Mercury in Organic Chemistry. V.[1] The Direct Esterification of Alkyl Halides

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The direct esterification of alkyl halides using stoichiometric amounts of sodium, mercury, and silver carboxylates is examined. Treatment of unhindered primary alkyl iodides and bromides, as well as allyl and benzyl chloride, bromide, and iodide, with sodium acetate in HMPA at room temperature provides excellent yields of the corresponding esters. Mercuric acetate in diglyme will react directly only with *tert*-butyl halides, allyl iodide, and benzyl bromide and iodide. However, this reaction is greatly catalyzed by the addition of triacyloxyboranes. Unhindered primary alkyl iodides and *tert*-butyl, allyl, and benzyl chlorides, bromides, and iodides, as well as α-phenethyl chloride, all react to give good to excellent yields of esters. Optically active α-phenethyl chloride gives predominant racemization. These reactions are examined in some detail and appear promising for the direct esterification of hindered highly ionizable alkyl halides such as *tert*-butyl chloride and α-phenethyl chloride. Silver carboxylates show a reactivity pattern similar to that of the mercury salts, but generally give lower yields.

Numerous methods are presently available for achieving the direct esterification of carboxylic acids. Some of these procedures utilize alkyl halides. Seldom, however, have any of these procedures been applied with the synthetic objective of achieving the direct high yield esterification of an alkyl halide. In fact, no systematic survey of this possibility has apparently ever been undertaken. From this viewpoint, therefore, present procedures suffer certain major disadvantages. They often are limited to the esterification of alkyl halides which readily undergo bimolecular nucleophilic substitution reactions, most commonly methyl and ethyl iodide. In a few instances solvolytic conditions have been applied to the esterification of allylic and benzylic halides. No procedures have yet been reported which will effect the direct esterification of tertiary halides in good yield. In most instances a large excess of the halide has been employed and elevated temperatures and/or extended reaction times are required. The presence of bases which might effect elimination or rearrangement in delicate molecules provides an additional complication.

Our earlier work on the direct anti-Markovnikov esterification of alkenes[2] suggested that some of the difficulties encountered with previous procedures might be overcome by the utilization of mercuric carboxylates in the presence of catalytic amounts of triacycloxyboranes. We have examined this possibility and wish now to report a complete study of these reactions, as well as a comparison with the reactions of silver and sodium carboxylates.

Mercury Carboxylates

Introduction. We recently reported a convenient new method for the direct anti-Markovnikov esterification of alkenes using a hydroboration–mercuration–iodination sequence.[2] During the course of that investigation we observed that mercuric acetate readily reacts with primary alkyl iodides in the presence of catalytic amounts of "triacetoxyborane," $B(OAc)_3$, to give excellent yields of the corresponding acetate esters. This discovery initiated a thorough examination of the reaction of mercuric carboxylates with alkyl halides. Particular attention was paid to the effect of various solvents, catalysts, alkyl halides, and mercuric carboxylates on the yield of ester. However, no special effort was made to optimize the yield of ester in any of these reactions. Instead primary emphasis was placed on determining the limitations of these new esterification reactions.

Esterification of *n*-Butyl Iodide. The reaction of *n*-butyl iodide with mercuric acetate has been examined in some detail (Table I) (eq 1). Although no reaction occurs in

$$n\text{-}C_4H_9I + Hg(OAc)_2 \longrightarrow n\text{-}C_4H_9OAc + IHgOAc \quad (1)$$

tetrahydrofuran (THF) at room temperature, the iodide completely disappears upon refluxing 24 hr. However, only a 30% yield of *n*-butyl acetate results. By increasing the polarity of the solvent and hence the solubility of the mercuric acetate, one greatly facilitates the reaction with *n*-butyl iodide (entries 3–9). Thus, utilization of hexamethylphosphoric triamide (HMPA) produces a 96% yield of *n*-butyl acetate in 48 hr at room temperature. However, similar results (99%) can be achieved by the use of sodium acetate, suggesting that the mercury cation plays little role in these reactions.

We have also examined the effect of added mercuric iodide on the reaction of *n*-butyl iodide and mercuric acetate in THF. Mercuric acetate completely dissolves in THF in the presence of mercuric iodide (1:1) probably due to the formation of "iodomercuric acetate," IHgOAc. This reagent, while slightly more reactive than mercuric acetate, is little more effective in the esterification of the halide (9%).

However, the reaction of *n*-butyl iodide and mercuric acetate in THF can be markedly accelerated by the addition of Lewis acid catalysts. Addition of 10% of "triacetoxyborane" (made from "borane" and acetic acid) results in a rapid disappearance of the *n*-butyl iodide and the formation of *n*-butyl acetate in 88% yield. In attempting to utilize both of the acetate groups of mercuric acetate in this reaction, we have examined the use of both "iodomercuric acetate" and mercuric acetate (entries 12 and 13). The reaction of "iodomercuric acetate" is also catalyzed by "triacetoxyborane," but only a 72% yield of ester is obtained, and significant amounts of the alkyl iodide (11%) remain. The use of only half as much mercuric acetate as previously used produces an excellent yield of the ester (83%), but 6% of the iodide remained. Thus, an equimolar ratio of mercuric acetate and alkyl halide appears desirable.

