DIASTEREOSELECTIVE CONJUGATE RADICAL ADDITIONS TO β-PYRONES

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By

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Title

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

ABSTRACT

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A convenient protocol for functionalization of β-pyrones has been developed. Conjugate radical addition and tandem addition-trapping protocols allowed accessing highly substituted pyrones in a single operation with high selectivity. Different radical sources were utilized in the reaction. nOe experiments were performed to confirm the relative stereochemistry of the substituents in the conjugate addition products. Initial studies on the enantioselectivity of the reaction were carried out. Unfortunately, the catalysts chosen for the initial studies did not show any promise regarding enantioselectivity.

ACKNOWLEDGEMENTS

Graduate life is indeed tough and requires time and effort. More importantly, it requires individuals to have support and encouragement, which could only come from people. First, my sincerest thanks and deepest gratitude to my mentor Dr. Mukund P. Sibi for his patience and input. I really appreciate the moments when he challenges me to think and learn to solve problems scientifically. Thank you for providing a laboratory that is conducive to intellectual discussions and exchange of ideas. Most of all, thank you for the encouragement even through the roughest and toughest times of my personal life while I was in graduate school.

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Other than the chemicals in the laboratory, I have interaction with people that have made graduate life in the Sibi group fun and interesting, to the say the least. Thanks to all the former and present members of the group as well as exchange students from different countries. Thank you Regina, Max, Ken, Hiroto, Hector, Masayuki, Takahiro, Sukanya, Frank, Julien, Seiji, Keisuke, Hiroshi, Norihiko, Yonghua, Miguel, Sunggi, Kalyani, Digamber, Brandon, Wilfredo, Naveen, Sreehari, and Kelsey. Special thanks to Jake and Levi for all the discussions, suggestions, and insights but most especially for helping me

keep my sanity the many times that I almost lost it. Thanks also for playing country music in the laboratory everyday. I learned to appreciate it in some ways.

My church friends are also worth mentioning for serving as my family here in the United States. Thanks for being there for emotional and moral support. Thanks to all the other graduate students, you know who you all are, from the department for making late nights in the laboratory fun, eventful, and memorable.

DEDICATION

This work is dedicated to

My father and my grandmother:

Jayme Yu and Gloria Estiva

Thank you for supporting me in venturing out in a different country and supporting my choice for my career path. Thank you for all the love and understanding. Words are not enough to express how much I appreciate you and how grateful I am. You both have been very big parts of my life and shaped who I am as an individual.

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GLOSSARY

Ac.....Acetyl

AIBN.....2,2'-Azobis(isobutyronitrile)

Boc.....*t*-Butoxycarbonyl

Br_2.....Bromine

n-Bu.....*n*-Butyl

t-Bu.....*t*-Butyl

Bu_3SnH.....Tributyltin hydride

calc'd.....Calculated

CF_3COOH.....Trifluoroacetic acid

CH_2Cl_2.....Methylene chloride

CuCN.....Copper (I) cyanide

δ.....Chemical shift in parts per million down-field from TMS

dr.....Diastereoselective ratio

ESI.....Electron spray ionization

equiv.....Equivalent

Et.....Ethyl

Et_2O.....Diethyl ether

Et_2Zn.....Diethylzinc

Et_3B.....Triethylborane

Et_3N.....Triethylamine

h.....Hours

c-Hex.....Cyclohexyl

Hz.....Hertz

HPLC.....High pressure liquid chromatography

HRMS.....High resolution mass spectroscopy

J.....Coupling constants (in NMR)

LA.....Lewis acid

M.....Metal

MeLi.....Methyllithium

MeOH.....Methyl alcohol

Me_2Zn.....Dimethylzinc

mol.....Moles

Mol. Wt.....Molecular weight

$NaBH_4$.....Sodium borohydride

$NaHCO_3$.....Sodium bicarbonate

nd.....Not determined

NMR.....Nuclear magnetic resonance

nOe.....Nuclear overhauser effect

NTf_2.....Triflimide

O_2.....Oxygen

OMe.....Methoxy

OTf.....Triflate

c-Pent.....Cyclopentyl

Ph.....Phenyl

$PhSiH_3$.....Phenylsilane

Ph_2SiH_2.....Diphenylsilane

ppm.....Parts per million

n-Pr.....*n*-Propyl

i-Pr.....*iso*-Propyl

R.....Alkyl group

rt.....Room temperature

Temp.....Temperature

TBS.....Tributylsilyl

THF.....Tetrahydrofuran

TLC.....Thin-layer chromatography

TMS.....Trimethylsilyl

1. INTRODUCTION

One of the many uses of radical reactions is in the formation of multiple bonds in a single operation.[1,2] The selective formation of carbon-carbon bonds is one of the main goals of organic synthetic chemists. There has been numerous publications regarding the development of both diastereoselective and enantioselective organic reactions.[3] These reactions are typically ionic. Due to this nature, it leads to potential problems. Protection and deprotection of sensitive functional groups and removal of water need to be considered. These are usually not issues with radical reactions.

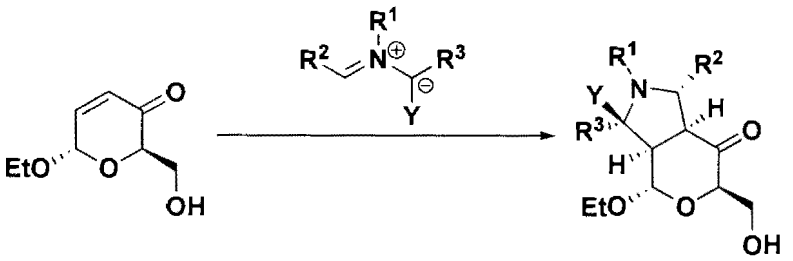
For a time, radicals were thought of as not useful for selective chemistry due to their high reactivity. Despite this, they are compatible with functional groups. Protection for functional groups such as carbonyls, hydroxyls, amines, and other reactive ones are not a requirement for radical reactions. For this reason, the development of diastereoselective and enantioselective free radical chemistry has grown rapidly.[4]

Lewis acids play important roles in organic chemistry.[5] The use of acyclic molecules as substrates is often problematic in stetroselective reactions. The flexibility of acyclic molecules often creates low levels of stereocontrol. One of the ways to alleviate this problem is with the aid of Lewis acids. Lewis acid complexation with Lewis basic sites decreases the rotational degrees of freedom of flexible molecules, thus enhancing the difference in energy between competing transition states. Lewis acids can also influence a reaction by adjusting the electronic and steric factors of functionalities adjacent to the chemical transformation site.

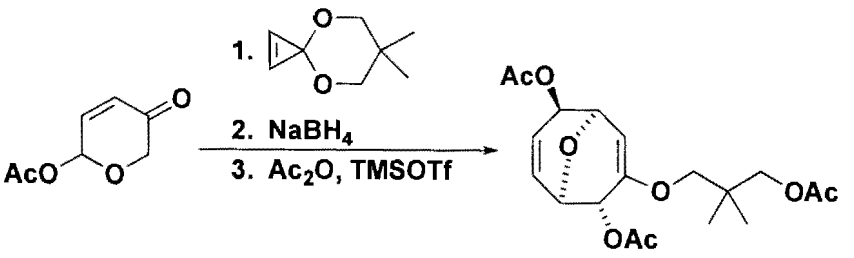
Conjugate addition to β-pyrones has been studied and typically these reactions involve the use of a chiral catalyst in order to obtain enantioselectivity for the product. β-

Pyrones are very versatile molecules. Some of their applications are in conjugate additions, cycloaddition reactions and as building blocks for the synthesis of large biologically active molecules.[6] They are ideal intermediates because they can be easily functionalized or transformed into different groups.

The use of pyranones in cycloadditions reactions has been reported in the literature. Bashiardes and co-workers[7] reported regio- and enantioselective synthesis of novel functionalized pyranopyrrolidines by 1,3-dipolar cycloaddition of carbohydrates (Scheme 1). Delgado and co-workers[8] also performed a similar type of reaction (Scheme 2). A [5+2] oxidopyrrylium-cyclopropenone acetal cycloaddition followed by ring opening of the cyclopropane of the adduct led to highly functionalized 1,5-oxa-bridged cyclooctenes consisting of up to four stereocenters. The protocol formally constitutes a [5+3] annulation process.

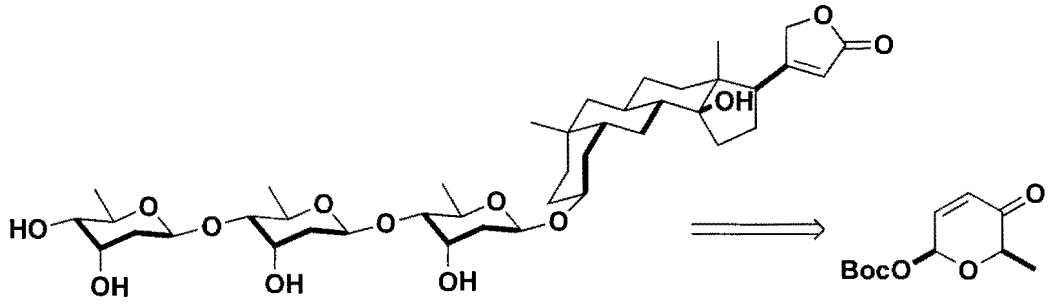


Scheme 1. Synthesis of a Pyranopyrrolidine by 1,3-Dipolar Cycloaddition.



