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1,3-Diastereocontrol in acyclic radical allylations

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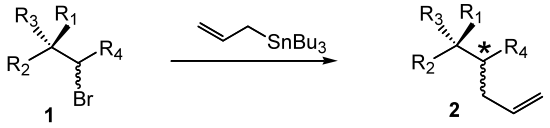
Abstract—The radical allylation of an acyclic α-hydroxyketone with allyltributyltin under chelation-controlled conditions is reported. Several reaction conditions were explored, including radical initiators, solvents, and temperatures to improve the yield and the diastereomeric ratio. Some Lewis acids, like magnesium bromide etherate and zinc chloride, gave superior diastereomeric ratios (up to 100:1) and good yields.

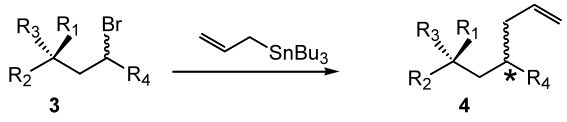
Adequate methods for diastereoselective reactions in a wide variety of acyclic systems have been examined.[1] Similar concepts can now be applied to radical reactions, where high levels of diastereoselectivity can be realized.[2] It is also clear that excellent acyclic diastereocontrol in free radical reactions is possible by the use of chelation with Lewis acids, following from seminal studies by Guindon and co-workers.[3]

The most common form of diastereocontrol emanates from a single chiral center exerting its influence on an adjacent carbon-centered radical. As shown in Scheme 1A, the more studied transformation of **1**→**2** involves a halogen-substituted carbon leading to 1,2-diastereocontrol next to the chiral center. In radical-mediated asymmetric synthesis, close proximity is generally the key to good stereochemical control. The second, and more poorly understood variation of this process, involves 1,3-diastereocontrol, shown in Scheme 1B as **3**→**4**. This more difficult situation does not have the close proximity as before; now the new carbon center is further away and less able to be directed by the R_1, R_2 and R_3 substituents.

A. 1,2-Diastereocontrol in a Radical Allyation Reaction:

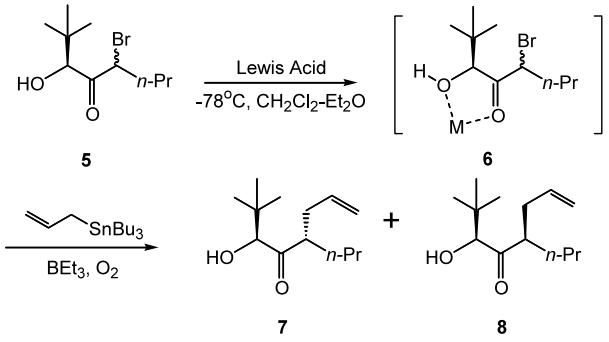


B. 1,3-Distereocontrol in a Radical Allylation Reaction:



Scheme 1.

One of our goals was to design radical precursors that would employ Lewis acids in chelation effects of α-hydroxyketones. This work seeks to more clearly define the effects of asymmetric 1,3-diastereocontrol over a more demanding two-carbon span separated by a ketone, as shown in the transformation in Scheme 2.[4] For the best chances for success, a large steric bias, such as a *t*-butyl group, would block one face of a metal-chelated or hydrogen-bonded ring, as shown in **6** in Scheme 2. Degrees of freedom and rotation about the two-carbon span were to be disfavored by placing a ketone between the two interacting groups. The ketone



Scheme 2.

Keywords: free radical; diastereoselective; allyltributyltin.

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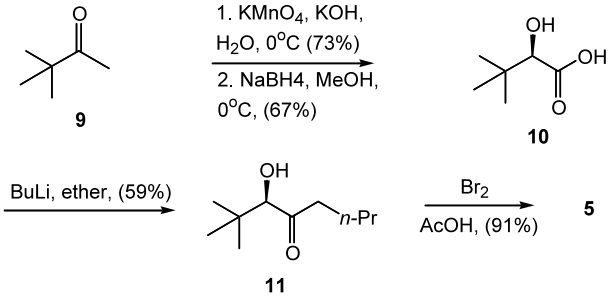
would also play an important role in the chelation and at the same time rigidify the substrate. Note that the carbon bearing the bromide will eventually become a carbon centered radical that, unlike other chelation-based five-membered asymmetric methodology, is outside of the metal-mediated ring in **6** and it is free to rotate.[5] In these studies we hoped that diastereoselective induction would occur in a completely predictable fashion so that one product, **7**, would be favored from conformation **6**. In addition, we also predicted that without Lewis acids, hydrogen bonding might favor the same products expected with Lewis acids but only experimental scrutiny would bear this out.