Catalyst Preparation. The remarkable catalytic effects of "triacetoxyborane" in these reactions suggested an examination of alternate routes to this catalyst. Our initial work employed "triacetoxyborane" prepared by the low temperature addition of "borane" to acetic acid (eq 2). It

$$BH_3 + 3HOAc \longrightarrow B(OAc)_3 + 3H_2 \quad (2)$$

was hoped that this reagent might also be generated through an exchange reaction between boron trifluoride and mercuric acetate (eq 3). Addition of boron trifluoride

$$3Hg(OAc)_2 + 2BF_3 \longrightarrow 2B(OAc)_3 + 3HgF_2 \quad (3)$$

to mercuric acetate and *n*-butyl iodide in sufficient

Table I
The Direct Esterification of *n*-Butyl Iodide by Mercuric Acetate

$n\text{-}C_4H_9I \longrightarrow n\text{-}C_4H_9O_2CCH_3$

Entry	Mercuric carboxylate[a]	Catalyst[b]	Solvent[c] (10 ml)	Temp, °C	Reaction time, hr	Ester yield,[d] %	Unreacted alkyl halide,[d] %
1	$Hg(OAc)_2$		THF	25	24	0	100
2				65		30	0
3			DG	25		1	99
4			CH_3OH			5	0
5			DMSO			13	17
6			DMF			25	14
7			Pyridine			38	0
8			HMPA			92	6
9					48	96	1
10	IHgOAc		THF		24	9	66–77
11	$Hg(OAc)_2$	$B(OAc)_3$				88	0
12	IHgOAc					72	11
13	0.5 $Hg(OAc)_2$					83	6
14	$Hg(OAc)_2$	3 $Hg(OAc)_2$–$2BF_3$				34	0
15				−78		26	0
16		3 AgOAc–BF_3		25		18	0
17		$B(OH)_3$–$3(Ac)_2O$				10	60
18		B_2O_3–$3(Ac)_2O$				86	0
19		3 $Hg(OAc)_2$–BH_3				87	0

[a] At 10 mmol unless otherwise indicated. [b] Total boron catalyst was 1 mmol. [c] Abbreviations indicated in the text. [d] Glpc analysis using an internal standard.

amounts to generate 10% of the "triacetoxyborane" catalyst brought about an extremely rapid reaction and complete disappearance of the iodide (entry 14). However, only 34% of the desired ester was obtained. Addition of the iodide to the other reagents (which were stirred 1 hr together prior to addition) gave similar results. Lowering the temperature to −78° only lowered the yield further (26%). It would appear from these results that no exchange between mercuric acetate and boron trifluoride has occurred. Instead, boron trifluoride is functioning as the catalyst in these reactions.

We have also examined the analogous exchange reaction between silver acetate and boron trifluoride (eq 4). Subsequent mercuration provided results similar to those above. Apparently no exchange occurs. Instead a very rapid reaction with *n*-butyl iodide is observed, but only an 18% yield of the ester results. It is apparent that boron trifluoride greatly catalyzes the reaction of alkyl halides with mercury carboxylates, but the yields are substantially lower than those obtained using "triacetoxyborane."

$$3AgOAc + BF_3 \longrightarrow B(OAc)_3 + 3AgF \qquad (4)$$

We have attempted the preparation of "triacetoxyborane" through the esterification of boric acid (eq 5) and boric oxide (eq 6).[3] The indicated reagents were stirred together both at room temperature and at reflux in THF for 24 hr. Subsequent esterification of *n*-butyl iodide with mercuric acetate gave 10 and 8% yields from boric acid and 46 and 86% yields from boric oxide, respectively (entries 17 and 18). Thus, the high temperature boric oxide route provides a convenient alternate route to this useful catalyst.

$$B(OH)_3 + 3(Ac)_2O \longrightarrow B(OAc)_3 + 3HOAc \qquad (5)$$

$$B_2O_3 + 3(Ac)_2O \longrightarrow 2B(OAc)_3 \qquad (6)$$

The rapid reduction of mercuric acetate by "borane" suggested another route to "triacetoxyborane" (eq 7). Indeed, addition of "borane" directly to mercuric acetate at −78° and warming to room temperature generated a catalyst which facilitates the rapid esterification of *n*-butyl io-

$$BH_3 + 3Hg(OAc)_2 \longrightarrow B(OAc)_3 + 1.5H_2 + 1.5Hg_2(OAc)_2 \qquad (7)$$

