Asymmetric Catalysis

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Enantioselective Alkylation of Acyclic α,α-Disubstituted Tributyltin Enolates Catalyzed by a {Cr(salen)} Complex**

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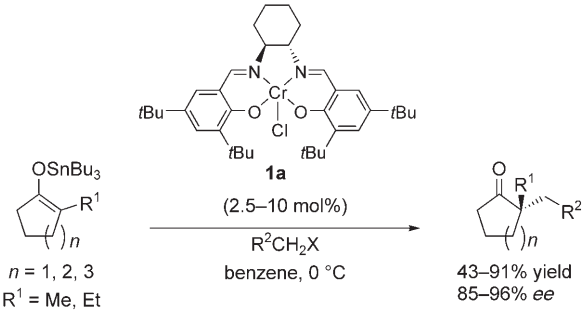
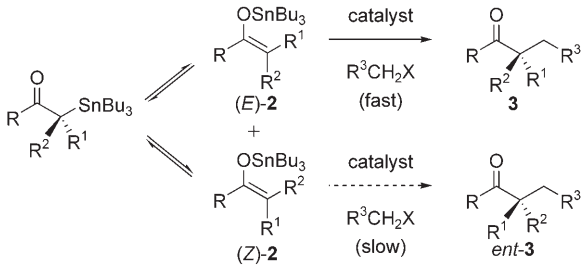
Dedicated to Professor Robert G. Bergman on the occasion of his 65th birthday

Catalytic α-carbonyl C–C bond-forming reactions represent a proven strategy for the construction of quaternary stereocenters.[1] Most approaches involve the addition of enolates to carbon-centered electrophiles in which both the π-facial selectivity and the enolate geometry govern the stereoselectivity of the C–C bond-forming event.[2–8] Unfortunately, the synthesis of stereodefined enolates from simple α,α-disubstituted carbonyl compounds that lack either tethered substituents or specific chelating functionality remains a significant challenge in organic synthesis.[9] As a result, successful examples of asymmetric catalytic enolate addition reactions that generate α-carbonyl quaternary stereocenters are limited to β-cyano esters, β-keto esters, and cyclic ketones, and relatively little progress has been made with simple acyclic systems.[10] Our own efforts in the area of enantioselective reactions with enolates have led to the recent discovery of a {Cr(salen)}-catalyzed asymmetric α-alkylation of cyclic tin enolates to provide 5-, 6-, and 7-membered-ring ketones that contain α quaternary stereocenters (salen=*N*,*N*′-bis(salicylidene)ethylenediamine dianion; Scheme 1).[11] While the preparation of acyclic α,α-disubstituted tin enolates leads inevitably to mixtures of *E* and *Z* isomers, tin enolates are known to undergo tautomerization between their *O*-stannyl and *C*-stannyl forms in solution.[12] We were intrigued by the possibility that enantioselective alkylation of acyclic enolates might be achievable by a dynamic mechanism such as that outlined in Scheme 2,



Scheme 1. {Cr(salen)}-catalyzed alkylation of tetrasubstituted tin enolates derived from cyclic ketones.



Scheme 2. Strategy for the enantioselective alkylation of acyclic tributyltin enolates **2**.

wherein mixtures of acyclic tin enolates might undergo reaction selectively through one geometric isomer under the {Cr(salen)}-catalyzed alkylation conditions. Herein, we report our progress to this end, and discuss how these studies have enhanced our understanding of the mechanism of the catalytic reaction.

Initial studies were performed using the tributyltin enolate of 3-methyl-2-pentanone **2a**, which was prepared as a 1.8:1 mixture of *E* and *Z* isomers.[13] Treatment of **2a** with allyl bromide and the [Cr(salen)Cl] complex **1a** at 4 °C afforded the alkylation product **3a** in 80 % yield and 21 % *ee* (Table 1, entry 1). Variation of the substituents on the salen ligand revealed that the OTIPS derivative **1b** was both more reactive and more enantioselective than the *t*Bu derivative (Table 1, entry 2, 84 % yield, 36 % *ee*).[14] A significant effect of the catalyst counterion on enantioselectivity and conversion was observed (Table 1, entries 2–4), with the iodide complex **1d** catalyzing the alkylation reaction in 93 % yield and 56 % *ee* (3.6:1 e.r.).[15] This result established unambiguously that the enantioselectivity of the alkylation product **3a** was not limited by the *E*/*Z* ratio of enolate isomers of **2a** (see below). Interestingly, a small increase in enantioselectivity was observed in reactions run with 5 mol % Bu_3SnOMe as an additive (Table 1, entries 5 and 6), perhaps as a result of acceleration of enolate tautomerization and equilibration. Further variation of the reaction parameters led to identification of conditions that provided **3a** in 94 % yield and 79 % *ee* when the reaction was run at −27 °C in *o*-xylene with