Preparation of racemic bromide **5** began (Scheme 3) by conversion of commercially available pinacolone **9** to the α-hydroxyketone **10** by permanganate oxidation to the corresponding acid followed by reduction with sodium borohydride using a modification of a literature procedure.[6,7] Ketone **11** was next obtained by treatment with excess *n*-BuLi, followed by Br_2 in acetic acid to give **5**. We reacted α-hydroxyketone **5** with allyltributyltin under various free radical conditions of initiators, temperatures, Lewis acids and solvents. We are pleased to report excellent results with diastereoselectivities up to 100:1. Of the two products, **7** was indeed favored over **8** and in some cases by a wide margin, as shown in Table 1.

A brief examination of Table 1 shows several trends. In the absence of Lewis acids, lowering the temperature of the reaction surprisingly only slightly increased diastereoselectivity. The reaction at −78°C gave a 5:1 ratio versus 3:1 at higher temperatures. In these reactions, hydrogen bonding in **5** between the alcohol and the ketone forms a five-membered ring conformation but still favors **7** over **8**. It is interesting to note that Et_3B in the absence of Lewis acids resulted in substantial decomposition of the starting material **5** affording only modest yields at best. The low yields in the absence of Lewis acids might result from the enoxyl radical undergoing homolytic substitution at boron to make a boron enolate which may react further with the ketone.



Scheme 3.

When a Lewis acid was employed, diastereomeric ratios increased substantially. The initiator system of triethylborane and O_2 was used in these reactions at low (−78°C) temperatures. We predicted that the steric bulk provided by the *t*-butyl group would enhance our selectivities to some degree (vide infra). Lewis acids $ZnCl_2$ and $MgBr_2{\cdot}OEt_2$ proved to be superior Lewis acids producing high 100:1 diastereomeric ratios in good yields.

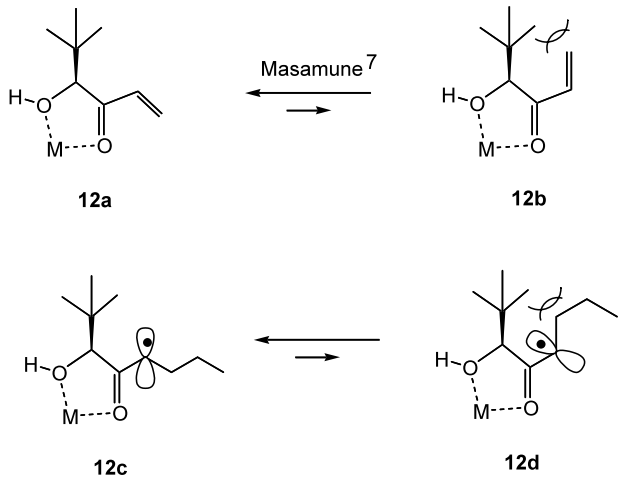
Lewis acid complexation appears to accelerate many examples of radical reactions. This occurs by weakening the C–Br bond or increasing the electrophilic nature of the radical. Porter and co-workers have found that a C–Br bond next to a carbonyl, as in **6**, is weakened by chelation with a Lewis acid.[5a] Clark and Wayner[8] have also studied this bond-weakening effect suggesting that the carbonyl destabilizes the C–Br bond dipole in the parent compound, stabilizing the radical with respect to the parent. Thus, a chelated carbonyl with a carbon bearing bromine (CHBr) has a dramatic effect on the normal C–Br dipole and weakens the C–Br bond.

There were several lines of evidence that confirmed the major stereochemistry in **7**. First, an analogy to a very similar series of Diels–Alder reactions performed by Masamune and co-workers in 1983 produced products *trans* to the *t*-butyl group by attacking the back face of alkene **12a** (Scheme 4).[7] In the related sp^2 to sp^3 radical reaction of **12c**, the rotation in the *n*-butyl side chain is also limited by the bulky *t*-butyl group. Because of this, **12c** is favored over **12d** in the equilibrium for the two radical species. This leads to the *trans* product **7** predominating over the *cis* product **8**.

A second line of evidence used to determine the stereochemistry of **7** was based on energy minimizations and

Table 1. Results of radical allylations

Radical initiator	Temp. (°C)	Solvent system	Lewis acid (equiv.)	Ratio of **7**:**8**	Yield (%)
AIBN	80	Benzene	None	4:1	90
Et_3B, O_2	25	CH_2Cl_2	None	3:1	40
Et_3B, O_2	0	CH_2Cl_2	None	3:1	23
Et_3B, O_2	0	CH_2Cl_2/THF	$ZnCl_2$ (2)	6:1	75
Et_3B, O_2	0	CH_2Cl_2/Et_2O	$MgBr_2{\cdot}OEt_2$ (2)	6:1	91
Et_3B, O_2	0	CH_2Cl_2	$Yb(CF_3SO_3)_3$ (2)	5:1	66
Et_3B, O_2	−78	CH_2Cl_2	None	5:1	33
Et_3B, O_2	−78	CH_2Cl_2/THF	$ZnCl_2$ (2)	100:1	76
Et_3B, O_2	−78	CH_2Cl_2/Et_2O	$MgBr_2{\cdot}OEt$ (2)	100:1	81
Et_3B, O_2	−78	CH_2Cl_2	$Yb(CF_3SO_3)_3$ (2)	9:1	48