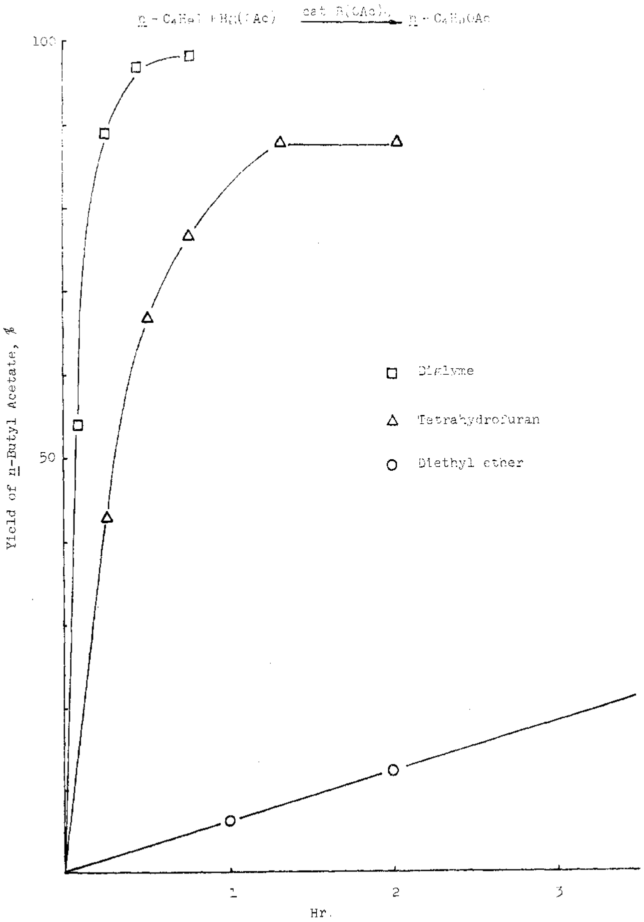


Figure 1. Effect of solvent on rate of esterification.

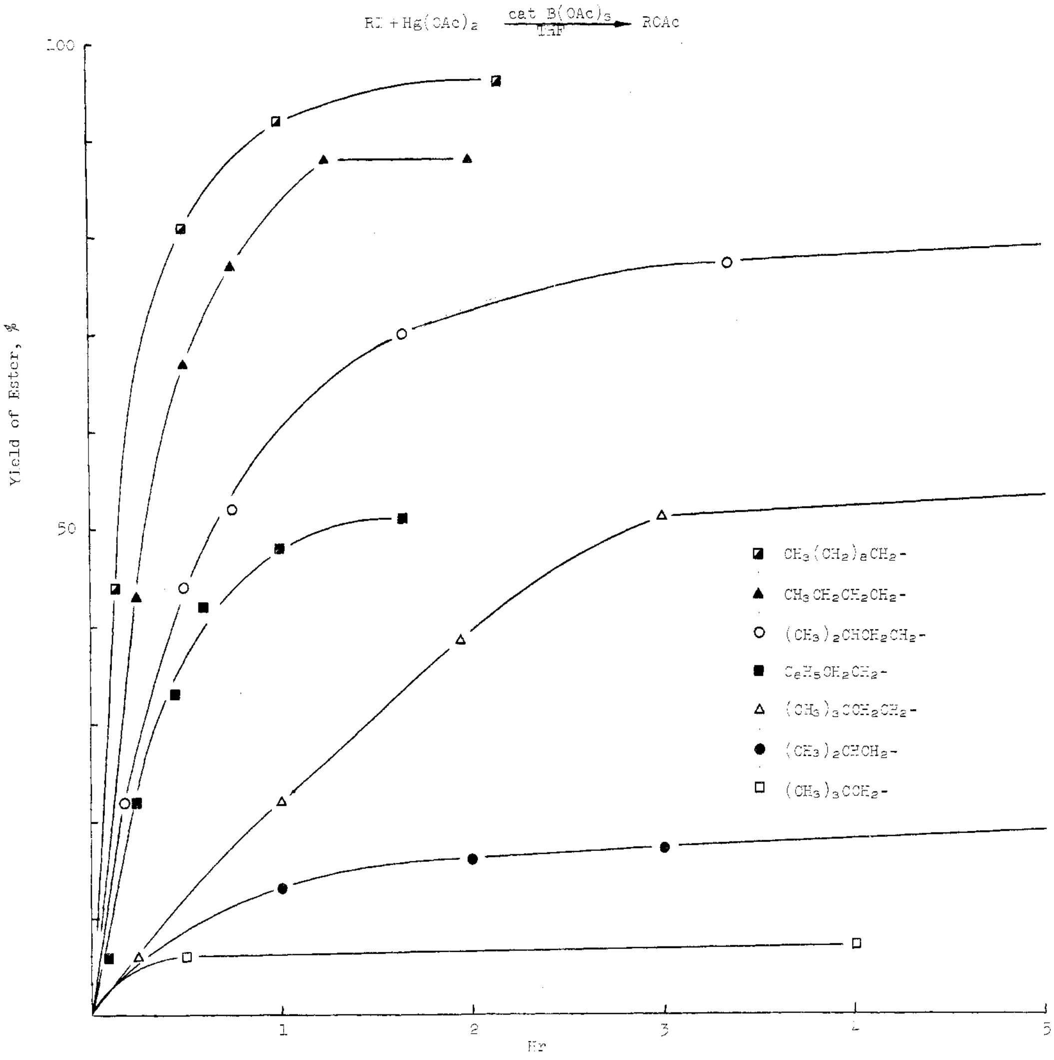
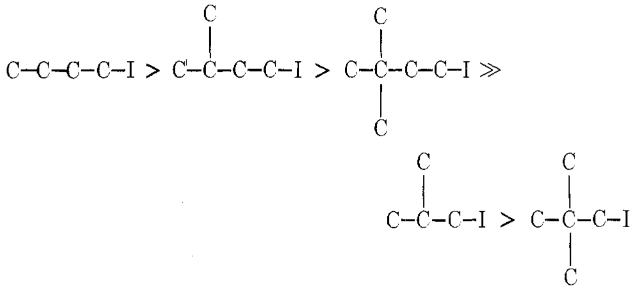