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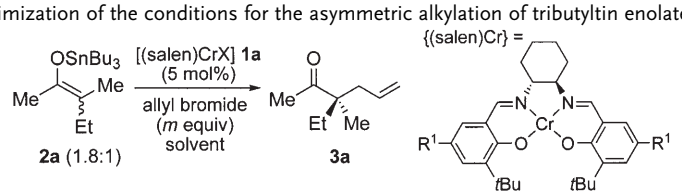
Table 1: Optimization of the conditions for the asymmetric alkylation of tributyltin enolate **2a**.[a]



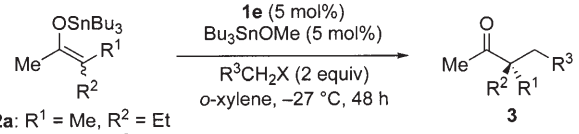
Entry	Catalyst	X	R^1	Solvent	*m* [equiv]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	Cl	*t*Bu	benzene	4	4	80	21
2	**1b**	Cl	OTIPS	benzene	4	4	84	36
3	**1c**	Br	OTIPS	benzene	4	4	90	49
4	**1d**	I	OTIPS	benzene	4	4	93	56
5	**1d**	I	OTIPS	benzene	2	4	90	60
6[d]	**1d**	I	OTIPS	*o*-xylene	2	4	95	65
7[d]	**1e**	I	$OSiThMe_2$	*o*-xylene	2	4	94	68
8[d]	**1e**	I	$OSiThMe_2$	*o*-xylene	2	−27	94	79

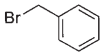
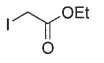
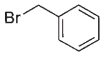
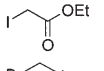
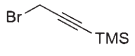
[a] Reactions were carried out with **1** (0.005 mmol) and **2a** (0.1 mmol) in 250 μL of solvent; TIPS = triisopropylsilyl, Th = thexyl = 1,2,2-trimethylpropyl. [b] Determined by GC analysis using 1-decene as an internal standard. [c] Determined by GC analysis on a chiral stationary phase compared with an authentic racemic sample. [d] Bu_3SnOMe (5 mol%, 0.005 mmol) was added.

catalyst **1e**, in which the salen ligand contained a $OSiThMe_2$ group (Table 1, entry 8).

Under the optimized conditions, the alkylation of enolate **2a** with allyl iodide afforded **3a** in 83% yield and 82% *ee* (Table 2, entry 2). Alkylation of **2a** with other common sp^3-hybridized electrophiles, which included benzyl bromide and ethyl iodoacetate, proceeded in good yield and enantioselectivity (Table 2, entries 3 and 4). Variation of the enolate substituent was investigated with the tin enolate **2b** (R^1 = Me; R^2 = *n*Bu), which was prepared as a 1.5:1 mixture of *E* and *Z* isomers. Alkylation of **2b** proved more selective than alkylation of **2a** with a variety of electrophiles in spite of the lower *E*/*Z* ratio of **2b** (Table 2, entries 5–8). For example, alkylation of **2b** with allyl iodide provided the ketone **3d** in 92% yield and 87% *ee*. However, significant limitations to the nucleophile scope remain. For example, enolates containing branched aliphatic substituents (for example, **2**; R^1 = Me; R^2 = *i*Pr) underwent alkylation with low enantioselectivity. Additionally, the presence of aromatic substitution on **2** (for example, R^1 = Me; R^2 = Ph) led to reduced reactivity of the enolate such that the alkylation proceeded only to very low conversion.

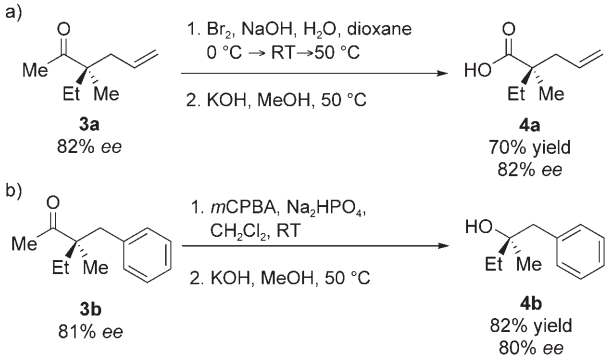
Table 2: Enantioselective alkylation of tributyltin enolates **2** with alkyl halides.