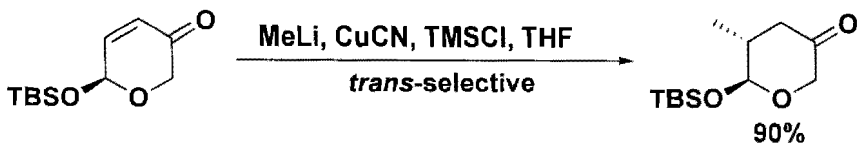
Scheme 2. Stereoselective Synthesis of a Highly Functionalized 1,5-Oxa-Bridged Cyclooctene.

One of the most common strategies used in organic synthesis is utilization of advanced intermediates as one of the key steps in order to shorten the overall synthesis of a compound. O'Doherty and co-workers[6] utilized a pyrone as an intermediate to synthesize digitoxin. They used a convergent and stereocontrolled route to bring together two natural products to obtain digitoxin, which possesses potent cardiac and anticancer activities (Scheme 3).



Scheme 3. Retrosynthetic Pathway for the Synthesis of Digitoxin from Digitoxigenin.

Sugawara and co-workers[9] performed a transformation utilizing a pyrone as an intermediate (Scheme 4) to eventually synthesize hexahydro-TMC-69 (Figure 1). This is an example of establishing a stereocenter in a pyranone and carrying out further transformations to the molecule.



Scheme 4. *Trans*-selective Methylation of a β-Pyrone.

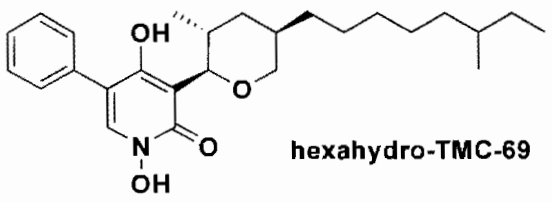
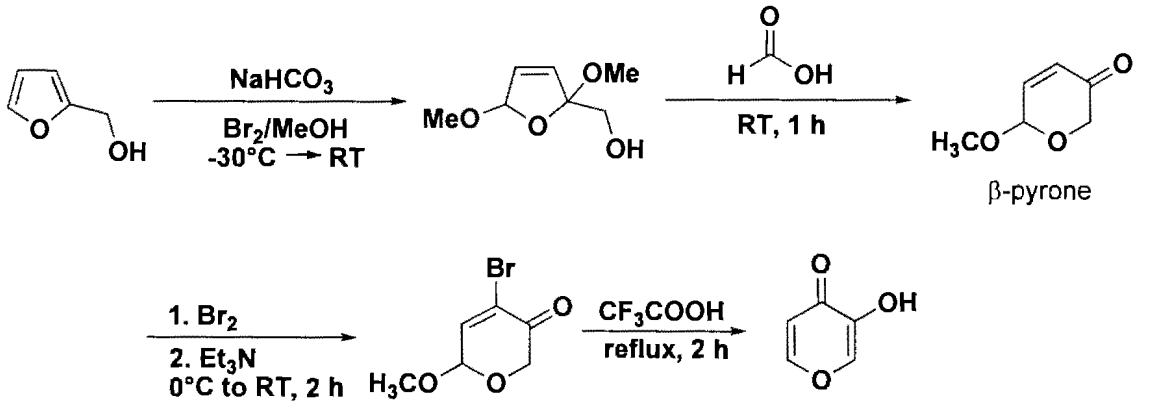


Figure 1. Structure of Hexahydro-TMC-69.

2. OBJECTIVE

The initial objective of this project was the exploration of different conjugate radical additions to pyromeconic acid derivatives. The goal was to study the effects of varying the different side groups and investigate the trends or behaviors based on variations in steric bulk and electronic properties. During the course of synthesizing the parent compound, pyromeconic acid, we noticed an interesting intermediate (Scheme 5). This intermediate seemed like a close relative of pyromeconic acid, which is a γ-pyrone. The interesting intermediate was a β-pyrone.

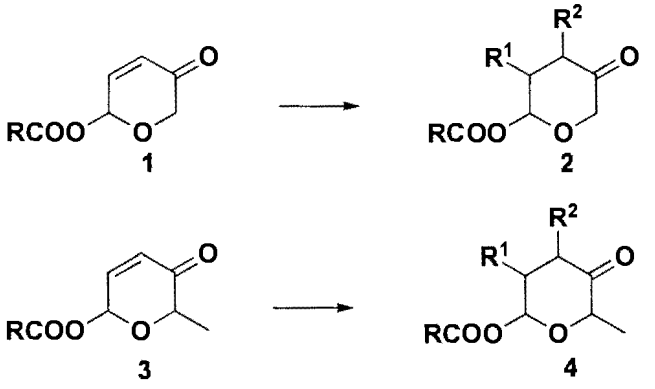


Scheme 5. Synthesis of Pyromeconic Acid from 2-(Hydroxymethyl)furan.

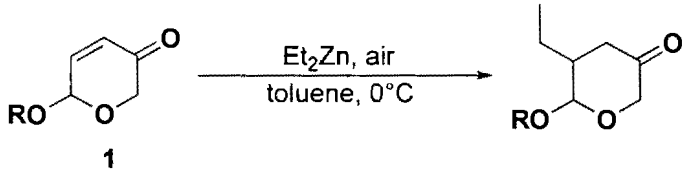
Therefore the focus of the project changed to investigating β-pyrones in radical reactions. The advantage to utilizing this compound is that the synthesis is three steps shorter and does not have any regioselective issues in the conjugate addition. In addition, the enantioselective reactions were investigated.

The Sibi group has recently demonstrated that γ-pyrones such as pyromeconic and kojic acid derivatives undergo highly efficient conjugate radical additions.[10] As mentioned

above, we have been interested in extending this chemistry to the functionalization of β-pyrones (Scheme 6). Feringa and co-workers reported that an ethyl radical derived from diethylzinc/oxygen adds to **1** (R = Ph) in good yield and selectivity (Scheme 7).[11]



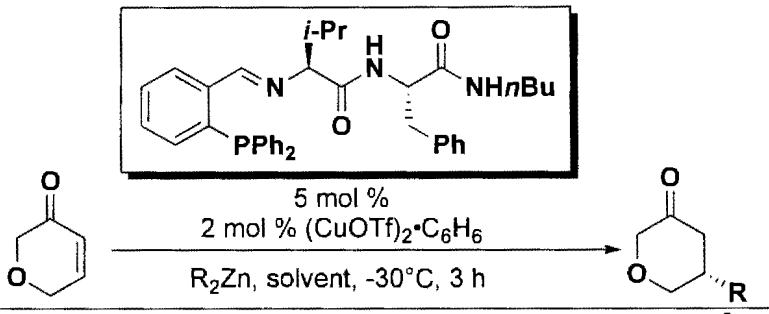
Scheme 6. Functionalization of β-Pyrones Through Addition to the Double Bond.



Scheme 7. Conjugate Addition to β-Pyrones Using Diethylzinc/Oxygen.

Hoveyda and co-workers have demonstrated that enantioselective conjugate additions are possible with β-pyrones as substrates (Table 1).[12] Several organic solvents were screened and dialkyl zinc was used as the alkylating agent. With THF as solvent, their best enantioselective ethylation was performed with 66% yield and 98% enantiomeric excess. With the same solvent, their best methylation had 58% yield and >98% enantiomeric excess.

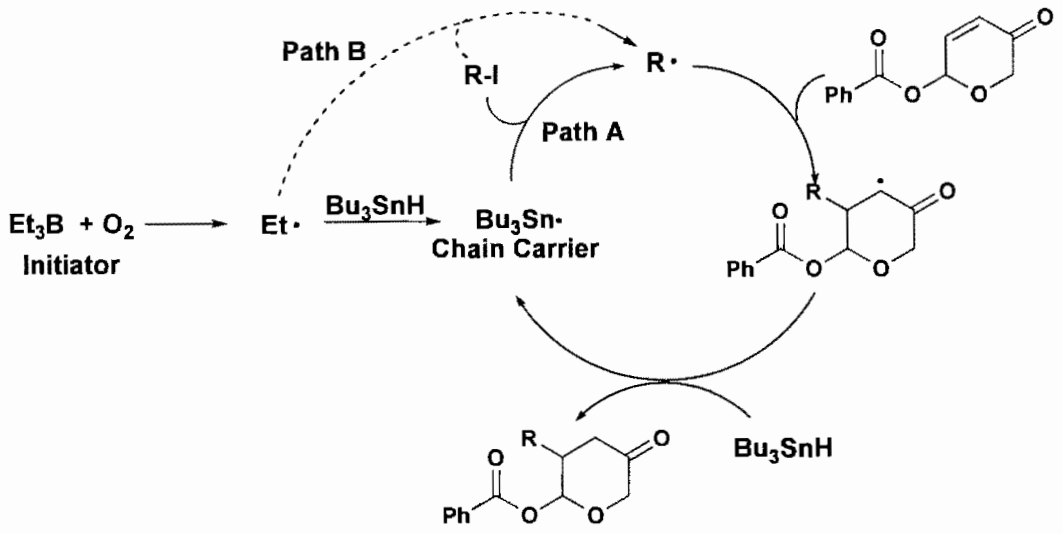
Table 1. Enantioselective Conjugate Addition to β-Pyrones Utilizing Dialkylzinc Reagents.