Figure 2. Relative rates of esterification of primary alkyl iodides.

dide by mercuric acetate. After 24 hr at room temperature an 87% yield of the ester was observed. Although perhaps more convenient for some purposes, this procedure produces an insoluble material, presumably mercurous acetate, which makes it impossible to follow the reaction by watching the dissolution of the insoluble mercuric acetate. For this reason the direct reaction of "borane" and the carboxylic acid seemed preferable and was utilized for all subsequent reactions.

Relative Rates. The solvent for these catalytic esterification reactions has a major effect on the rate of the reaction. The reaction of *n*-butyl iodide in diglyme requires only about 0.5 hr to reach completion (99% yield), while THF (88% yield in 75 min) and diethyl ether (99% yield in 120 hr) require considerably longer reaction times (Figure 1). This trend probably results from the decreasing solubility of the mercuric acetate in proceeding from diglyme to THF to diethyl ether. Doubling the concentration of the catalyst from 0.1 to 0.2 *M* further increases the reaction rate (approximately 30 min to reach completion in THF—84% yield).

The effect of the structure of the primary alkyl iodide on the relative rates and yields has been examined in some detail (Figure 2). Increasing the steric hindrance about the methylene iodide portion of the molecule markedly decreases the rate of esterification and results in sharply reduced yields of ester. This is clearly indicated by comparing the following alkyl iodides



$$\text{C–C–C–C–I} > \text{C–}\overset{\text{C}}{\text{C}}\text{–C–C–I} > \text{C–}\overset{\text{C}}{\underset{\text{C}}{\text{C}}}\text{–C–C–I} \gg \text{C–}\overset{\text{C}}{\text{C}}\text{–C–I} > \text{C–}\overset{\text{C}}{\underset{\text{C}}{\text{C}}}\text{–C–I}$$

The reaction for all practical purposes fails with any kind of substitution on the β-carbon atom.

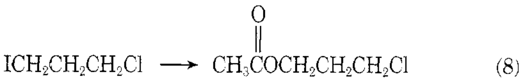
Yields. The rate of esterification and the yield of ester is significantly increased by the use of diglyme. The yields of a variety of esters have been determined using a standard procedure (10 ml of diglyme, 10 mmol of alkyl iodide, 10 mmol of mercuric carboxylate, and 1.0 mmol of "triacetoxyborane" at room temperature) and are presented in Table II. The reaction generally provides good to excellent yields of esters from unhindered primary alkyl iodides. In attempting to extend the reaction to *n*-butyl bromide and tosylate, no significant amount of *n*-butyl acetate was obtained. However, boron trifluoride catalysis of the *n*-butyl bromide reaction did give a 20% yield of *n*-butyl acetate. This tremendous difference in relative rates has allowed the selective esterification of 1-chloro-3-iodopropane in 95% yield (eq 8).

Table II
The Direct Esterification of Primary Alkyl Halides by Mercuric Carboxylates

$$RX + Hg(O_2CR') \xrightarrow[\text{diglyme}]{B(O_2CR')_3} RO_2CR'$$

Alkyl halide (Registry no.)	Carboxylate[a] (Registry no.)	Yield of ester, %[b]
n-Butyl iodide (542-69-8)	Acetate (1600-27-7)	99
n-Decyl iodide (2050-77-3)		96
Isoamyl iodide (541-28-6)		96
3,3-Dimethyl-1-butyl iodide (15672-88-5)		88
2-Phenylethyl iodide (17376-04-4)		61
Isobutyl iodide (78-86-4)		14
Neopentyl idodide (15501-33-4)		22
1-Chloro-3-iodopropane (6440-76-7)		95
Ethyl iodide (75-03-6)	Butyrate (19348-32-4)	99
n-Butyl iodide	Butyrate	99
n-Butyl iodide	Benzoate (583-15-3)	54[c]
n-Butyl bromide (109-65-9)	Acetate	18[d]

[a] Mercuric carboxylate and triacyloxyborane. [b] Glpc analysis after 24 hr. [c] At 0.5 equiv of tribenzoyloxyborane. [d] Analysis after 190 hr.



