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Pyrones to Pyrans: Enantioselective Radical Additions to Acyloxy Pyrones

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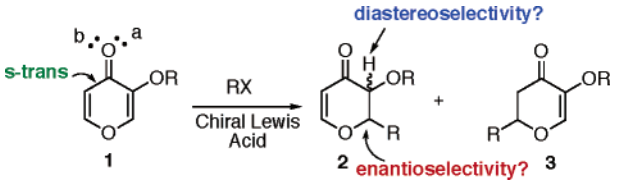
Enantioselective Lewis acid-mediated free radical reactions continue to attract interest.[1] Detachable achiral auxiliaries play a pivotal role in most of the enantioselective radical chemistry reported in the literature to date.[2] These auxiliaries provide an extra donor atom that enables Lewis acid chelation. Another significant structural feature is that, in general, α,β-unsaturated carbonyl compounds that have undergone enantioselective radical additions have reacted via *s-cis* conformers.

We have been interested in developing enantioselective radical additions onto substrates that will not require an achiral template[3] and react via an *s-trans* geometry. Stereocontrolled functionalization of readily available hydroxypyrones[4] is important since they provide access to pyrans, a structural unit present in compounds with significant biological activity. For example, marine natural products apicularen, phorboxazole, and spongistatin all contain pyran rings with various substitution patterns.[5] Recently, Hoveyda has demonstrated enantioselective conjugate additions to chromones.[4e] This communication addresses several challenging issues for Lewis acid-catalyzed conjugate radical additions to hydroxypyrones (Scheme 1): (1) How reactive are they toward conjugate radical additions?

Scheme 1

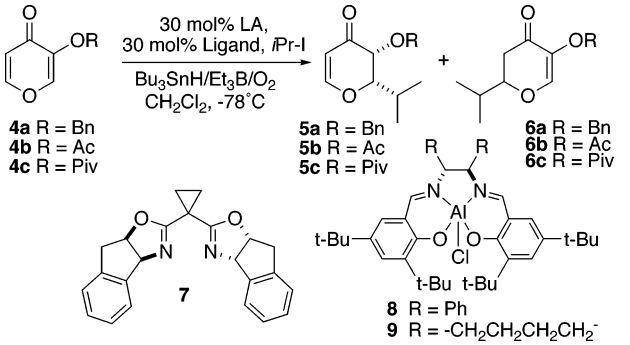


(2) What is the C-2 versus C-6 site selectivity (**2** vs **3**) and will electronic or steric factors act as control elements? (3) What will be the optimal chiral Lewis acid system for stereoselectivity?

Our initial studies began using pyromeconic acid derivatives **4** (Table 1). It was found early on that the enol hydroxyl group needed to be functionalized with an electron-withdrawing group in order to achieve good reactivity (entry 1). No reaction took place (<5%) for substrates **4a**−**c** without a Lewis acid. More interesting was the effect of the Lewis acid in these reactions. Initial racemic reactions showed that magnesium and scandium salts yielded a mixture of isomers (entries 2−5).[6] Traditional bisoxazoline ligands were screened with magnesium and scandium Lewis acids, but only low to moderate enantioselectivities were achieved (entries 6−8). Promising results were obtained using chiral aluminum salen derived catalysts (entries 9−11).[7] The commercially available **9** gave **5c** in excellent yield and diastereoselectivity with the major isomer possessing *syn* stereochemistry.[8] The C-2 isomer was preferentially formed (≥10:1) in the Al-salen catalyzed reactions with moderate enantioselectivities (entry 11).[9]

We next investigated the addition of various radicals to substrate **4c** under the optimized conditions (Table 2). Addition of secondary radicals gave good yields, excellent diastereoselectivity, and moderate enantioselectivity for the major C-2 product (**5**) (entries 1−3). The minor C-6 products (**6**) were analyzed in two cases and found to be much less selective with enantiomeric excesses <40% (entries 2 and 5). In contrast, reactions with bulky tertiary radicals yielded the major C-2 adducts with excellent diastereo- and enantioselectivities (>90%) (entries 4−6). Another important point of note is that lowering the catalytic loading to 30 mol % showed no erosion of enantioselectivity (compare entry 4 with 5).

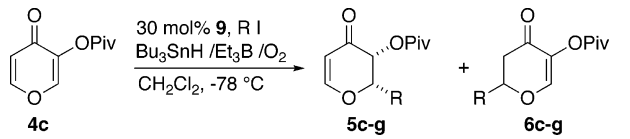
Table 1. Lewis Acid Screening with Pyromeconic Acid Derivatives[a]



entry	R	Lewis acid	ligand	yield (%)[b]	dr (**5**)[c] syn/anti	**5**:**6**	ee of **5**[d] (%)
1	Bn	$Sc(OTf)_3$		trace			
2	Ac	$Mg(NTf_2)_2$		22	95:5	3.3:1	
3	Ac	$Sc(OTf)_3$		78	86:14	1.9:1	
4	Piv	$Mg(NTf_2)_2$		60	99:1	5.3:1	
5	Piv	$Sc(OTf)_3$		76	91:9	2.6:1	
6	Piv	$Mg(NTf_2)_2$	**7**	40	91:9	1.1:1	62
7	Piv	$Mg(ClO_4)_2$	**7**	33	99:1	4.0:1	16
8	Piv	$Sc(OTf)_3$	**7**	80	88:12	4.5:1	3
9	Piv	**8**	**8**	71	99:1	13:1	30
10	Ac	**9**	**9**	60	99:1	4.0:1	49
11	Piv	**9**	**9**	80	99:1	10:1	70

[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Diastereomeric ratio and site selectivity (**5**:**6**) were determined by ^{1}H NMR (400 MHz). [d] Determined by chiral HPLC.