Entry	R_2Zn	Solvent	Yield (%)[a]	ee (%)[b]
1	Et_2Zn	toluene	nd	64
2	Et_2Zn	Et_2O	nd	72
3	Et_2Zn	THF	66	98
4	Me_2Zn	toluene	nd	56
5	Me_2Zn	THF	58	>98

[a] Yields are for isolated and column-purified materials.
[b] Ees were determined by chiral GC.

The initiator for our free radical reactions was triethylborane in the presence of oxygen (Scheme 8). This combination produces ethyl radical that can abstract a hydrogen atom from tributyltin hydride to generate a tributyltin radical. The corresponding tin radical efficiently reacts with alkyl halides to produce the corresponding alkyl radical (Path A). Alternatively, the ethyl radical can abstract an iodine atom from the alkyl halide to generate an alkyl radical (Path B). Through this pathway, it is possible to form radicals that are more stable than the initial ethyl radical. The alkyl radical then undergoes a conjugate addition to the substrate and generates another radical intermediate. This intermediate abstracts a H-atom from tributyltin hydride, yields the product, and regenerates the chain carrier.



Scheme 8. Intermolecular Radical Conjugate Addition.

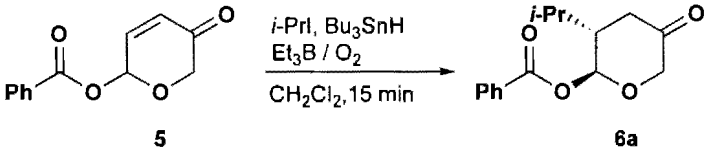
3. RESULTS AND DISCUSSION

This study showed that β-pyrones **1** underwent conjugate addition reactions with a wide variety of nucleophilic radicals and gave products in good yields and high diastereoselectivities. Similarly, tandem protocols such as radical addition/allyl stannane trapping also proceed in good yield and selectivity to provide **2**. Currently, the methodology allows for the preparation of highly functionalized pyrones **4** in enantioenriched form (see Scheme 6).[13]

This work began with the identification of reaction conditions for conjugate radical additions to 6-benzoyloxy-2,3-dihydro-6H-pyran-3-one (β-pyrone) **5** (Table 2).[14] Initial experiments began with standard conditions using isopropyl iodide as the radical source, triethylborane/oxygen as a radical initiator, and tributyltin hydride as a H-atom source as well as the chain carrier (Table 2 entry 1). Within 15 minutes, the reaction was complete providing product **6a** in good yield and high selectivity. At higher temperatures, it was found that reactions were equally efficient without any compromise in diastereoselectivity (entries 2 and 3). It is generally necessary to use 5 or more equivalents of tributyltin hydride at low temperatures to maintain reaction efficiency and obtain good yields. Noting that the reaction was efficient at room temperature, interest came in evaluating the minimum amount of tin hydride required for an efficient reaction. Lowering the amount of tin hydride from 5 equivalents to 2 equivalents did not diminish the yield or selectivity (entry 4). It was found that a further reduction in the amount of tin hydride led to lower yields and a small decrease in selectivity (entries 5 and 6). In the synthetic community, it is well recognized that tin hydride is toxic and removal of tin byproducts from the reaction products is often difficult.[15] Due to this, two environmentally benign silanes were evaluated

as H-atom sources and chain carriers. Results indicated that the two silanes were inferior compared to reaction with tributyltin hydride (compare entry 4 with entries 7 and 8). The

Table 2. Optimization of Reaction Conditions for Conjugate Radical Addition to β-Pyrone **5**.



5
Racemic

6a

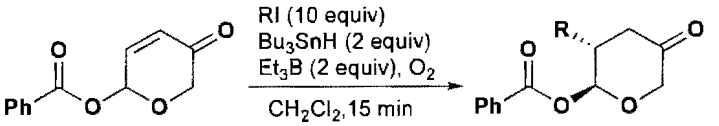
Entry	Bu_3SnH/Et_3B (equiv)	Temp	Yield (%)[a]	dr[b]
1	5	-78 °C	65	99:1
2	5	0 °C	62	98:2
3	5	RT	75	97:3
4	2	RT	69	97:3
5	1.5	RT	40	93:7
6	1	RT	44	92:8
7	$PhSiH_3$ (2 equiv)	RT	47	88:12
8	Ph_2SiH_2 (2 equiv)	RT	47	88:12

[a] Yields are for isolated and column-purified materials.
[b] Diastereomeric ratios were determined by NMR.

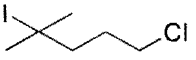
reactions with the silanes resulted in a decrease in diastereoselectivity from 97:3 to 88:12 and even after 15 minutes, the reaction was still incomplete.

After establishing reasonable reaction conditions for conjugate addition to **5**, we then evaluated the scope of the radical precursors. The results from these experiments are shown in Table 3. Modestly nucleophilic primary radicals were not efficient (entries 1-3). Addition of ethyl radical using ethyl iodide as a precursor gave the product in good yield and excellent diastereoselectivity. This result is similar to that obtained by Feringa using diethylzinc as a radical precursor.[11] However, the products from reactions with propyl and butyl radicals were contaminated with ethyl radical addition product (from triethylborane). Products **6c** and **6d** proved to be inseparable from ethyl addition product **6b**. Their

Table 3. Conjugate Radical Addition to β-Pyrone **5**



5 Racemic — **6a-k**

Entry	RI	Product	Yield (%)[a]	dr[b]
1	EtI	**6b**	62	>99:1
2	*n*-PrI	**6c**	42 (26, Et) (1.6:1)	>99:1 (>99:1)
3	*n*-BuI	**6d**	47 (25, Et) (1.9:1)	>99:1 (>99:1)
4	*i*-PrI	**6a**	69	97:3
5	*t*-BuI	**6e**	63	>99:1
6	*c*-PentylI	**6f**	70	94:6
7	*c*-HexylI	**6g**	69	95:5
8	adamantylI	**6h**	57	>99:1
9		**6i**	58	97:3
10	2-iodoethanol	**6j**	-	-
11	5-iodopentene	**6k**	-	-

[a] Yields are for isolated and column-purified materials.
[b] Diastereomeric ratios were determined by NMR.

respective diastereomeric ratios were estimated by NMR. Reaction with the secondary isopropyl radical was more efficient providing **6a** in good yield and selectivity (entry 4). Similarly, addition of tertiary butyl radical was also efficient and the diastereoselectivity was the highest observed for the different precursors examined (entry 5). Cyclic secondary and tertiary radicals were also effective in conjugate addition to **5** (entries 6-9). Although the yields varied in these reactions, the level of diastereoselectivity was high in all cases. Reaction with functionalized butyl radical was efficient giving the product in good yield and high selectivity (entry 10). In contrast, reactions with functionalized primary radicals were not efficient (entries 11 and 12).[16] In these reactions only the ethyl addition product was observed. These results demonstrate that a variety of radicals participate in conjugate additions to β-pyrones. As previously established in the work of Feringa, the relative stereochemistry for the radical addition is anti.[11] The anomeric acyloxy group controls the

relative stereochemistry of the radical addition.[17] One of the most common explanations of the anomeric effect is that the lone pairs of the polar atom connected to the carbon can be stabilized by overlapping with an antibonding orbital of the bond between the carbon and the other polar atom (Figure 2). Other sources of nucleophilic radical precursors such as chloroiodomethane and 2-bromo-1-chloro-2-methylpropane were tried attempted but they gave none of the desired products.

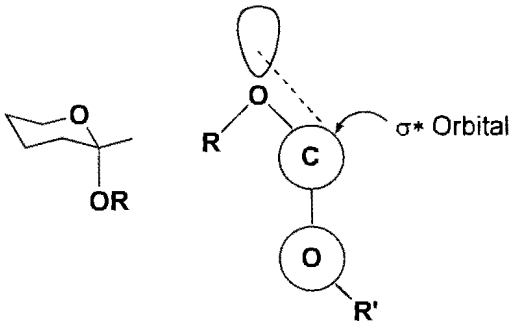
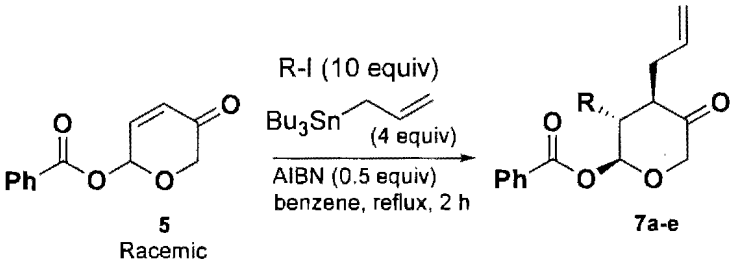


Figure 2. Illustration of the Anomeric Effect.