Entry	Tin enolate (*E*/*Z* ratio)	R^3CH_2X	Adduct	Yield [%][a]	*ee* [%][b]
1	**2a** (1.8:1)		**3a**	80	79
2			**3a**	83	82
3			**3b**	86	81
4			**3c**	73	76
5	**2b** (1.5:1)		**3d**	92	87
6			**3e**	83	86
7			**3f**	77	84[c]
8			**3g**	97	78[d]

[a] Yield of isolated product after chromatography on silica gel. [b] Determined by GC or HPLC analysis on a chiral stationary phase compared with an authentic racemic sample. [c] Analysis of the *ee* value was performed on the Weinreb amide. [d] Analysis of the *ee* value was performed on the desilylated alkyne.

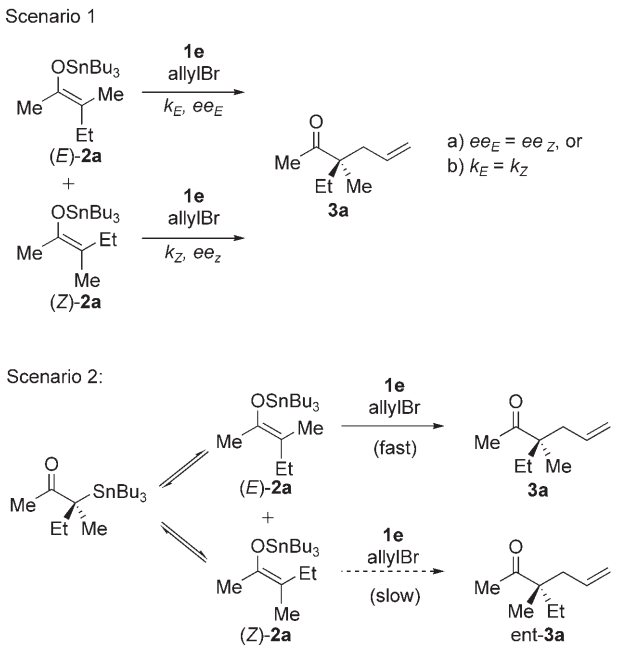
The methyl ketone products **3** have broad versatility as chiral building blocks for organic synthesis (Scheme 3). For example, ketone **3a** was converted into acid **4a** and tertiary



Scheme 3. Elaboration of the methyl ketone products. mCPBA = *meta*-chloroperoxybenzoic acid.

alcohol **4b** both with complete preservation of enantiomeric excess (Scheme 3).[16] Very few efficient catalytic routes to products with structures such as **4a** and **4b** have been identified because of the inherent difficulty associated with enantiodifferentiation of three sp^3-hybridized substituents.[17]

The Cr-catalyzed alkylation reaction generates α-quaternary ketones **3** in high yield with e.r. values significantly exceeding the *E*/*Z* ratios of the enolate starting material. This result requires that either: 1) both enolate isomers undergo alkylation to generate the same enantiomer of product preferentially (scenario 1, Scheme 4), or 2) the enolate isomers undergo rapid equilibration under the reaction conditions with selective reaction of one geometric isomer (scenario 2, Scheme 4). Acyclic α-monosubstituted tin enolates have been shown to undergo tautomerization between their *O*-stannyl and *C*-stannyl forms in solution.[18] In the present



Scheme 4. Possible pathways for the enantioselective alkylation of geometric mixtures of **2a**.