Table 2. Radical Additions to Pyromeconic Acid Pivalate



entry	R	**5**:**6**	yield (%)[a]	dr[b]	ee (%) of **5** (**6**)[c]
1	*i*-propyl **5c**	91:9	80	99:1	70
2	*c*-pentyl **5d**	93:7	74	99:1	76 (36)
3	*c*-hexyl **5e**	92:8	55	99:1	70
4	*tert*-butyl **5f**	90:10	76	99:1	92
5[d]	*tert*-butyl **5f**	93:7	60	99:1	92
6	$(CH_3)_2C(CH_2)_3Cl$ **5g**	92:8	45	99:1	95 (39)

[a] Isolated yield. [b] Diastereomeric ratio and site selectivity (**5**:**6**) were determined by ^{1}H NMR (400 MHz). [c] Determined by chiral HPLC. [d] 100 mol % of **9**.

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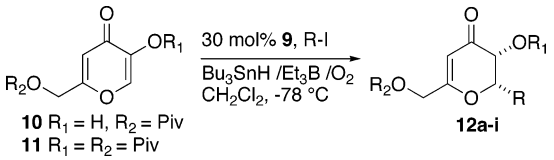
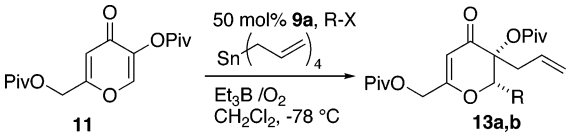
Table 3. Radical Addition to Kojic Acid Derivatives



entry	R	R_1	R_2	yield (%)[a]	dr[b]	ee (%)[c]
1	*i*-propyl **12a**	H	Piv	85	99:1	74
2	*c*-pentyl **12b**	H	Piv	67	99:1	76
3	*tert*-butyl **12c**	H	Piv	91	99:1	92
4	$(CH_3)_2C(CH_2)_3Cl$ **12d**	H	Piv	35	99:1	92
5	*i*-propyl **12e**	Piv	Piv	92	99:1	72
6	*c*-pentyl **12f**	Piv	Piv	74	99:1	76
7	*tert*-butyl **12g**	Piv	Piv	96	99:1	93
8[d]	*tert*-butyl **12g**	Piv	Piv	98	99:1	92
9	$(CH_3)_2C(CH_2)_3Cl$ **12h**	Piv	Piv	77	99:1	90

[a] Isolated yield. [b] Diastereomeric ratio was determined by ^{1}H NMR (400 MHz). [c] Determined by chiral HPLC. [d] 10 mol % of **9**.

Table 4. Quaternary Center Formation



entry	R	yield (%)[a]	dr[b]	ee (%)[c]
1	*i*-propyl **13a**	77	99:1	70
2	*c*-pentyl **13b**	90	99:1	69

[a] Isolated yield. [b] Diastereomeric ratio was determined by ^{1}H NMR (400 MHz). [c] Determined by chiral HPLC.

We next focused our attention on kojic acid, which is an inexpensive, commercially available starting pyrone. In this case, the C-6 position is functionalized with a hydroxymethyl moiety, which could provide a handle for further synthetic manipulations but also deactivates the C-6 position toward conjugate radical addition. Kojic acid is relatively insoluble in nonpolar solvents and thus was converted to **10** and **11** to increase solubility. Again, no reaction took place without Lewis acid for substrates **10** and **11** (Table 3). As was expected, radical addition occurs exclusively at the less substituted C-2 position. Addition of secondary radicals to **10** proceeded smoothly to yield **12a**,**b** in good yields, excellent diastereoselectivity, and moderate enantiomeric excesses (entries 1 and 2). More bulky tertiary radicals again proved to give enantioselectivities >90% (entries 3 and 4). We also examined the bispivalyl substrate **11**. Again, excellent yields and diastereoselectivities were obtained when secondary nucleophilic radicals were added, while tertiary radicals gave excellent enantiomeric excesses (entries 5−9).

We were also interested in forming two carbon−carbon bonds via conjugate addition of a nucleophilic radical followed by trapping of the electrophilic α-radical with an allyltin reagent.[10] This process establishes two new adjacent stereocenters with one being a quaternary carbon. Initial attempts using catalyst **9** were unsuccessful, but by utilizing a more reactive chiral Lewis acid (Cl exchanged to NTf_2, **9a**),[11] we were able to obtain good to excellent yields of the addition/trapping products **13a**,**b** (Table 4).[12] The enantioselectivities are modest and similar to what was observed under reductive tin hydride conditions for isopropyl radical addition (Table 3).

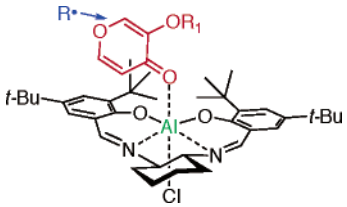


Figure 1. Stereochemical model.

The absolute stereochemistry for product **5e** was determined by conversion to a known compound.[13] Figure 1 shows a proposed chiral Lewis acid substrate model which accounts for the observed stereochemistry in pyromeconic acid radical conjugate additions. We propose that the substrate binds through the ketone carbonyl to the Al-salen catalyst.[14] The electron-withdrawing acyloxy substituent may facilitate addition at C-2, even though C-6 is more sterically accessible. Captodative effects may also impact regioselectivity. The bulky −OR group orients away from the axial hydrogen atoms on the cyclohexane ring, leaving the *si* face more open for nucleophilic radical addition. Subsequent hydrogen transfer to the α-carbon is apparently controlled not by the chiral ligand but by the newly formed *β*-stereocenter, with the radical R group shielding the top face.

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Supporting Information Available: Characterization data for compounds **4**−**13** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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