After establishing the reaction conditions for successful conjugate additions to β-pyrones, we next examined the feasibility of tandem radical reactions. It is well established in the literature that allyl stannanes function as efficient allyl group transfer reagents as well as radical chain carriers.[18] Tandem experiments using isopropyl iodide, allyl stannane, and triethylborane/oxygen as an initiator at -78 °C gave only the isopropyl addition product **6a** in 62% yield (89:11 dr). Reaction at room temperature also gave none of the addition/trapping product. Only the addition product was obtained in 62% yield (91:9 dr). Successful addition/trapping protocols were finally developed at reflux temperatures using AIBN as a radical initiator. Results from these experiments are tabulated in Table 4. For these experiments in benzene at reflux temperature, 10 equivalents of the radical precursor,

4 equivalents of allyl stannane, and 0.5 equivalents of AIBN were used. Addition trapping experiment with ethyl radical was successful in giving the allylated product in modest yield

Table 4. Radical Addition-Trapping Experiments with β-Pyrone **5**.

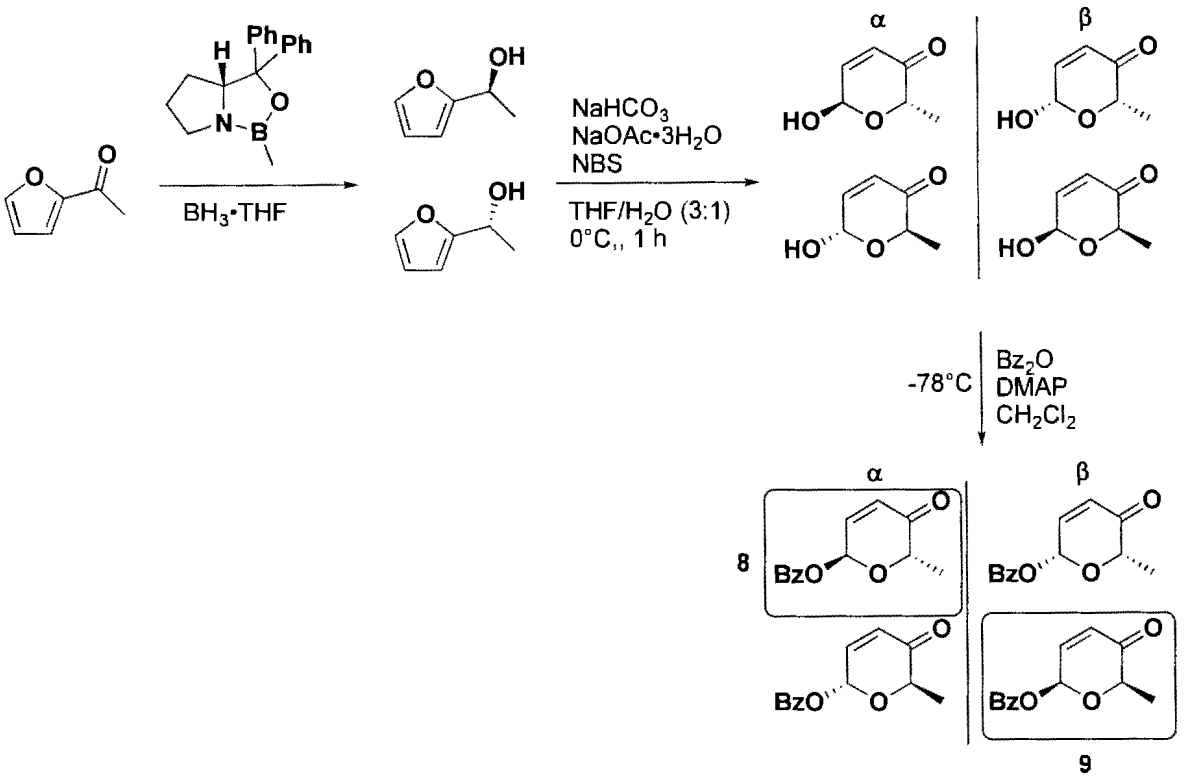


Entry	RI	Product	Yield (%)[a]	dr[b]
1	EtI	**7a**	45	88:12
2	*i*-PrI	**7b**	65	93:7
3	*t*-BuI	**7c**	60	94:6
4	*c*-Pentyl-I	**7d**	48	98:2
5	*c*-Hexyl-I	**7e**	59	90:10

[a] Yields are for isolated and column-purified materials.
[b] Diastereomeric ratios were determined by NMR.

and good diastereoselectivity (entry 1). Reaction with the more nucleophilic isopropyl radical gave the addition/trapping product in good yield and selectivity (entry 2). Tertiary butyl radical also gave the addition/trapping product in good yield and selectivity (entry 3). Cyclic secondary radicals, cyclopentyl and cyclohexyl, were also efficient in the addition/trapping experiments giving products in good yield and selectivity (entries 4 and 5). It is important to note that in these experiments three contiguous chiral centers are established. The relative stereochemistry for the addition/trapping product was established by NMR. The major diastereomer has the *anti/anti* configuration.

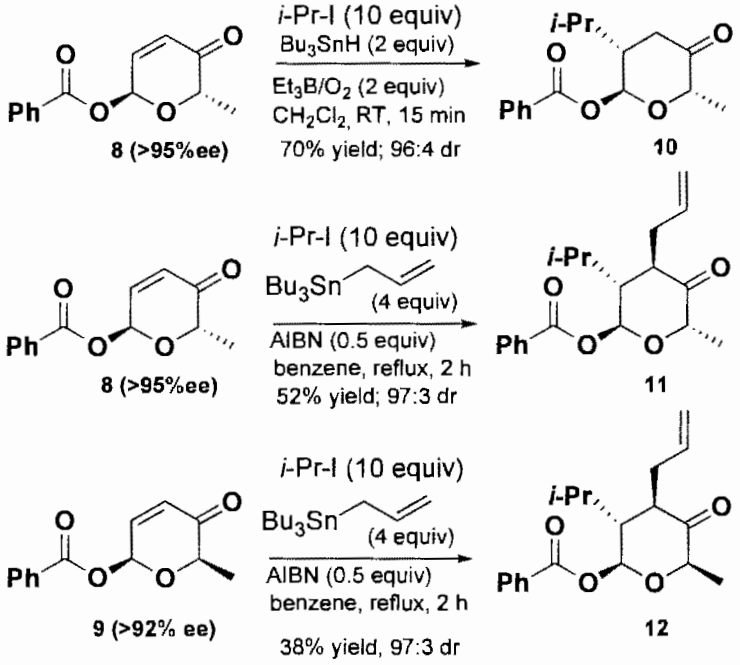
Additional substituted β-pyrones in enantioenriched form (Scheme 9) were prepared to further demonstrate the utility of the radical chemistry. Compounds **8** and **9** were prepared in good overall yields starting from 2-acetylfuran using the protocols developed by O'Doherty.[21] Under reductive conditions, isopropyl radical addition to **8** gave



Scheme 9. Synthesis of Enantioenriched Substrates.

the pyranone **10** in 71% yield (Scheme 10). The product was formed in a 96:4 diastereomeric ratio. Addition/trapping experiment with **8** was also successful using isopropyl iodide and allylstannane furnishing **11** in modest yield and high diastereoselectivity. Pyrone **9**, diastereomer of **8** also underwent addition/trapping furnishing **12** in high diastereoselectivity. These were unoptimized experiments (**11→12**). The anomeric acyloxy group is the primary determinant of relative stereochemistry in transformations with 2-substituted-6-acyloxy-3-pyranones.[18] We expect a similar scenario in our addition and addition/trapping reactions. nOe experiments were also carried out on pyrones **11** and **12** (Figures 3 and 4) to further support the *anti/anti* configuration. The

results described show that highly functionalized pyrans can be accessed in enantioenriched form using tandem radical reactions.



Scheme 10. Radical Addition-Trapping Experiments with Enantioenriched Substrates.

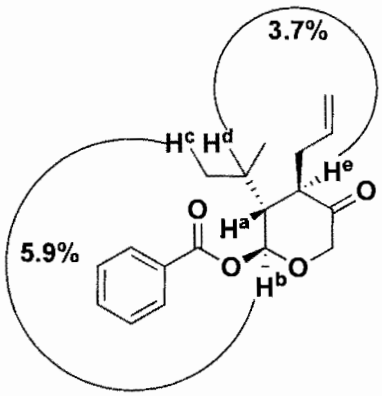


Figure 3. nOe Data for Addition-trapping Product **11**.

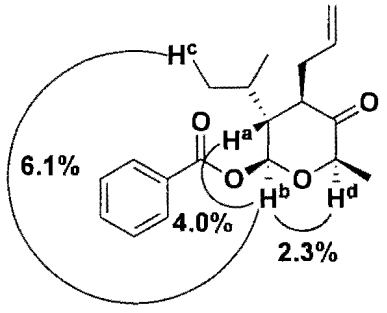


Figure 4. nOe Data for Addition-trapping Product **12**.