$$ICH_2CH_2CH_2Cl \longrightarrow CH_3\overset{\overset{\displaystyle O}{\|}}{C}OCH_2CH_2CH_2Cl \qquad (8)$$

Other mercuric carboxylates may also be utilized in these esterification reactions. Thus, ethyl iodide produced a 99% yield of ethyl butyrate upon treatment with mercuric butyrate and "tributyloxyborane." The preparation of benzoates, however, proved more difficult. By increasing the amount of "tribenzoyloxyborane" (0.5 equiv) one can obtain a respectable 54% yield of *n*-butyl benzoate from *n*-butyl iodide. The use of mercuric salts of strongly acidic carboxylic acids, such as trifluoroacetic acid, gives sharply reduced yields. Elimination and not substitution appears to predominate. Major limitations to these reactions are evident.

Secondary Alkyl Halides. A brief survey of the esterification of secondary alkyl halides has been undertaken. The reactions of *sec*-butyl and cyclohexyl halides with mercuric acetate in diglyme with and without a catalyst have been examined and are included in Table III.

Of the cyclohexyl halides only the iodide reacts in the absence of a catalyst. However, no ester was observed. Addition of "triacetoxyborane" facilitates reaction, but the yields of ester from both the bromide and iodide were less than 5%. The chloride still failed to react.

The *sec*-butyl halides produced similar results, although the yields were somewhat improved. Thus, only the iodide reacted with mercuric acetate in the absence of a catalyst (32%). The addition of "triacetoxyborane" produced similar results with the iodide (30%) but facilitated conversion of the bromide into *sec*-butyl acetate (34%). The chloride remained unreactive. Mercuric acetate and boron trifluoride produced only 6% of the ester from *sec*-butyl chloride. The use of THF gave slightly higher yields in most cases.

Although secondary alkyl halides are more reactive than primary halides, the yields are very poor, and direct esterification of secondary alkyl halides by mercury carboxylates does not appear synthetically useful.

Tertiary Alkyl Halides. In view of the results obtained with secondary alkyl halides, it was anticipated that tertiary halides would show high reactivity toward mercuric acetate. However, only trace amounts of the corresponding esters were anticipated. This later pessimism proved unwarranted (Table III). *tert*-Butyl iodide, bromide, and chloride react with mercuric acetate in the absence of a catalyst in diglyme to produce 68, 72, and 54% yields of *tert*-butyl acetate, respectively. THF gives lower yields in all cases. Addition of "triacetoxyborane" catalyst to these reactions fails to improve the yields of ester from the iodide or bromide. However, *tert*-butyl chloride now reacts readily to give a 73% yield.

Table III
The Direct Esterification of Alkyl Halides by Mercuric Acetate

$$RX + Hg(OAc)_2 \xrightarrow[\text{diglyme}]{} ROAc$$

Alkyl halide (Registry no.)	$B(OAc)_3$ catalyst	Yield of alkyl acetate, %
Cyclohexyl chloride (542-18-7)	−	0
chloride	+	0
bromide (108-85-0)	−	0
bromide	+	1
iodide (626-62-0)	−	0
iodide	+	0
sec-Butyl chloride (513-36-0)	−	0
chloride	+	1
bromide (78-77-3)	−	1
bromide	+	34
iodide (513-38-2)	−	32
iodide	+	30
tert-Butyl chloride (507-20-0)	−	54
chloride	+	73
bromide (507-19-7)	−	72
bromide	+	69
iodide (558-17-8)	−	68
iodide	+	54
Allyl chloride (107-05-1)	−	0
chloride	+	59
bromide (106-95-6)	−	5
bromide	+	77
iodide (556-56-9)	−	73
iodide	+	82
Benzyl chloride (100-44-7)	−	1
chloride	+	98
bromide (100-39-0)	−	71
bromide	+	95
iodide (620-05-3)	−	57
iodide	+	70
α-Phenethyl chloride (1459-15-0)	−	78
chloride	+	97

Allylic and Benzylic Halides. It was of obvious interest to see if allylic halides could also be conveniently esterified by mercury carboxylates. Allyl chloride, bromide, and iodide were chosen as representative allylic halides. Only the iodide reacts readily with mercuric acetate in the absence of a catalyst in diglyme (73% allyl acetate). The catalyst promotes rapid reaction of all three halides. Diglyme again results in higher yields than THF. Allyl chloride, bromide, and iodide produced 59, 77, and 82% yields of allyl acetate, respectively.

A similar pattern was observed with the benzyl halides. Both benzyl iodide and bromide react with mercuric acetate in diglyme to give 57 and 71% yields of benzyl acetate, respectively. The chloride fails to react. All three halides (Cl, Br, I) react smoothly with mercuric acetate in diglyme in the presence of "triacetoxyborane" to produce 98, 95, and 56% yields of the ester, respectively. THF again results in lower yields. α-Phenethyl chloride gives a 97% yield of α-phenethyl acetate in diglyme.