Scheme 4.

molecular dynamics (MD) simulations.[9] Since it was not possible to separate products **7** and **8**, the calculations were used in conjunction to NMR studies to determine stereochemistry by long distance proton–proton coupling constants for the methine hydrogens on each side of the ketone.[10] This third line of stereochemical evidence indicates a small, yet clearly observable, long distance H–H coupling in the minor product **8** because these hydrogens are nearly coplanar (4.62 ppm, d of d, $J=7.2$, 1.5 Hz). Major product **7**[11] gave no long distance H–H coupling (3.93 ppm, d, $J=7.2$ Hz).

In summary, the 1,3-diastereocontrolled radical allylation of acyclic α-hydroxyketones using allyltributyltin at low-temperature conditions (−78°C) is reported. A number of reaction conditions were studied to improve the yield and the diastereomeric ratio, that ranged from 3:1 to 100:1.

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9. Modeling experiments were carried out in the Brain Institute Computer Center, University of Florida, Gainesville, on a Silicon Graphics Indigo XZ4000 workstation using Discover as implemented in Insight II from Molecular Simulations, Inc., 1998. All energy minimizations and MD simulations were carried out using CVFF force field (MSI, Inc., 1998) in vacuum. Prior to MD, all structures were optimized using conjugated gradient algorithm to final gradients better than 0.005 kcal/mol A. Equilibration for 10 ps followed energy minimization. Structures were subject to a series of MD simulations for 10,000 steps, $T=300$ K, time step 1.00 fs, saving conformations every ten steps. Energetically accessible conformations were generated using MD simulations for the two possible products of the reaction: compounds **7** and **8**. A total of 1011 structures were analyzed for each molecule to determine lowest energy and average conformations. Selected conformers were analyzed. We determined that for **8**, both minimum energy and average structures show a conformation in which the two hydrogens in the chiral centers are closer to be in a plane than the equivalent hydrogens in product **7**. Starting with conformations in which the hydroxyl and the carbonyl group are closer to a hydrogen-bond five-ring conformation, further MD simulations were performed for each isomer. Lowest energy structures were selected and dihedral angles were measured. Despite the differences in the values of the dihedrals, the same tendency is observed; for isomer **8** the preferred conformation places the two

hydrogens in the chiral centers closer to the same plane compared to the preferred conformation of isomer **7**.

10. These findings suggest that a long distance H–H coupling (H1 and H6 in the chiral centers) would be observed for product **8** rather than product **7** because the hydrogens are closer to coplanarity. Signals in the NMR spectra indicate that this long distance coupling is taking place, i.e. signal at approx. 4.6 Hz corresponding to H1, in the minor product **8**, shows a coupling (doublets) constant of 1.5 Hz. This signal is equivalent to the signal at ca. 3.9 Hz in the major product **7** with no coupling observed. This observation suggests that a long distance H–H coupling occurs in minor product **8**. Since coplanarity is a requirement for this coupling, the minor product is assigned as compound **8**, while the major product is assigned as compound **7**.
11. **2-Hydroxy-3,3-dimethylbutanoic acid (10)**: To a stirred solution of 93.0 g (0.588 mol) of $KMnO_4$ and 30.0 g (0.75 mol) of NaOH in 720 mL of H_2O at 0°C was added a slurry of 30.0 g (37.5 mL, 0.300 mol) of 3,3-dimethyl-2-butanone (pinacolone) in 400 mL of H_2O over a 40 min period. After the addition, the mixture was stirred for 1 h at 0°C and for 6 h at room temperature. The reaction mixture was filtered, and the filtrate was acidified to pH 2 with concentrated HCl and extracted four times with ether. The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give an oil which was fractionally distilled to give 28.35 g (0.218 mol, 73%) of a liquid, which upon standing became a white solid (mp 32°C) **3,3-dimethyl-2-oxobutanoic acid**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (s, 1H), 1.31 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 201.37, 164.86, 42.49, 25.55. Next, a modification of an established procedure[5] was used to prepare the hydroxy-acid **10**. To a cold (0°C) stirred solution of 10.9 g (83.8 mmol) of 3,3-dimethyl-2-oxobutanoic acid was added slowly 3.17 g (83.8 mmol) of $NaBH_4$. After a further 2 h of stirring at 0°C, the reaction mixture was concentrated under reduced pressure and HCl 6N was slowly added to the residue with cooling until pH 2. The resulting mixture was extracted four times with ether. The organic phase was washed with H_2O until the pH of a washing became 4, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Recrystallization of the residue from ether–hexane solvent gave 7.39 g (55.9 mmol, 67%) of white crystals: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (s, 2H), 3.93 (s, 1H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.7, 78.3, 35.2, 25.7.