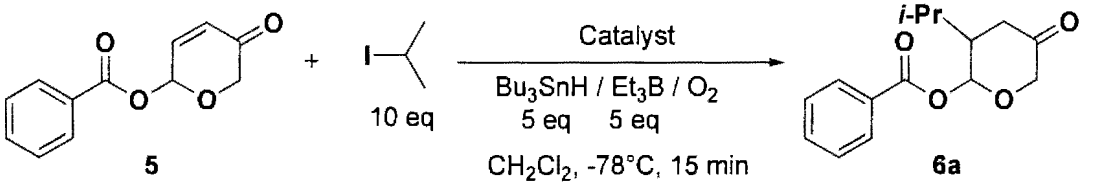
These reactions were further investigated to determine if they can be carried out enantioselectively. Reactions using different catalysts were performed using standard procedures. The choices for the catalysts to be investigated were based on previous success on enantioselective studies from the Sibi group. The first catalyst investigated was the salen catalyst **13** (Table 5). For both aluminum and chromium as the metal, the reactions resulted in comparable result (Table 5, entries 1 and 2) in terms of chemical efficiency and diastereoselectivity as in entry 1 in Table 1 but without enantioselectivity.

The second catalyst investigated was the indanol-derived bisoxazoline ligand **14** (Table 5 entries 3-7) paired with different Lewis acids that had been established to provide high enantioselectivity with different substrates. In the same manner as its diastereoselective counterpart, the reaction proceeded well and provided high diastereoselectivities. Unfortunately, no enantioselectivity resulted from these reactions.

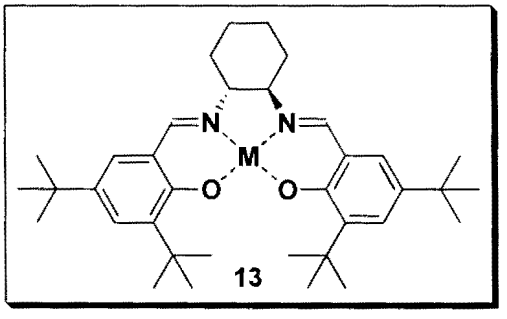
Due to the success of Barry Trost in his dinuclear zinc catalysis in aldol reactions[20], his ligand **15** was also investigated (Table 6). Instead of forming a dinuclear zinc catalyst, we were curious to know if it is possible to have a different mode of coordination of this ligand. Because of the presence of nitrogen atoms, we thought it would behave similar to the indanol-derived bisoxazoline ligand **14**. Various Lewis acids that were good pairs with

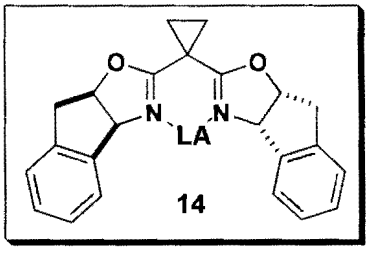
ligand **14** were investigated and paired with Trost's ligand. Similar to the previous attempts, none gave any promise of enantioselectivity although the chemical yield and diastereoselectivities seem to remain unaffected by these catalysts.

Table 5. Initial Enantioselective Investigation Using Different Combinations of **13**/metal and **14**/Lewis Acid Catalysts.



Catalysts:

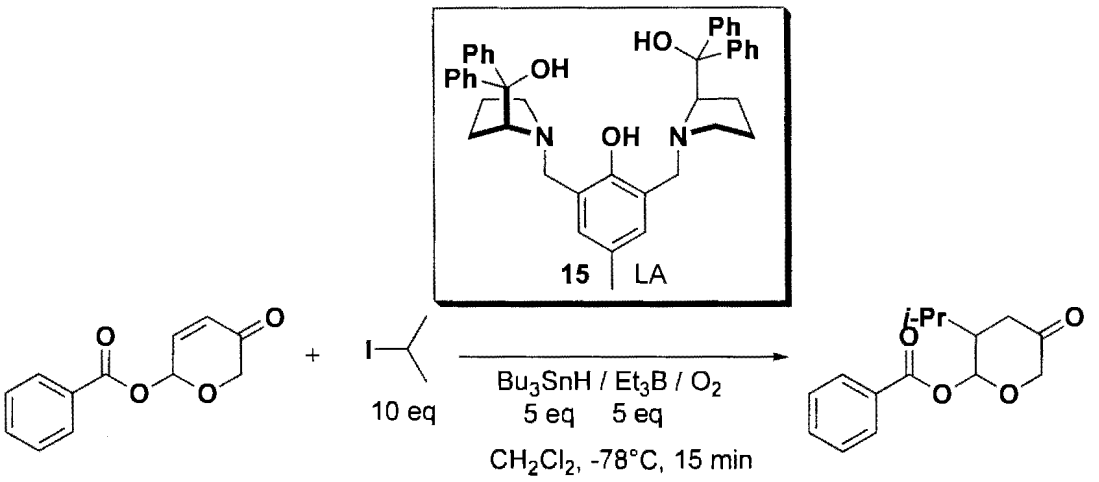




Entry	M or LA	Ligand	Yield (%)[a]	ee (%)	dr[b]
1	Al-Cl	**13**	58	None	95:5
2	Cr-Cl	**13**	60	None	93:7
3	$Mg(NTf_2)_2$	**14**	60	None	99:1
4	$Mg(ClO_4)_2$	**14**	68	None	95:5
5	$Mg(OTf)_2$	**14**	67	None	95:5
6	$Zn(OTf)_2$	**14**	55	None	95:5
7	$Sc(OTf)_3$	**14**	63	None	98:2

[a] Yields are for isolated and column-purified materials.
[b] Diastereomeric ratios were determined by NMR.

Table 6. Initial Enantioselective Investigation Using Trost's ligand **15** with Various Lewis Acids (LA).



Entry	LA	Yield (%)[a]	ee (%)	dr[b]
1	$Zn(OTf)_2$	56	None	96:4
2	$Al(OTf)_3$	70	None	94:6
3	$Eu(OTf)_3$	69	None	95:5
4	$Tb(OTf)_3$	42	None	95:5
5	$Pr(OTf)_3$	71	None	97:3
6	$Gd(OTf)_3$	58	None	96:4

[a] Yields are for isolated and column-purified materials.
[b] Diastereomeric ratios were determined by NMR.

4. CONCLUSIONS

Efficient protocols for functionalization of β-pyrones were developed. Radical additions and tandem reactions proceed with high diastereoselectivity allowing access to highly substituted pyrones. Various nucleophilic radicals were utilized and nOe experiments proved the relative stereochemistry of the substituents in the products. Currently, there is no catalyst found to work with these types of systems to provide enantioselectivity. For future work, the utilization of the newly developed radical methodology in the preparation of molecules of biological interest is underway in the laboratory.

5. EXPERIMENTAL SECTION

5.1. General Experimental Details

Dichloromethane was distilled from calcium hydride prior to use. HPLC grade benzene was utilized to carry out other reactions. Thin layer chromatographic separations were performed on silica gel Whatmann-60F glass plates, and components were visualized by illumination with UV light or by staining with phosphomolybdic acid and potassium permanganate. Flash chromatography was performed using E. Merck silical gel 60 (230-400 mesh). All glassware was oven-dried, assembled hot, and cooled under a stream of dry nitrogen before use.

^{1}H NMR was recorded on a Varian Unity/Inova-500 NB (500 MHz) or a Varian Unity/Inova-400 NB (400 MHz). Chemical shifts are reported in parts per million (ppm) downfield from TMS, and residual $CDCl_3$ (7.27 ppm) is used as an internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, tt = triplet of triplets, m = multiplet, b = broad), coupling constant(s), and integration. ^{13}C NMR was recorded on a Varian Unity/Inova-500 NB (125 MHz) or a Varian Unity/Inova-400 NB (100 MHz) spectrometer using broad band proton decoupling. Chemical shifts are reported in parts per million downfield from TMS, and the middle resonance of $CDCl_3$ (77.0 ppm) was used as an internal standard. High Resolution Mass Spectra (HRMS) were performed in-house on an electron spray ionization high resolution mass spectrometer.

5.2. Procedure for Substrate Synthesis

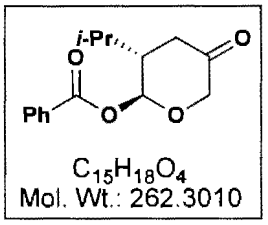
Compound **5** was prepared in racemic form using a literature procedure [Caddick, S.; Khan, S.; Frost, L. M.; Cheung, S.; Pairaudeau, G. *Tetrahedron* **2000**, *56*, 8953].

5.3. General Procedure for Conjugate Radical Addition

The substrate (0.20 mmol) was dissolved in CH_2Cl_2 (6 mL) and stirred at rt for 15 minutes in a 6 dram vial. The reaction was then initiated by sequential addition of the halide (2.0 mmol), Bu_3SnH (0.40 mmol), Et_3B (0.40 mmol, 1 M solution in hexanes) and oxygen (introduced via syringe). The reaction was monitored by TLC (30% EtOAc in hexane) and when judged complete (15 min) was quenched with silica gel (2 g), concentrated, washed with hexanes and extracted with ether. The ether extract was concentrated over silica gel and purified by silica gel chromatography (hexane-ethyl acetate) to give the products (**6a-i**).