Stereochemistry. In order to determine the stereochemical course of these esterification reactions, we have examined the esterification of (+)-(*R*)-α-phenethyl chloride. The chloride was prepared from the corresponding alcohol essentially as described previously.[4] Ten millimoles of 28% optically pure chloride ($[\alpha]_D$ +125.4°)[5] was subjected to our standard catalytic esterification procedure. Glpc purification gave (−)-(*S*)-α-phenethyl acetate ($[\alpha]_D^{21}$ −130.5)[6] of 1.7% optical purity, indicating only very slight inversion of configuration in this reaction. Racemization predominates.

Mechanism. Although a minimum of experimental results are presently at hand, some comment on the mechanism of these esterification reactions seems warranted. The relative reactivities of the alkyl halides exhibit characteristics of both SN1 and SN2 reactions. Thus, the relative rates observed with the primary iodides is indicative of a bimolecular nucleophilic substitution reaction. The increasing reactivity of the halides in the order iodide > bromide > chloride is also consistent with an SN2 reaction. The greater reactivity of the more highly substituted halides (tertiary > secondary > primary) is more in keeping with a unimolecular nucleophilic substitution reaction. Full kinetic details unfortunately are not presently available due to the heterogeneity of these reactions. The nearly complete racemization of α-phenethyl chloride is also consistent with an SN1 type reaction. It is, however, entirely possible that the mechanism of these reactions changes in proceeding from the less reactive primary alkyl halides to the highly reactive allylic and benzylic halides.

It is likely that the major side reaction competing with esterification is elimination to the alkene,[7] although this has not been studied. In general we observe that the boron trifluoride catalyst gives much lower yields than "triacetoxyborane." Similar results are observed in going from mercuric acetate to mercuric trifluoroacetate. The yields of ester also generally decrease in the order chloride > bromide > iodide. Thus, by increasing the electrophilicity of the mercury salt or the leaving ability of the halide, we sharply reduce the yield of ester probably due to ionization followed by elimination.

In this respect it was anticipated that the tertiary halides would undergo complete elimination and the yields of ester would be very low. This has not been observed, however. It seemed plausible that the tertiary esters might be arising instead from an elimination of the hydrogen halide followed by addition of the carboxylic acid as outlined below (eq 9 and 10). In order to test this possibility we have run the esterification of *tert*-butyl chloride in the presence of an excess of styrene as a trap for the *in situ* generated acetic acid. We have also attempted the esterification of α-phenethyl chloride in the presence of an excess of isobutylene. Although the yields of esters were reduced in both cases, none of the ester expected upon addition of acetic acid to the alkene could be observed. This appears to rule out an elimination–addition mechanism and suggests that direct substitution may indeed be occurring in the esterification of even tertiary halides. However, it remains somewhat a puzzle why the yields of tertiary esters should exceed those of the secondary esters which would be expected to undergo substitution more readily.

Table IV
The Direct Esterification of Alkyl Halides by Sodium Carboxylates

$$RX + NaO_2CR' \xrightarrow[HMPA]{} RO_2CR'$$

Alkyl halide (Registry no.)	Sodium carboxylate (Registry no.)	Yield of ester, %[a]
n-Butyl iodide	Acetate (127-09-3)	99
iodide	Benzoate (532-32-1)	96
iodide	Trifluoroacetate (2923-18-4)	70–80
bromide	Acetate	96
chloride (109-69-3)		29
sec-Butyl iodide		38
bromide		19
chloride		0
Cyclohexyl iodide		0
bromide		0
chloride		0
tert-Butyl iodide		0
bromide		0
chloride		0
Allyl iodide		90
bromide		96
chloride		76
Benzyl iodide		62
bromide		92
chloride		93
α-Phenethyl chloride		5

[a] Glpc analysis after 24 hr.

$$(CH_3)_3CX + Hg(OAc)_2 \longrightarrow (CH_3)_2C{=}CH_2 + XHgOAc + HOAc \quad (9)$$

$$(CH_3)_2C{=}CH_2 + HOAc \longrightarrow (CH_3)_3COAc \quad (10)$$

Sodium Carboxylates

Numerous examples of the esterification of alkyl halides by sodium carboxylates have appeared.[8–11] Unfortunately, most of these procedures have had as their major objective the conversion of a particular carboxylic acid into the corresponding methyl or ethyl ester in high yield. Consequently, a large excess of methyl or ethyl iodide has been employed obscuring the scope of these reactions. In those cases where other esters have been prepared, the alkyl halide was again used in large excess. In no case have these reactions been employed to effect high conversions of alkyl halides into esters.

