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Completely Diastereoselective Radical Reactions Using Arenechromium Tricarbonyl Complexes

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Abstract: Reaction of chromium tricarbonyl complexed aryl aldehydes and ketones with samarium(II) iodide and methyl acrylate results in formation of cyclic lactones as single diastereomers. Complete diastereoselectivity is demonstrated with aldehydes and ketones α or β to the aromatic ring with radical coupling directed *anti* to the chromium tricarbonyl moiety.

Radical reactions have found tremendous utility in organic synthesis, but control of stereochemistry remains a formidable challenge.[1] While there are reports of excellent stereoselectivity for systems employing proximal chirality, chiral auxiliaries, dimerization of prochiral substrates, chiral radical traps, and chiral reagents, most approaches have delivered modest stereoselectivity and none of the processes achieve complete stereocontrol in a general sense.[2] In contrast, transition metal-templated ionic reactions are exceptional in their oftentimes formation of single isomeric products.[3] The chromium tricarbonyl moiety, in particular, is a useful metal template for numerous anionic and cationic reactions of arene substrates since it exerts a large steric influence which generally directs reactants exclusively *anti* to the arene face bound to chromium.[4] Considering the efficacy of the chromium tricarbonyl moiety to control reaction stereochemistry, we initiated studies[5] on stereoselective radical reactions of arene complexes and report herein on intermolecular radical coupling reactions of chromium complexed arenes which result in single, diastereomerically pure products.[6]

We modeled these studies on the radical coupling reactions developed by Fukuzawa[7] which utilize samarium diiodide[8] to reductively generate ketyl radicals. Thus, reaction of chromium-complexed indanone **1** with 2.5 equivalents of samarium(II) iodide[9] and methyl acrylate in the presence of *t*-butanol afforded the spirolactone **2** as a single diastereomer (Table 1, entry 1).[10] Methyl methacrylate and methyl crotonate were relatively efficient radical traps, though substitution at the β-position of the ester decreased the product yield somewhat (entries 2,3). The stereochemistry at the methyl substituent in **3** and **4** was approximately one to one in each case; however, the diastereoselectivity at the benzylic position was not compromised. The tetralone chromium complex **5** is similar in reactivity to the chromium-bound indanone and again the diastereoselectivity was 100% (entry 4). The fluorenone complex **7** was slightly less reactive under the standard conditions. Remarkably, the steric influence of the chromium tricarbonyl moiety extends to aryl β-ketones. Reaction of chromium-bound 2-indanone **9** with methyl acrylate under the standard reaction conditions gave the spirolactone **10** again as a single diastereoisomer (entry 6). The modest yield is presumably due to the

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instability of the starting ketone complex.[11] Even ortho substituted aldehydes serve as partners for stereoselective reaction (entries 7 and 8).[12] The selectivity seen with these substrates arises from reaction of the preferred conformation (shown) as seen in anion addition reactions.[4f]

A significant challenge was assignment of the relative stereochemistry in these products which lack a convenient spectroscopic handle to relate the lactone and arene stereochemistries. Mechanistically, the coupling reaction is presumed to begin with reduction of the aryl ketone **1** with samarium(II) iodide to afford the ketyl-radical **I** (Scheme 1).[8] Subsequent trapping of the radical with an unsaturated ester affords the ester-stabilized radical **II**. Another samarium(II) donates an electron to the ester-stabilized radical to give the anionic compound **III** which is quenched by *t*-BuOH and cyclizes to give **2**. Although a two electron reduction followed by anionic coupling is possible, and ketone reduction based on that is known,[13] the absence of reduced products in the presence of two equivalents of alcohol argues against an anionic pathway. The relative stereochemistry of each product was initially assigned based upon the model of ester trapping from the face opposite the chromium tricarbonyl moiety. Subsequent X-ray crystallographic analysis confirmed the proposed stereochemistry of lactone **6** and the other products were assigned by analogy. A major mechanistic question remaining is whether the chromium moiety exerts a stabilizing or destabilizing effect on the presumed benzylic radical. In light of the fact that chromium complexation strongly stabilizes both benzylic anions and benzylic cations,[4] the expectation is that the interaction is stabilizing. However, there is one report that chromium complexation destabilizes benzylic radicals.[6d] Experiments to directly compare reactivities (**IV** vs **V**) and assess the degree of radical localization on chromium (**V** vs **VI**) are in progress (Figure 1).