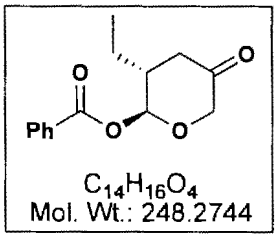
5.4. General Procedure for Tandem Radical Addition

The substrate (0.20 mmol) and AIBN (0.10 mmol) were dissolved in benzene (6 mL). Allyltributyltin (0.80 mmol) and the halide (2.0 mmol) were then added to the mixture and the reaction was refluxed. The reaction was monitored by TLC (30% EtOAc in hexane) and when judged complete (2 h) was quenched with silica gel (2 g), concentrated, washed with hexanes and extracted with ether. The ether extract was concentrated over silica gel and purified by column chromatography (hexane-ethyl acetate) to give the products (**7a-e**).



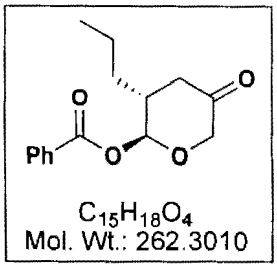
$C_{15}H_{18}O_4$
Mol. Wt.: 262.3010

(2*S*,3*S*)-Tetrahydro-3-isopropyl-5-oxo-2H-pyran-2-yl benzoate (6a): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 1.5, 8.5 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 6.40 (d, *J* = 6.0 Hz, 1H), 4.29 (d, *J* = 17.5 Hz, 1H), 4.03 (d, *J* = 17.5 Hz, 1H), 2.56 (dd, *J* = 5.0, 16.0 Hz, 1H), 2.51 (dd, *J* = 11.0, 16.0 Hz, 1H), 2.18-2.12 (m, 1H), 1.92-1.85 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 209.6, 165.6, 133.8, 130.0, 129.8, 128.8, 94.4, 68.0, 43.8, 37.2, 29.7, 20.2, 19.3. ESI-HRMS: *m/z* calc'd for $C_{15}H_{19}O_4 \cdot Na^+$: 285.1097; found: 285.1096.



$C_{14}H_{16}O_4$
Mol. Wt.: 248.2744

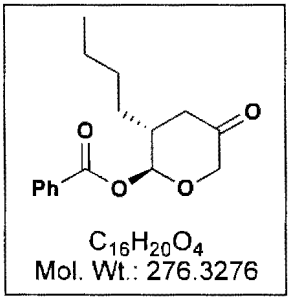
(2*S*,3*R*)-3-Ethyl-tetrahydro-5-oxo-2H-pyran-2-yl benzoate (6b): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.05-8.02 (m, 2H), 7.59-7.55 (m, 1H), 7.46-7.42 (m, 2H), 6.26 (d, *J* = 5.2 Hz, 1H), 4.27 (d, *J* = 17.2 Hz, 1H), 4.02 (d, *J* = 17.2 Hz, 1H), 2.67 (dd, *J* = 4.8, 16.0 Hz, 1H), 2.43 (dd, *J* = 9.4, 16.2 Hz, 1H), 2.27-2.19 (m, 1H), 1.71-1.60 (m, 1H), 1.54-1.43 (m, 1H), 0.97 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 208.3, 165.6, 133.8, 130.0, 129.8, 128.8, 95.3, 68.6, 39.6, 39.5, 25.6, 11.3. ESI-HRMS: *m/z* calc'd for $C_{14}H_{16}O_4 \cdot Na^+$: 271.0941; found: 271.0950.



$C_{15}H_{18}O_4$
Mol. Wt.: 262.3010

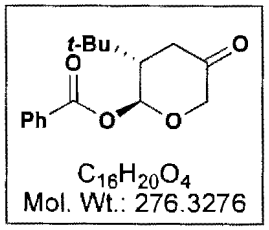
(2*S*,3*R*)-Tetrahydro-5-oxo-3-propyl-2H-pyran-2-yl benzoate (6c): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.09 (dd, *J* = 1.5, 8.5 Hz 2H), 7.63 (tt, *J* = 1.5, 7.5 Hz, 1H), 7.51-7.48 (m, 2H), 6.30 (d, *J* = 5.0 Hz, 1H), 4.32 (d, *J* = 17.5 Hz, 1H), 4.08 (d, *J* = 17.5 Hz, 1H), 2.72 (dd, *J* = 5.0, 16.0 Hz, 1H), 2.48 (dd, *J* = 9.0, 16.0 Hz, 1H), 2.40-2.33 (m, 1H), 1.68-

1.60 (m, 1H), 1.52-1.37 (m, 3H), 0.96 (t, J = 7.0 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 208.3, 165.6, 133.8, 130.0, 129.8, 128.8, 95.5, 68.6, 39.9, 37.8, 34.8, 19.9, 14.2. ESI-HRMS: *m/z* calc'd for $C_{15}H_{18}O_4 \cdot Na^+$: 285.1097; found: 285.1088.



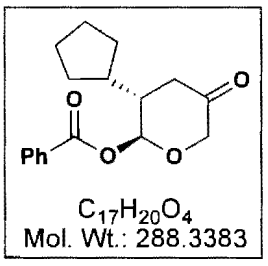
$C_{16}H_{20}O_4$
Mol. Wt.: 276.3276

(2*S*,3*R*)-3-Butyl-tetrahydro-5-oxo-2H-pyran-2-yl benzoate (6d): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.10-8.08 (m, 2H), 7.64-7.61 (m, 1H), 7.49 (t, J = 7.5 Hz, 2H), 6.30 (d, J = 5.0 Hz, 1H), 4.32 (d, J = 17.5 Hz, 1H), 4.08 (d, J = 17.0 Hz, 1H), 2.73 (dd, J = 4.5, 16.0 Hz, 1H), 2.48 (dd, J = 9.5, 16.0 Hz, 1H), 2.38-2.31 (m, 1H), 1.68-1.62 (m, 1H), 1.53-1.46 (m, 1H), 1.44-1.33 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 208.2, 165.6, 133.8, 130.0, 129.8, 128.8, 95.5, 68.6, 39.9, 38.1, 32.3, 28.8, 22.8, 14.1. ESI-HRMS: *m/z* calc'd for $C_{16}H_{20}O_4 \cdot Na^+$: 299.1254; found: 299.1247.

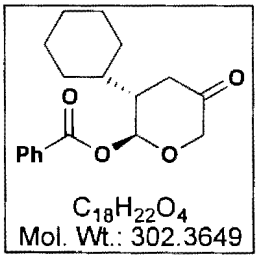


$C_{16}H_{20}O_4$
Mol. Wt.: 276.3276

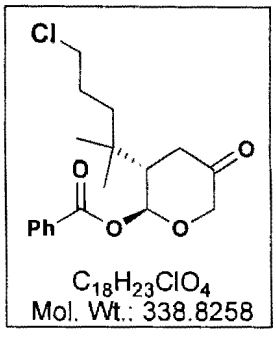
(2*S*,3*S*)-3-Tertbutyl-tetrahydro-5-oxo-2H-pyran-2-yl benzoate (6e): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04-8.01 (m, 2H), 7.56 (tt, J = 1.6, 7.6 Hz, 1H), 7.45-7.41 (m, 2H), 6.41 (d, J = 5.6 Hz, 1H), 4.21 (d, J = 18.0 Hz, 1H), 3.98 (d, J = 17.6 Hz, 1H), 2.50 (d, J = 8.4 Hz, 2H), 2.04 (dt, J = 6.0, 8.8 Hz, 1H), 0.95 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 210.9, 165.4, 133.8, 130.0, 129.8, 128.8, 93.3, 67.3, 47.5, 36.7, 32.4, 27.4. ESI-HRMS: *m/z* calc'd for $C_{16}H_{20}O_4 \cdot Na^+$: 299.1254; found: 299.1241.



(2*S*,3*S*)-3-Cyclopentyl-tetrahydro-5-oxo-2H-pyran-2-yl benzoate (6f): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04-8.02 (m, 2H), 7.56 (tt, *J* = 1.2, 7.0 Hz, 1H), 7.43 (tt, *J* = 1.6, 9.2 Hz, 2H), 6.34 (d, *J* = 4.8 Hz, 1H), 4.25 (d, *J* = 17.6 Hz, 1H), 4.00 (d, *J* = 17.2 Hz, 1H), 2.66 (dd, *J* = 4.8, 16.0 Hz, 1H), 2.50 (dd, J = 10.0, 16.0 Hz, 1H), 2.18-2.11 (m, 1H), 1.93-1.78 (m, 3H), 1.65-1.48 (m, 4H), 1.23-1.09 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 208.9, 165.5, 133.8, 130.0, 129.8, 128.8, 95.1, 68.3, 43.3, 43.1, 39.3, 30.6, 30.56, 25.3, 24.8. ESI-HRMS: *m/z* calc'd for $C_{17}H_{20}O_4$•Na^+: 311.1254; found: 311.1268.

