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Enantioselective Alkylations of Tributyltin Enolates Catalyzed by Cr(salen)Cl: Access to Enantiomerically Enriched All-Carbon Quaternary Centers

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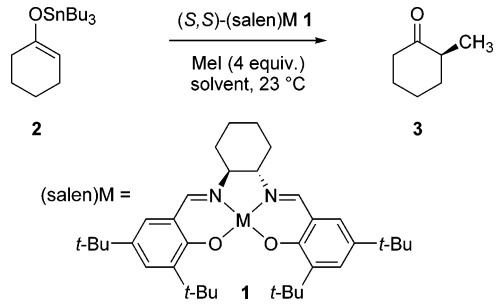
α-Alkylations of carbonyl compounds are indispensable C−C bond-forming reactions in synthetic organic chemistry.[1] Asymmetric variants rely predominantly upon the use of chiral auxiliaries, which often provide exceptional levels of selectivity.[2] For both practical and fundamental reasons, broadly applicable *catalytic* asymmetric alkylation reactions of enolates have been a long-sought goal. Whereas highly efficient transition-metal-catalyzed asymmetric α-allylations,[3] arylations,[4] and vinylations[5] of ketones have been identified, relatively limited progress has been made in catalytic alkylations with sp^3-hybridized electrophiles. Three distinct strategies for catalytic alkylation with alkyl halides have been reported, each involving organic molecules as catalysts.[6−8] In most cases, these systems enable preparation of carbonyl products bearing α-tertiary stereocenters. Access to enantioenriched carbonyl products bearing α-quaternary centers by catalytic means remains largely an unsolved, albeit highly important, problem.[9,10] Herein, we report the catalytic asymmetric α-alkylation of tributyltin enolates with a range of commonly used electrophiles catalyzed by a chiral Cr(salen) complex. Alkylations of tetrasubstituted tin enolates of five-, six-, and seven-membered ring ketones proceed with high enantioselectivity and in synthetically useful yields to afford alkylation products bearing quaternary stereocenters.

On the basis of promising activity displayed by salen metal complexes in catalytic epoxide addition and iodoetherification reactions, we explored the possible utility of these catalysts in enolate alkylation reactions.[11,12] Initial screens revealed that among various enolates of cyclohexanone, tributyltin derivative **2** was uniquely reactive for alkylation with methyl iodide promoted by M(salen) complexes **1a**−**e** (Table 1).[13,14] Whereas Ti (**1b**), Al (**1c**), and Mn (**1d**) complexes all provided α-alkylation product **3** in low enantioselectivity, chromium complex **1e** catalyzed the alkylation in a more promising 30% ee, albeit in low yield. Efforts to optimize this result led to the following observations.[14] (1) Steric and electronic variations of the salen ligand framework influenced both the reactivity and the enantioselectivity of the chromium catalyst, with complexes bearing electron-withdrawing ligand substituents proving completely unreactive. Best results were obtained with complex **1e**. (2) The reaction enantioselectivity was solvent-dependent, with aromatic solvents, such as benzene and chlorobenzene, affording best results. (3) Decreasing the reaction temperature led to marked increases in enantioselectivity (entries 6−9). At temperatures below 4 °C, however, product yield was significantly depressed even at prolonged reaction times.

Despite the encouraging enantioselectivity obtained in these exploratory studies, the yields of alkylation product were generally low. Best yields (69%) were obtained at elevated catalyst loading (20 mol % **1e**) and increased reaction concentration, but further efforts directed toward optimization of this system with this substrate combination proved unfruitful. Moreover, the specific conditions developed for alkylation with methyl iodide did not extend well to other electrophiles; reactions with benzyl bromide and allyl bromide afforded alkylation products in modest yields and enantioselectivities.[15]

Table 1. Preliminary Screen of Tributyltin Enolate Alkylation[a]



entry	catalyst	M	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	**1a**	CoCl	TBME	23	0	
2	**1b**[d]	$TiCl_2$	TBME	23	14	14
3	**1c**	AlCl	TBME	23	15	5
4	**1d**[d]	MnCl	TBME	23	34	4
5	**1e**	CrCl	TBME	23	42	30
6	**1e**	CrCl	C_6H_6	23	38	49
7	**1e**[d,e]	CrCl	C_6H_6	4	69	60
8	**1e**[d,e]	CrCl	C_6H_5Cl	4	53	58
9	**1e**[d,e]	CrCl	C_6H_5Cl	−40	26	84

[a] Unless noted otherwise, reactions were carried out with 0.007 mmol of catalyst **1**, 0.07 mmol of tin enolate, and 0.28 mmol of methyl iodide in 500 μL of solvent. [b] Determined by GC analysis relative to 1-decene as internal standard. [c] Determined by chiral GC analysis. [d] Reactions carried out using 175 μL of solvent. [e] Reaction carried out using 20 mol % catalyst.