Scheme 1

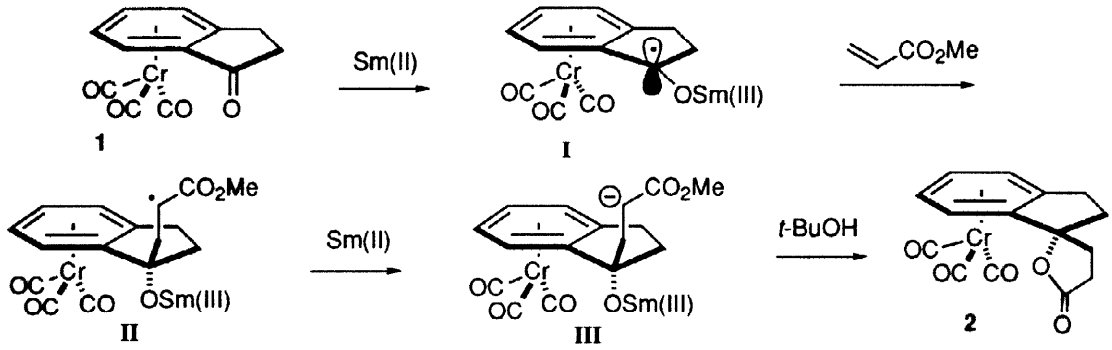
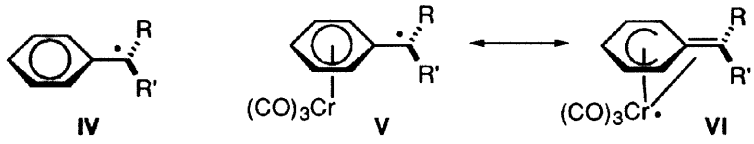
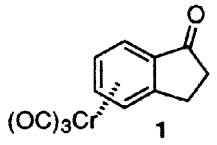
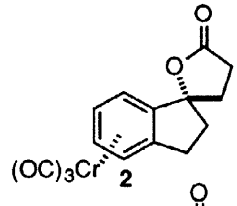
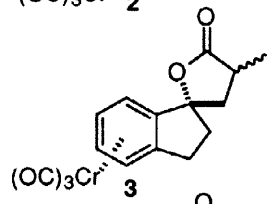
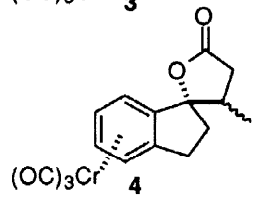
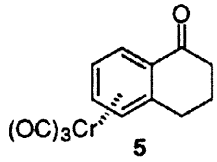
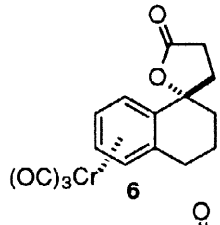
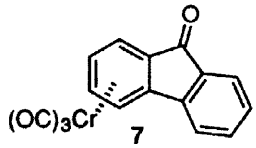
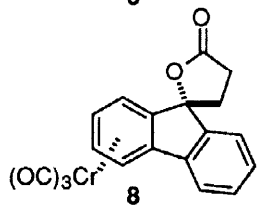
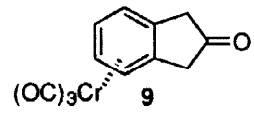
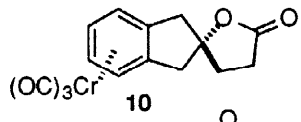
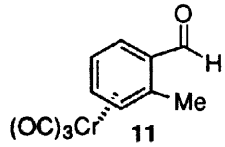
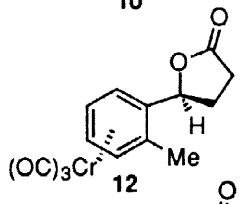
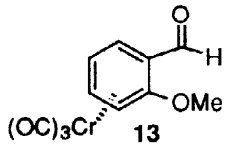
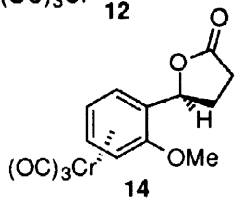


Figure 1



In summary, use of the chromium tricarbonyl moiety as a metal template for radical reactions provides for complete control of diastereoselectivity. The selectivity is attributed to the unique stereochemical control exerted by the chromium tricarbonyl group which effectively shields one face of the arene from reaction. Diastereoselectivity occurs with aryl aldehyde and α and β aryl ketone substrates. Using enantiopure aryl ketone complexes, enantiocontrolled synthesis of lactones can be readily achieved.[4f]

Table 1. Radical reactions of aryl aldehyde and ketone complexes.

Entry	Complex[a]	Radical Trap[b]	Product	Yield (%)
1	 1	A	 2	71
2	1	B	 3	71
3	1	C	 4	41
4	 5	A	 6	65
5	 7	A	 8	57
6	 9	A	 10	33
7	 11	A	 12	77
8	 13	A	 14	83

a) All are racemic. b) A: methyl acrylate, B: methyl methacrylate, C: methyl crotonate

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10. Preparation of **2**: A solution of **1** (50.0 mg, 0.20 mmol), *t*-BuOH (30 mL, 0.40 mmol), methyl acrylate (90 mL, 1.0 mmol) and THF (7 mL) was purged with argon and cannulated into a SmI_2 (0.50 mmol) solution. After 5 min, the reaction was quenched with sat K_2CO_3 (1 mL), filtered through a pad of silica gel, washed with EtOAc and absorbed onto celite. The residue was chromatographed using 2:1 Hex:EtOAc followed by EtOAc as the eluent to afford 42.6 mg (71%) of a yellow solid. ^1H NMR (500 MHz, C_3D_6O) δ: 2.22 (1H, d, J = 9.0 Hz), 2.36 (1H, d, J = 9.9 Hz), 2.45 (1H, s), 2.56 (1H, s), 2.73 (1H, d, J = 6.7 Hz), 2.76-2.81 (2H, m), 3.01 (1H, d, J = 6.0 Hz), 5.47 (1H, s), 5.62 (1H, s), 5.74 (1H, s), 5.92 (1H, s). ^{13}C NMR (100 MHz, C_6D_6) δ: 27.2, 28.8, 33.7, 35.9, 86.8, 88.0, 88.9, 90.1, 93.7, 112.6, 112.7, 174.5, 232.6. HRMS (EI): Calcd for $C_{15}H_{12}CrO_5$: 324.0089; Found: 324.0088.

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