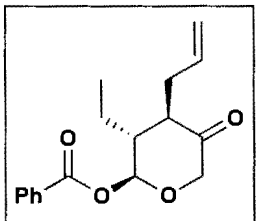


(2*S*,3*S*)-3-Cyclohexyl-tetrahydro-5-oxo-2*H*-pyran-2-yl benzoate (6g): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.08 (dd, *J* = 1.5, 8.5 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 2H), 6.42 (d, *J* = 5.5 Hz, 1H), 4.29 (d, *J* = 18.0 Hz, 1H), 4.04 (d, *J* = 17.5 Hz, 1H), 2.60-2.50 (m, 2H), 2.19-2.13 (m, 1H), 1.83-1.66 (m, 5H), 1.55-1.49 (m, 1H), 1.29-1.09 (m, 4H), 1.04-0.96 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 209.8, 165.6, 133.8, 130.0, 129.9, 128.8, 94.3, 68.0, 43.1, 39.7, 37.4, 30.5, 29.8, 26.5, 26.43, 26.4. ESI-HRMS: *m/z* calc'd for $C_{18}H_{22}O_4$•Na^+: 325.1410; found: 325.1425.



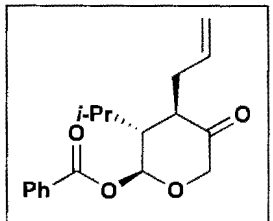
(2*S*,3*S*)-3-(5-Chloro-2-methylpentan-2-yl)-tetrahydro-5-oxo-2H-pyran-2-yl benzoate (6i): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.04-8.01 (m, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.46 (d, *J* = 5.6 Hz, 1H), 4.23 (d, *J* = 18.0 Hz, 1H), 4.00 (d, *J* = 18.0 Hz, 1H), 3.39 (t, J = 6.8 Hz, 2H), 2.57-2.44 (m, 2H), 2.18-2.12 (m,

1H), 1.78-1.65 (m, 2H), 1.41-1.37 (m, 2H), 0.96 (s, 6 H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 209.6, 165.3, 133.9, 130.0, 129.6, 128.8, 93.0, 67.3, 45.7, 45.4, 37.5, 36.3, 34.7, 27.3, 24.6, 24.4. ESI-HRMS: *m/z* calc'd for $C_{18}H_{23}ClO_4 \cdot Na^+$: 361.1177; found: 361.1174.



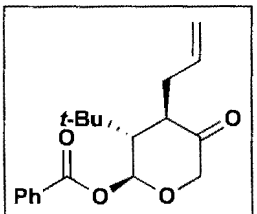
$C_{17}H_{20}O_4$
Mol. Wt.: 288.3383

(2*S*,3*R*,4*R*)-4-Allyl-3-ethyl-tetrahydro-5-oxo-2*H*-pyran-2-yl benzoate (7a): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 4.5, 7.5 Hz, 2H), 7.62 (t, J = 1.2 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 6.38 (d, *J* = 5.0 Hz, 1H), 5.86-5.78 (m, 1H), 5.15-5.09 (m, 2H), 4.32 (d, *J* = 17.5 Hz, 1H), 4.12 (d, *J* = 17.5 Hz, 1H), 2.65-2.57 (m, 1H), 2.48-2.43 (m, 1H), 2.14-2.08 (m, 1H), 1.78-1.63 (m, 3H), 1.03 (t, J = 7.5 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 210.0, 165.5, 135.0, 133.8, 130.0, 129.7, 128.9, 117.9, 95.8, 68.2, 47.1, 42.1, 30.8, 23.6, 10.3. ESI-HRMS: *m/z* calc'd for $C_{17}H_{20}O_4 \cdot Na^+$: 311.1254; found: 311.1274.

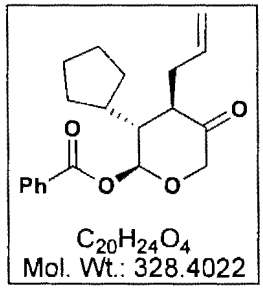


$C_{18}H_{22}O_4$
Mol. Wt.: 302.3649

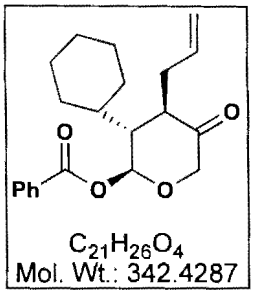
(2*S*,3*R*,4*R*)-4-Allyl-tetrahydro-3-isopropyl-5-oxo-2H-pyran-2-yl benzoate (7b): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.07-8.05 (m, 2H), 7.64-7.60 (m, 1H), 7.51-7.47 (m, 2H), 6.45 (d, *J* = 4.0 Hz, 1H), 5.88-5.80 (m, 1H), 5.15-5.08 (m, 2H), 4.30 (d, *J* = 17.5 Hz, 1H), 4.11 (d, *J* = 17.5 Hz, 1H), 2.70-2.60 (m, 2H), 2.45-2.39 (m, 1H), 2.13-2.07 (m, 2H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 210.7, 165.2, 135.1, 133.8, 130.0, 129.8, 128.8, 117.9, 93.3, 68.0, 46.1, 46.0, 30.8, 27.5, 20.7, 16.8. ESI-HRMS: *m/z* calc'd for $C_{18}H_{22}O_4 \cdot Na^+$: 325.1410; found: 325.1415.



(2*S*,3*S*,4*R*)-3-*Tert*-Butyl-4-allyl-tetrahydro-5-oxo-2*H*-pyran-2-yl benzoate (7c): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.04-8.03 (m, 2H), 7.64-7.61 (m, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 2.0 Hz, 1H), 5.81-5.73 (m, 1H), 5.06-5.02 (m, 2H), 4.31 (d, *J* = 17.5 Hz, 1H), 4.15 (d, *J* = 17.5 Hz, 1H), 2.71-2.58 (m, 3H), 2.06-2.05 (m, 1H), 1.07 (s, 9H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 209.9, 164.9, 135.4, 133.8, 130.0, 129.7, 128.9, 118.4, 93.9, 68.3, 51.0, 46.5, 38.1, 33.7, 28.0. ESI-HRMS: *m/z* calc'd for $C_{19}H_{24}O_4$•Na^+: 339.1567; found: 339.1571.

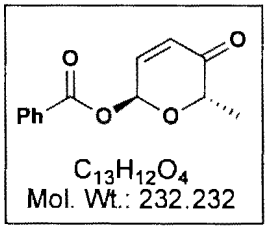


(2*S*,3*R*,4*R*)-4-Allyl-3-cyclopentyl-tetrahydro-5-oxo-2*H*-pyran-2-yl benzoate (7d): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.04 (dd, *J* = 1.5, 8.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 6.42 (d, *J* = 3.0 Hz, 1H), 5.85-5.75 (m, 1H), 5.11-5.07 (m, 2H), 4.32 (d, *J* = 17.5 Hz, 1H), 4.14 (d, *J* = 17.5 Hz, 1H), 2.66-2.60 (m, 2H), 2.57-2.51 (m, 1H), 2.22-2.14 (m, 1H), 1.94-1.88 (m, 1H), 1.83-1.54 (m, 6H), 1.47-1.41 (m, 1H), 1.25-1.19 (m, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 209.9, 165.2, 135.4, 133.8, 130.1, 130.0, 128.8, 118.0, 94.5, 68.1, 48.2, 45.0, 41.5, 33.3, 30.6, 28.7, 25.4, 25.2. ESI-HRMS: *m/z* calc'd for $C_{20}H_{24}O_4$•Na^+: 351.1567; found: 351.1578.

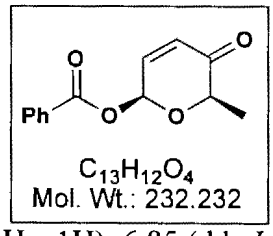


(2*S*,3*R*,4*R*)-4-Allyl-3-cyclohexyl-tetrahydro-5-oxo-2*H*-pyran-2-yl benzoate (7e): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 6.47 (d, *J* = 4.5 Hz, 1H), 5.88-5.79 (m, 1H), 5.15-5.08 (m, 2H), 4.27 (d, *J* =

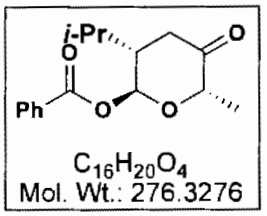
17.5 Hz, 1H), 4.10 (d, J = 17.5 Hz, 1H), 2.74-2.70 (m, 1H), 2.62-2.57 (m, 1H), 2.46-2.41 (m, 1H), 2.08-2.05 (m, 1H), 1.77-1.69 (m, 5H), 1.32-1.08 (m, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 210.8, 165.3, 135.2, 133.8, 130.0, 129.8, 128.8, 117.8, 93.7, 67.9, 46.1, 45.5, 38.1, 31.1, 27.3, 27.1, 26.6, 26.5. ESI-HRMS: *m/z* calc'd for $C_{21}H_{26}O_4$•Na^+: 365.1723; found: 365.1714.