    3-Hydroxy-2,2-dimethyl-4-octanone (11): Under a nitrogen atmosphere a hexane solution of 2 M *n*-BuLi (12 mL, 24 mmol) was added dropwise to a cold (−78°C) stirred ether solution of the hydroxyacid **10** (0.5 g, 3.78 mmol). The reaction was allowed to warm to room temperature and stirred for 5 h. The reaction mixture was slowly transferred, via cannula, into a rapidly stirred aqueous HCl solution approximately 1.5N. After extraction with ether (3×30 mL) the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated on a rotary evaporator. The residue was pre-adsorbed onto silica and chromatographed on flash silica gel (15% ethyl acetate/hexane) to give 381 mg (2.21 mmol, 59%) of a yellowish oil: ^{1}H NMR (300 MHz, $CDCl_3$ and some drops of D_2O): δ 3.85 (s, 1H), 2.62–2.43 (m, 2H), 1.65–1.55 (m, 2H), 1.39–1.27 (m, 2H), 0.98(s, 9H), 0.91 (t, $J=7.2$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.9, 84.0, 41.9, 35.7, 26.4, 26.1, 22.5, 14.0. Anal. calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C: 69.72; H, 11.82%.

    5-Bromo-3-hydroxy-2,2-dimethyl-4-octanone (5): A 50 mL, three-necked round-bottomed flask was charged with 335 mg (1.95 mmol) of **11** which was diluted in 20 mL of CH_2Cl_2. This mixture was stirred under reflux with a magnetic stirrer. Acetic acid (5 mL) was added. Bromine (312 mg, 1.95 mmol) diluted in CH_2Cl_2 was added dropwise to the heated solution over a period of 30 min. The reaction was stirred for a further 3 h under reflux. To the cooled solution was added H_2O and the organic phase was separated. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was washed three times with H_2O, saturated aqueous $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give 477 mg of a yellow oil which was pre-adsorbed onto silica and purified by flash chromatography (20% ethyl acetate/hexane) to yield 445 mg (1.77 mmol, 91%) of a light yellowish oil. Note that **5** must be stored in a frozen benzene matrix to avoid decomposition. Data for major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$ and some drops of D_2O): δ 4.54 (t, $J=7.2$, 1H), 4.28 (s, 1H), 2.03–1.95 (m, 2H), 1.42–1.37 (m, 2H), 0.99 (s, 9H), 0.96 (t, $J=7.5$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.9, 81.8, 51.3, 37.0, 34.6, 26.9, 21.3, 14.2; IR: 3477.1, 2959.1, 2873.3, 1702.5 cm^{-1}; MS (FAB positive): m/z 251.06. Anal. calcd for $C_{10}H_{19}BrO_2$: C, 47.82; H, 7.62. Found: C: 47.87; H, 7.97.

    3-Hydroxy-2,2-dimethyl-5-propyl-7-octen-4-one (7). Bromide **5** (1.0 equiv.) was allowed to react with allyltributyltin (2.0 equiv.) in the presence of AIBN (0.1 equiv.) at 80°C using benzene as solvent (to 0.5 M). A second low-temperature procedure reacted **5** (1.0 equiv.) in the presence of triethylborane (0.3 equiv.) with or without different Lewis acids ($MgBr_2{\cdot}OEt_2$, $ZnCl_2$ or $Yb(CF_3SO_3)_3$) at room temperature, at 0°C and at −78°C, using CH_2Cl_2 (0.5 equiv.) as solvent. Oxygen was added by syringe at 20-min intervals. A minimum amount of dry THF or ether was added in some cases to solubilize Lewis acids. After completing the reaction (TLC), the reaction mixture was quenched with concentrated $NaHCO_3$ solution. The organic phase was separated and extracted three times with CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by column chromatography using silica with KF on the top and hexane as eluent to give a yellowish oil (91% yield). Spectroscopic data for the major compound: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.77–5.63 (m, 1H), 5.07–5.01 (m, 2H), 3.93 (d, $J=7.8$, 1H), 3.17 (d, $J=7.5$, 1H), 2.87–2.78 (m, 1H), 2.32–2.16 (m, 2H), 1.69–1.59 (m, 1H), 1.5–1.38 (m, 1H), 1.34–1.24 (m, 1H), 1.00 (s, 9H), 0.91 (t, $J=7.2$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.2, 134.9, 118.2, 83.6, 50.9, 37.6, 36.4, 31.8, 26.8, 21.1, 14.8; MS m/z 213.188 [$M^{\cdot+}$+1]. Anal. calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C: 73.86; H, 11.14%.