Whereas trisubstituted enolate **2** was observed to undergo decomposition during the course of the reaction, tetrasubstituted enolate **4a** proved to be significantly more robust as a reacting partner. This nucleophile was more reactive and underwent alkylation with an enantioselectivity higher than that of **2** under the reaction conditions outlined above with a broad range of common electrophiles (Table 2). Furthermore, catalyst loadings as low as 2.5 mol % **1e** could be used, and the reactions were complete within 2 h at 0 °C. In addition to five-membered ring substrate **4a**, six- and seven-membered ring tetrasubstituted enolates **4b**−**d** underwent alkylation in good yield and high enantiomeric excess. In all cases, S_N2 addition was observed exclusively, in preference to S_N2' or carbonyl addition, and with minimal (<5%) generation of over-alkylation products.[16] Alkylation of tin enolates **4a** and **4d** with propargyl bromide, for example, proceeded to form **5b** and **5i** as the only detectable products in 96 and 92% ee, respectively. The more hindered tin enolate **4c** also proved to be a competent reacting partner, affording products **5g** and **5h** in modest yield and good enantiomeric excess.[17]

The sense of absolute stereoinduction in the alkylation reactions was reversed for products **5e**, **5g**, and **5h** relative to the other

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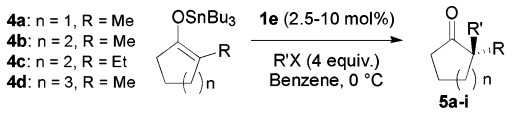
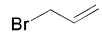
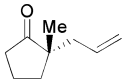
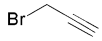
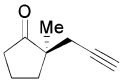
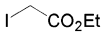
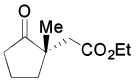
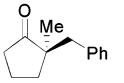
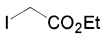
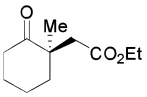
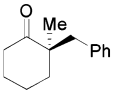
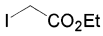
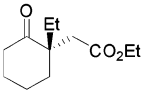
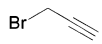
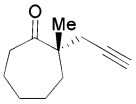
Table 2. Enantioselective Alkylation of Tetrasubstituted Tin Enolates[a]



5a-i

enolate	R'X	catalyst config.	product	yield (%)[b]	ee (%)[c]
4a[e]		*R*,*R*	 **5a**	84	94
4a[e]		*S*,*S*	 **5b**	81	96
4a[f]		*R*,*R*	 **5c**	73	96
4a[e]		*S*,*S*	 **5d**	91	93[d]
4b[f]		*R*,*R*	 **5e**	67	95
4b[f]		*S*,*S*	 **5f**	80	85[d]
4c[g]		*S*,*S*	 **5g**	72	89
4c[f]	CH_3I	*S*,*S*	 **5h**	43	90
4d[g]		*R*,*R*	 **5i**	58	92

[a] Reactions were carried out on a 0.5 mmol scale with external temperature control (ice bath). [b] Isolated yield after silica gel chromatography. [c] Determined by chiral GC analysis unless noted otherwise. [d] Determined by chiral HPLC analysis. [e] Reaction carried out using 2.5 mol % catalyst. [f] Reaction carried out using 5.0 mol % catalyst. [g] Reaction carried out using 10 mol % catalyst.

products,[14] a rather striking result given the uniformly high enantioselectivities obtained in each case. Possible mechanisms involving enolate activation (via Sn or Cr ate complexes) and/or alkyl halide activation by the chiral Cr complex are being evaluated in the context of this intriguing stereochemical phenomenon.

This method provides efficient and highly selective access to enantioenriched α-carbonyl all-carbon-substituted quaternary stereocenters. To our knowledge, it also represents the only transition-metal-catalyzed system for α-alkylation of carbonyl substrates with alkyl halides. The synthetic and mechanistic implications of this discovery are the focus of our ongoing efforts.

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Supporting Information Available: Representative experimental procedures, characterization data, and chiral chromatographic analyses of racemic and enantiomerically enriched products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See Supporting Information for details.
(15) For example, in chlorobenzene at −40 °C, 2-benzyl cyclohexanone was obtained in 83% yield and 53% ee, and 2-allyl cyclohexanone was obtained in 60% yield and 46% ee.
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(17) Product **5h** could not be accessed by the alternative approach involving alkylation of **4b** with ethyl iodide.

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