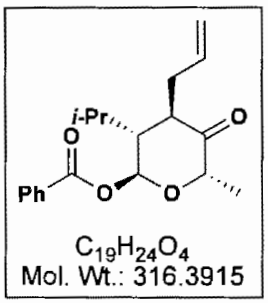
(2*S*,6*S*)-5,6-Dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl benzoate (8): ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.03 (dd, J = 3.6, 10.2 Hz, 1H), 6.77 (d, J = 3.9 Hz, 1H), 6.30 (d, J = 10.5 Hz, 1H), 4.73 (q, J = 6.9 Hz, 1H), 1.45 (d, J = 6.9 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.2, 165.3, 141.9, 133.9, 130.4, 130.1, 128.8, 128.7, 87.8, 72.7, 15.6. ESI-HRMS: *m/z* calc'd for $C_{13}H_{12}O_4$•Na^+: 255.0628; found: 255.0620.



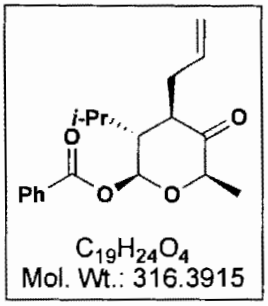
(2*S*,6*R*)-5,6-Dihydro-6-methyl-5-oxo-2H-pyran-2-yl benzoate (9): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, J = 7.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.04 (dd, J = 2.5, 10.0 Hz, 1H), 6.85 (dd, J = 1.0, 2.5 Hz, 1H), 6.32 (dd, J = 1.0, 10.5 Hz, 1H), 4.49 (q, J = 7.0 Hz, 1H), 1.59 (d, J = 7.5 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 196.3, 165.2, 143.5, 134.0, 130.2, 129.3, 128.9, 128.5, 88.5, 76.1, 19.1. ESI-HRMS: *m/z* calc'd for $C_{13}H_{12}O_4$•Na^+: 255.0628; found: 255.0622.



(2*S*,3*S*,6*S*)-Tetrahydro-3-isopropyl-6-methyl-5-oxo-2*H*-pyran-2-yl benzoate (10): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 7.0 Hz, 2H), 7.64-7.61 (m, 1H), 7.50 (t, *J* = 7.50 Hz, 2H), 6.42 (d, *J* = 5.5 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 1H), 2.55-2.52 (m, 2H), 2.22-2.17 (m, 1H), 1.91-1.85 (m, 1H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 211.8, 165.6, 133.7, 130.04, 130.01, 128.8, 94.7, 73.0, 44.3, 36.7, 29.8, 20.3, 19.3, 15.6. ESI-HRMS: *m/z* calc'd for $C_{16}H_{20}O_4$•Na^+: 299.1254; found: 299.1240.



(2*S*,3*R*,4*R*,6*S*)-4-Allyl-tetrahydro-3-isopropyl-6-methyl-5-oxo-2*H*-pyran-2-yl benzoate (11): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.0 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 6.45 (d, *J* = 4.0 Hz, 1H), 5.88-5.79 (m, 1 H), 5.14-5.08 (m, 2H), 4.35 (q, *J* = 7.0 Hz, 1H), 2.71-2.67 (m, 1H), 2.63-2.58 (m, 1H), 2.43-2.37 (m, 1 H), 2.13-2.07 (m, 2H), 1.35 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.985 (d, *J* = 7.0 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 213.1, 165.2, 135.2, 133.7, 130.0, 129.9, 128.8, 117.7, 93.1, 73.0, 46.6, 44.7, 30.7, 27.5, 20.8, 16.7, 16.6. ESI-HRMS: *m/z* calcd for $C_{19}H_{24}O_4$•Na^+: 339.1567; found: 339.1569.



(2*S*,3*R*,4*R*,6*R*)-4-Allyl-tetrahydro-3-isopropyl-6-methyl-5-oxo-2H-pyran-2-yl benzoate (12): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99-7.97 (m, 2 H), 7.57 (tt, J = 1.6, 7.6 Hz, 1H), 7.46-7.42 (m, 2H), 6.32 (d, J = 4.4 Hz, 1H), 5.82-5.70 (m, 1H), 5.11-5.02 (m, 2H), 4.25

(q, J = 6.8 Hz, 1H), 2.57-2.52 (m, 1H), 2.52-2.45 (m, 2H), 2.13-2.06 (m, 1 H), 1.99-1.91 (m, 1 H), 1.36 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 211.3, 165.2, 135.5, 133.7, 130.0, 129.8, 128.8, 117.9, 94.0, 76.5, 48.6, 47.1, 34.4, 29.4, 20.6, 18.6, 18.4. ESI-HRMS: m/z calc'd for $C_{19}H_{24}O_4 \cdot Na^+$: 339.1567; found: 339.1579.

6. REFERENCES

(1) (a) *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**; Vols. 1 and 2. (b) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (c) Zimmerman, J.; Sibi, M. P. *Topics in Current Chemistry* **2006**, *263* (Radicals in Synthesis 1), 107-162.

(2) For a recent review on tandem radical reactions see: Albert, M.; Fensterbank, L.; Lacote, E.; Malacria, M. *Topics in Current Chemistry* **2006**, *264* (Radicals in Synthesis II), 1.

(3) *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; Smith, M. B.; March, J.; Wiley-Interscience, **2007**.

(4) Enantioselective Free Radical Reactions. Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163-171.

(5) North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* **2008**, *108(12)*, 5146-5226.

(6) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339-4342.

(7) Bashiardes, G.; Cano, C.; Mauzé, B. *Synlett* **2005**, *4*, 587-590.

(8) Delgado, A.; Castedo, L; Mascareñas, J. *Org. Lett.* **2002**, *4*, 3091-3094.

(9) Sugawara, K.; Imanishi, Y.; Hashiyama, T. *Heterocycles* **2007**, *71*, 597-607.

(10) Sibi, M. P.; Zimmerman, J. *J. Am. Chem. Soc.* **2006**, *128*, 13346.

(11) van der Deen, H.; Kellogg, R. M.; Feringa, B. L. *Org. Lett.* **2000**, *2*, 1593.

(12) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2005**, *44*, 5306-5310.

(13) For work from Fraser-Reid and co-workers, see: (a) Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 1065. (b) Fraser-Reid, B.; Holder, N. L.; Hicks, D. R.; Walker, D. L.

Can. J. Chem. **1977**, *55*, 3978. (c) Benko, Z.; Fraser-Reid, B.; Mariano, P. S.; Beckwith, A. L. J. *J. Org. Chem.* **1988**, *53*, 2066. For selected examples on the use of β-pyranones is synthesis from other groups, see: (d) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *121*, 3428. (e) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 392. (f) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 5149. (g) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714. (h) van den Heuvel, M.; Cuiper, A. D.; van der Deen, H.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron Lett.* **1997**, 38, 1655. (i) Furstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5361. (j) Krishnan, K. S.; Smitha, M.; Suresh, E.; Radhakrishnan, K. V. *Tetrahedron* **2006**, *62*, 12345. (k) Panfil, I.; Chmielewski, M. *Tetrahedron* **1985**, *41*, 4713. (l) Giese, B; Witzel, T. *Tetrahedron Lett.* **1987**, *28*, 2571.

(14) Compound **5** was prepared in racemic form using a literature procedure. Caddick, S.; Khan, S.; Frost, L. M.; Cheung, S.; Pairaudeau, G. *Tetrahedron* **2000**, *56*, 8953.

(15) All new compounds showed analytical and spectral characteristics consistent with their structure. An experimental procedure and spectral data for select products are provided.

(16) For recent reviews see: Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072. (b) Parsons, A. F. *Chemistry in Britain* **2002**, *38*, 42. Alternatives to tin hydrides: Selected examples: (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188. (b) Leca, D.; Fensterbank, L.; Lacote, E.; Malacria, M. *Chem. Soc. Rev.* **2005**, *34*, 858. (c) Studer, A.; Amrein, S. *Synthesis* **2002**, 835. (d) Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans 1* **1999**, 3071. (e) Studer, A.; Amrein, S.;

Schleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 5726. (f) Cho, D. H.; Jang, D. O. *Bull. Kor. Chem. Soc.* **2003**, *24*, 15. (g) Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003**, *5*, 2971.

(17) For an example on the use of functionalized radicals in conjugate addition see: Sibi, M. P.; Guerrero, M. *Synthesis* **2005**, 1528.

(18) For related examples of stereochemical control with acyloxy-β-pyrones see: Bashiardes, G.; Cano, C.; Mauze, B. *Synlett* **2005**, 587. Sugawara, K.; Imanishi, Y.; Hashiyama, T. *Heterocycles* **2007**, *71*, 597.

(19) For selected review articles see: (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Curran, D. P. *Aldrichimica Acta* **2000**, *33*, 104-110. For intermolecular radical addition and allyl stannane trapping see: (d) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472. (e) Sibi, M. P.; Aasmul, M.; Hasegawa, H.; Subramanian, T. *Org. Lett.* **2003**, *5*, 2883. (f) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (g) Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190.

(20) (a) Trost, B.M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Trost, B.M.; Silcoff, E.; Ito, H. *Org. Lett.* **2001**, *3*, 2497. (c) Trost, B.M.; Ito, H.; Silcoff, E. *J. Am. Chem. Soc.* **2001**, *123*, 3367-3368.

(21) Compounds **8** and **10** were prepared following literature procedures. (a) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921. (b) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339. (c) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485. (d) Yonghong, G.; Fangning, Z.; Xinfu, P. *J. Chem. Research (S)* **1999**, 488.