In order to compare and determine the synthetic utility of the mercury esterification reactions, we have had to systematically examine the corresponding reactions with sodium carboxylates (Table IV). *n*-Butyl iodide fails to react

Table V
The Direct Esterification of Alkyl Halides by Silver Carboxylates

$$RX + AgO_2CR' \xrightarrow[THF]{} RO_2CR'$$

Alkyl halide	Silver carboxylate (Registry no.)	Catalyst	Yield of ester, %[a]	Comment
n-Butyl iodide	Acetate (563-63-3)		5	Room temperature
iodide			77	Reaction refluxed
iodide			100	HMPA solvent
iodide		$B(OAc)_3$	77	
iodide		BF_3	12	
iodide	Benzoate (532-31-0)	$B(O_2CC_6H_5)_3$	20	
bromide	Acetate	$B(OAc)_3$	0	No reaction
chloride		$B(OAc)_3$	0	No reaction
Ethyl iodide	Trifluoroacetate (2966-50-9)	$B(O_2CCF_3)_3$	10	
Cyclohexyl iodide			11	
iodide		$B(OAc)_3$	8	
bromide		$B(OAc)_3$	2	
chloride		$B(OAc)_3$	0	No reaction
sec-Butyl iodide			26	
iodide		$B(OAc)_3$	44	
bromide			14	
bromide		$B(OAc)_3$	28	
chloride			0	No reaction
chloride		$B(OAc)_3$	0	No reaction
tert-Butyl iodide			39	
bromide			41	
chloride			47	Reaction refluxed
chloride		$B(OAc)_3$	38	
Allyl iodide			57	
iodide		$B(OAc)_3$	31	
bromide		$B(OAc)_3$	24	
chloride		$B(OAc)_3$	3	
Benzyl iodide			28	
bromide			52	
chloride		$B(OAc)_3$	5	
α-Phenethyl chloride		$B(OAc)_3$	37	

[a] Glpc analysis after 24 hr.

with sodium acetate in THF with or without "triacetoxyborane." If the reaction is carried out in HMPA instead, a 99% yield of *n*-butyl acetate is realized. Sodium benzoate gives a comparable yield (96%). Even sodium trifluoroacetate gives good yields (70–80%), although a considerable amount of the iodide remains even after reaction for a couple of days at room temperature. Doubling the amount of the sodium salt fails to increase the yield. *n*-Butyl bromide (96%) and chloride (29%) also react with sodium acetate in HMPA to give *n*-butyl acetate.

None of the cyclohexyl halides gave any cyclohexyl acetate in 24 hr, and significant amounts of these halides remained unreacted. Under identical conditions, *sec*-butyl chloride failed to react, and the bromide (19%) and iodide (38%) give only poor yields with much of the starting halide still present.

All three *tert*-butyl halides (chloride, bromide, iodide) failed to react completely and gave only traces of *tert*-butyl acetate.

All of the allyl and benzyl halides gave good to excellent yields of allyl and benzyl acetate, respectively: allyl chloride (76%), bromide (96%), iodide (90%), and benzyl chloride (93%), bromide (92%), iodide (62%). However, α-phenethyl chloride gave only 5% of the acetate.

The esterification of alkyl halides with sodium carboxylates works well only in those cases where bimolecular nucleophilic substitution reactions are particularly facile. HMPA is necessary to achieve high yields. In few cases do the actual yields exceed those obtained using the mercury catalyzed reactions. However, these reactions do appear more widely applicable with respect to the types of sodium carboxylates and halides which can be employed.

Silver Carboxylates

Silver acetate has been previously utilized to achieve the direct esterification of alkyl halides.[12–16] Again, however, no systematic survey of the synthetic utility of these reactions has ever appeared. We have briefly examined the generality of these reactions (Table V).

The esterification of primary alkyl halides by silver acetate closely parallels the mercuric acetate reactions. Although *n*-butyl iodide gives only a 5% yield of *n*-butyl acetate after 24 hr at room temperature in THF, a good yield is obtained upon refluxing (77%). Addition of 10% "triacetoxyborane" again greatly facilitates the reaction at room temperature (77%). Boron trifluoride catalysis sharply reduces the yield (12%). The silver benzoate (20%) and trifluoroacetate (10% from ethyl iodide) catalyzed reactions again fail. *n*-Butyl bromide and chloride fail to react.

The secondary alkyl halides again give poor results. Of the cyclohexyl halides only the iodide reacts with silver acetate in the absence of "triacetoxyborane" (11%). Cyclohexyl iodide (8%) and bromide (2%) react in the presence of the catalyst, but the chloride remains unreactive. The *sec*-

butyl halides in THF again give higher yields with (Br, 28%; I, 44%) or without the catalyst (Br, 14%; I, 26%). The chloride fails to react.

tert-Butyl iodide (39%) and bromide (41%) react in minutes with silver acetate in THF. The chloride requires either refluxing (47%) or the addition of "triacetoxyborane" (38%). The yields from mercury carboxylates are higher in almost every case.

Of the allyl halides only the iodide (57%) reacts in the absence of a catalyst. "Triacetoxyborane" in THF again significantly increases the reactivity (I, 31%; Br, 24%; Cl, 3%).

Both benzyl iodide (28%) and bromide (52%) react with silver acetate at room temperature in THF. Although benzyl chloride fails to react, α-phenethyl chloride partially reacts to give a 37% yield of the acetate. Catalysis of the benzyl chloride reaction fails (5%).