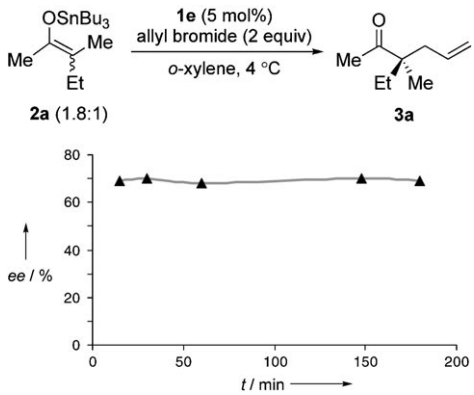
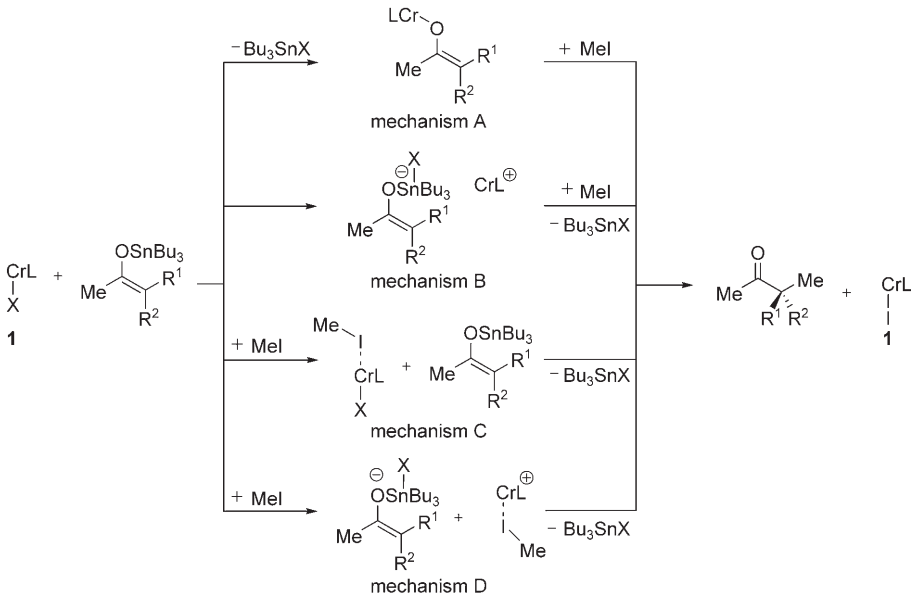


Figure 1. Enantioselectivity over the course of the reaction.

context, enolate tautomerization could serve as a viable mechanism for *E*/*Z* equilibration as long as the C tautomer is accessible from α,α-disubstituted tin enolates. Furthermore, differences in reactivity of *E* and *Z* enolates have ample literature precedent.[19] When the course of the alkylation reaction of **2a** with allyl bromide was monitored from 5% to 100% conversion, the *ee* value of the product **3a** was observed to remain invariant (Figure 1). This is fully consistent with scenario 2 in Scheme 4, but is only possible within the constraint of scenario 1 if the *E* and *Z* isomers undergo alkylation with identical enantioselectivity or at exactly the same rate. Given the implausibility of such scenarios, the equilibration mechanism in scenario 2 appears most likely.

The pronounced influence of the counterion to the chromium catalyst **1** on the *ee* value of the alkylation reaction (Table 1) holds clear mechanistic implications. A similar observation was made in the alkylation of cyclic tin enolates, however the trend was in the opposite direction, with catalyst **1a** being more enantioselective than the corresponding [(salen)CrBr] or [(salen)CrI] complexes. Evidently, the counterion of the chromium catalyst **1** is part of the enantiodetermining step in the catalytic cycle. This rules out a mechanism for catalysis that involves the generation of a [(salen)Cr(enolate)] complex as the only role of the {(salen)Cr} catalyst (mechanism A, Scheme 5).[20] Preliminary studies reveal a first-order kinetic dependence on the chromium catalyst, which suggests that a mechanism in which the catalyst serves a dual role as a Lewis acid activator of the alkyl halide and as a counterion for the enolate is not operative.[21]

Nucleophilic activation of tin enolates can occur not only by transmetalation but also by coordination of a Lewis base such as hexamethylphosphoramide (HMPA) or Bu_4NBr to the metal to generate pentacoordinate anionic (ate) complexes.[22] Thus, chromium catalyst **1** could act in an analogous fashion to Bu_4NBr, by activating the tin enolate through halide addition, thus generating a tin ate complex with a cationic {(salen)Cr} counterion (mechanism B, Scheme 5).[23] It is particularly relevant in this context that neutral tetracoordinate tin enolates have been shown to add to α-halocarbonyl electrophiles at the carbonyl group, whereas pentacoordinate tin enolates react by halide displacement.[24] In mechanism B, enantioselectivity would be imparted solely



Scheme 5. Possible mechanisms for the {(salen)Cr}-catalyzed alkylation of tributyltin enolates **2** with alkyl halides. L = salen ligand.

by ion pairing; consistent with this possibility, the enantioselectivities of alkylation reactions were found to be strongly solvent dependent, with reactions that were carried out in nonpolar solvents such as benzene or *o*-xylene affording better results than those carried out in polar solvents such as acetonitrile or tetrahydrofuran.

