 152.8, 169.6, 193.9; IR (neat) 3376, 3060, 2991, 2943, 2904, 2831, 1741, 1663, 1595, 1511, 1450, 1285, 1240, 1204, 1151, 1105, 1031, 942, 822, 755 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{26}INO_6$ (M)$^+$ 539.0805, found 539.0807.

*4.3.3. Ethyl (Z)-3-benzoyl-4-iodo-5-(methoxymethoxy)-2-[(4-methoxyphenyl)amino]pent-3-enoate (**Z-9**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J=7.1 Hz, 3H), 3.53 (s, 3H), 3.74 (s, 3H), 4.16–4.30 (m, 2H), 4.44 (br s, 1H), 4.45 (d, J=13.5 Hz, 1H), 4.83 (d, J=6.9 Hz, 1H), 4.85 (d, J=6.9 Hz, 1H), 4.87 (d, J=13.5 Hz, 1H), 5.30 (s, 1H), 6.58–6.62 (m, 2H), 6.71–6.75 (m, 2H), 7.29–7.33 (m, 2H), 7.45–7.50 (m, 1H), 7.79–7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 55.7, 56.2, 59.3, 62.5, 70.3, 95.7, 103.0, 114.8, 115.1, 128.4, 129.7, 133.5, 134.2, 139.9, 145.6, 153.0, 169.2, 196.3; IR (neat) 3377, 3060, 2992, 2945, 2898, 2830, 1740, 1664, 1596, 1511, 1449, 1239, 1208, 1151, 1105, 1034, 944, 822, 755 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{26}INO_6$ (M)$^+$ 539.0805, found 539.0807.

4.4. Synthesis of tetra-substituted furans

*4.4.1. (Z)-3-(Diethoxymethyl)-2-[hydroxy(phenyl)methyl]-1,5-diphenylpent-2-en-4-yn-1-one (**10**).*[18a] A mixture of $PdCl_2(PPh_3)_2$ (3.5 mg, 0.0050 mmol), CuI (3.8 mg, 0.020 mmol), phenyl acetylene (20.5 mg, 0.201 mmol), Et_3N (0.5 mL), and the iodide ***E*-3a** (46.6 mg, 0.0999 mmol) in DMF (0.5 mL) was heated at 90 °C under an argon atmosphere for 20 h. The reaction mixture was cooled to room temperature and quenched with H_2O, 2 M HCl, and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (*n*-hexane/EtOAc=5/1 as an eluent) to give the enynol **10** (32.1 mg, 73%); Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J=6.9 Hz, 3H), 1.01 (t, J=6.9 Hz, 3H), 3.14–3.28 (m, 2H), 3.41–3.58 (m, 3H), 4.82 (s, 1H), 6.35 (d, J=5.9 Hz, 1H), 7.13–7.53 (m, 13H), 7.64–7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 14.7, 61.8, 62.1, 74.7, 84.2, 99.2, 99.4, 122.6, 123.9, 125.9, 127.7, 128.1, 128.3, 128.4, 128.9, 129.1, 131.8, 133.1, 137.5, 141.1, 147.6, 197.2; IR (neat): 3433, 3022, 2929, 1649, 1214, 1050, 747 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{28}O_4$–C_2H_5O (M)$^+$ 395.1647, found 395.1646.

*4.4.2. [5-Benzyl-4-(diethoxymethyl)-2-phenylfuran-3-yl](phenyl)methanone (**11**).*[18a] A mixture of $PdCl_2(CH_3CN)_2$ (3.6 mg, 0.0138 mmol) and the enynol **10** (32.0 mg, 0.726 mmol) in THF (0.5 mL) was heated at reflux under an argon atmosphere for 2 h. The reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (*n*-hexane/EtOAc=4/1 as an eluent, developed twice) to give the furans **11** (5.9 mg, 18%) and **12** (9.7 mg, 36%); Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J=6.9 Hz, 6H), 3.38 (dq, J=6.9, 9.2 Hz, 2H), 3.52 (dq, J=6.9, 9.2 Hz, 2H), 4.25 (s, 2H), 5.56 (s, 1H), 7.13–7.25 (m, 4H), 7.30–7.40 (m, 8H), 7.46–7.50 (m, 1H), 7.86–7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 33.3, 61.2, 97.0, 120.6, 120.7, 126.0, 126.3, 128.0, 128.4, 128.4, 128.8, 129.7, 133.1, 127.7, 128.3, 150.2, 151.5, 193.6; IR (neat): 3062, 3029, 2976, 2928, 2892, 2882, 1667, 1598, 1582, 1560, 1493, 1448, 1415, 1390, 1340, 1315, 1285, 1257, 1228, 1174, 1127, 1086, 1054, 1027, 902, 767 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{28}O_4$ (M)$^+$ 440.1988, found 440.1991.

*4.4.3. 4-Benzoyl-2-benzyl-5-phenylfuran-3-carbaldehyde (**12**).*[18a] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (s, 2H), 7.24–7.53 (m, 13 H), 7.85–7.87 (m, 2H), 9.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 119.3, 123.3, 126.6, 127.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.1, 129.6, 133.7, 135.9, 137.2, 152.3, 161.2, 184.8, 191.9; IR (neat) 3020, 1684, 1559, 1495, 1448, 1216, 1024, 900, 757 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{18}O_3$–C_6H_5 (M)$^+$ 289.0865, found 289.0860.

*4.4.4. {5-Benzyl-4-[(methoxymethoxy)methyl]-2-phenylfuran-3-yl}(phenyl)methanone (**13**).*[18a] A mixture of $PdCl_2(PPh_3)_2$ (33.8 mg, 0.0482 mmol), CuI (36.6 mg, 0.192 mmol), phenyl acetylene (197 mg, 1.93 mmol), Et_3N (1.0 mL), and the iodide ***E*-5a** (416 mg, 0.949 mmol) in DMF (1.0 mL) was heated at 90 °C under an argon atmosphere for 6 days. The reaction mixture was cooled to room temperature and quenched with saturated NH_4Cl and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined extracts were dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC on silica gel (*n*-hexane/EtOAc=4/1 as an eluent, developed twice) to give the furan **13** (191 mg, 49%). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 3H), 4.13 (s, 2H), 4.47 (s, 2H), 4.47 (s, 2H), 7.16–7.19 (m, 3H), 7.29–7.38 (m, 9H), 7.43–7.47 (m, 1H), 7.82–7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.4, 55.2, 59.0, 95.6, 119.0, 121.1, 126.6, 126.8, 128.2, 128.3, 128.6, 128.6, 129.6, 129.7, 133.1, 137.4, 147.5, 152.1, 152.5, 193.1; IR (neat) 3061, 3027, 2933, 2879, 2823, 1657, 1597, 1580, 1560, 1495, 1448, 1401, 1320, 1224, 1148, 1100, 1036, 971, 906 cm^{-1}; HRMS (EI) calcd for $C_{27}H_{24}O_4$ (M)$^+$ 412.1675, found 412.1655.

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Appendix A. Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra and Cartesian coordinates) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.09.020.

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