Alternatively, the Cr-catalyzed alkylation reaction could proceed by activation of the alkyl halide by the neutral Cr catalyst (mechanism C, Scheme 5). However, neutral metal complexes of alkyl halides find no precedent in the literature. By contrast, coordination complexes of alkyl halides with cationic transition metals are known and have been shown to accelerate S_N2 alkylation reactions.[25] An intriguing variant to mechanism B would thus involve activation of the alkyl halide by the cationic chromium complex formed upon halide transfer to the tin atom (mechanism D, Scheme 5). At this stage we have been unable to obtain definitive experimental evidence to rule out either of the mechanisms B or D, but several compelling aspects of mechanism D justify its careful consideration. First, the mechanism invokes minimal charge separation in the association of the leaving group of the electrophile with the chromium catalyst to close the catalytic cycle. Second, it suggests a basis for stereoinduction in the enolate alkylation reaction that has strong precedent in epoxidation and epoxide-opening reactions, in which the enantioselectivity results from nucleophilic addition to a metal-bound electrophile located within the chiral salen framework.[26]

In conclusion, we have identified a system for the catalytic asymmetric alkylation of acyclic tetrasubstituted tin enolates to generate α-carbonyl quaternary stereocenters. We are able to use tin enolates prepared as their thermodynamic *E* and *Z* mixtures under the alkylation conditions and obtain high yields and good enantioselectivities with a variety of sp^3-hybridized electrophiles. Catalysis likely proceeds by generation of a tin ate species from the [Cr(salen)X] catalyst, perhaps with concomitant activation of the alkyl halide by the cationic chromium complex generated in situ. Alkyl halide activation is unprecedented in alkylation catalysis, and future studies will be necessary to ascertain the validity of this proposal.

Experimental Section

3-Ethyl-3-methyl-hex-5-en-2-one (**3a**): A Schlenk flask (10 mL) was flame dried under vacuum, cooled to 23 °C, and charged with the catalyst (*R*,*R*)-**1e** (23.7 mg, 0.0025 mmol, 5 mol %) under nitrogen. The flask was evacuated for 10 min and then flushed with nitrogen. Then *o*-xylene (500 μL) and allyl iodide (91 μL, 1 mmol, 2 equiv) were added by syringe. The solution was stirred at −27 °C under nitrogen in an immersion cooler for 10 min. A solution of tin enolate (195 mg, 0.5 mmol, 1 equiv) and tributyltin methoxide (7 μL, 0.025 mmol, 5 mol %) in *o*-xylene (0.75 mL) was prepared in a flame-dried 2-dram vial. The solution was cooled to −27 °C in an acetone/dry-ice bath with vigorous stirring under nitrogen for 5 min and was then added in one portion by syringe to the Schlenk flask. The rubber septum on the Schlenk flask was exchanged for a greased glass stopper, the nitrogen inlet was sealed shut, and the reaction was stirred at −27 °C for 48 h. The reaction was diluted with pentane (2 mL) and transferred into a disposable test tube (durex borosilicate glass, 18 × 150 mm), which contained saturated NaCl solution (0.5 mL) at 0 °C. Solid potassium fluoride (ca. 1 g) was added, accompanied by the formation of white precipitate. The mixture was filtered through a bed of sodium sulfate (rinsing with pentane) into a flask cooled to 0 °C, and was concentrated to around 1.5 mL by rotary evaporation with a bath at 4 °C. The residue was purified by column chromatography on silica gel, with 2 % diethyl ether in pentane as the eluent. Concentration of the desired fractions was again performed with a bath at 4 °C and the product was isolated as a clear oil (58.2 mg, 83 % yield). The enantiomeric excess was determined to be 82 % by GC analysis on a chiral stationary phase (γ-TA 50 °C (isothermal), t_r(minor) = 61.1 min, t_r(major) = 58.0 min); $[\alpha]_D^{24} = -0.65$ ($c = 6.7$, $CHCl_3$); IR (thin film): $\tilde{\nu} = 3070$ (w), 2955 (m), 2910 (m), 2860 (w), 1706 (s), 1461 (w), 1355 cm^{-1} (m); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.71$–5.61 (1H, m), 5.07–5.02 (2H, m), 2.34 (1H, dd, $J = 14.4$, 7.6 Hz), 2.19 (1H, dd, $J = 12.8$, 7.6 Hz), 2.10 (3H, s), 1.65 (1H, dq, $J = 14$, 7.6 Hz), 1.50 (1H, dq, $J = 14$ Hz, 7.6 Hz), 1.07 (3H, s), 0.79 ppm (3H, t, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 208.6$, 134.2, 118.1, 51.8, 42.2, 31.0, 22.6, 20.5, 8.9 ppm; LRMS (ES): 141 (100 %) $[M+H]^+$.

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[15] Treatment of the [(salen)CrCl] complex **1b** with NaI at room temperature resulted in the quantitative exchange of the counterion; see the Supporting Information for details

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