Although the silver carboxylates show a pattern very similar to those of the mercuric carboxylates, the yields are lower in practically every case. The greater cost of these salts also makes them of questionable utility for the direct esterification of alkyl halides.

Experimental Section

General Comments. THF, diglyme, and HMPA were distilled from lithium aluminum hydride and stored under nitrogen. All other solvents were used directly as obtained commercially. All alkyl halides used are either commercially available or readily available by standard synthetic procedures. The commercial materials were usually used directly as obtained unless they were obviously quite colored in which case they were distilled before use. The "borane" used was prepared by the procedure of Brown and Sharp.[17] The boron trifluoride, boric acid, and oxide were used directly as obtained commercially, as were the sodium and silver salts. Mercuric acetate (J. T. Baker) was pumped free of acetic acid overnight on a vacuum pump before using. The preparation of the other mercury carboxylates is described elsewhere.[18]

General Esterification Procedures. The following general procedure was employed for most esterification reactions. In a 50-ml round-bottom flask with septum inlet was placed 10 mmol of the metal carboxylate and the flask was flushed with nitrogen. Approximately 1 ml of an appropriate hydrocarbon glpc internal standard was added followed by 10 ml of the appropriate solvent. The reaction mixture was cooled by stirring in an ice bath while the alkyl halide was slowly added. After addition the flask was placed in a room temperature water bath, and microliter samples were taken at the appropriate time and analyzed by glpc. The ester could be isolated by filtering, adding ether, washing with water and aqueous sodium thiosulfate, drying, and distilling.

The triacyloxyborane catalyzed reactions were run essentially as indicated above; however, the catalyst was prepared as indicated below in the appropriate solvent, and the metal salt and alkyl halide were added to the catalyst.

Catalyst Preparation. One millimole of catalyst was used in all catalytic reactions. "Triacetoxyborane" can be prepared by any of the following methods: (1) slow addition of "borane" in THF to acetic acid (3 mmol) in diglyme or THF at −78° and allowing to slowly warm to room temperature, (2) slow addition of "borane" (1 mmol) in THF to mercuric acetate (3 mmol) at −78° and slow warming to room temperature, or (3) addition of acetic anhydride (1.5 mmol) to boric oxide, B_2O_3 (0.5 mmol), and refluxing 24 hr. The various unsuccessful boron trifluoride exchange reactions were also run stoichiometrically so as to generate 1 mmol of the catalyst.

Stereochemistry. (+)-(*R*)-α-Phenethyl alcohol was obtained from Norse Laboratories and used directly. (+)-(*R*)-α-Phenethyl chloride was prepared as follows.[4] To a dry 50-ml round-bottom flask was added 15 ml of freshly distilled thionyl chloride and 15 ml of pentane. To this solution was slowly added 6.1 g (50 mmol) of (+)-(*R*)-α-phenethyl alcohol. A drying tube was placed on the flask and the reaction was allowed to stir overnight. Water (10 ml) was slowly added to the reaction mixture and the reaction mixture was stirred until no more gas evolved. The organic layer was washed with four 10-ml portions of water. The aqueous layers were combined and reextracted with pentane. The combined organic layers were washed with three 10-ml portions of 10% aqueous sodium carbonate solution and dried overnight over anhydrous Na_2SO_4. After filtration, the pentane was removed and the chloride distilled under vacuum: bp 79–80° (16 mm), yield 60%, $[\alpha]D^{25}$ +31.06° (27.7% optical purity).

The esterification was run as follows. To a dry 50-ml round-bottom flask with a septum inlet under nitrogen was added 17.5 ml of dry diglyme and 5.33 mmol of acetic acid. This solution was cooled to −78° and 1.77 mmol of "borane" (0.76 ml of 2.33 *M*) was added. The cooling bath was removed and the mixture was allowed to slowly warm to room temperature. After 3 hr, the mixture was cooled to 0° and 17.7 mmol of mercuric acetate (5.65 g) was added while back-flushing with nitrogen. Then 17.7 mmol of (+)-(*R*)-α-phenethyl chloride (2.49 g) was added by syringe. The reaction mixture was stirred overnight at room temperature. Eighty-five milliliters of ether was added to the reaction mixture and the organic layer was washed with five 25-ml portions of water, and the aqueous portions were reextracted with 35 ml of ether. The combined organic portions were washed with five 35-ml portions of a saturated $Na_2S_2O_3$ solution, and then with two 35-ml portions of a saturated $NaHCO_3$ solution, and finally with five 35-ml portions of water. After having dried over anhydrous Na_2SO_4, the ester solution was filtered, stripped of solvent, and isolated by preparative glpc (160° on a 10% UCON polar column). The (−)-(*S*)-α-phenethyl acetate obtained before and after glpc had essentially the same optical rotation ($[\alpha]D^{25}$ −2.19°) indicating approximately 1.7% optical purity. Predominant racemization with very slight inversion occurs. All readings were taken on an O. C. Rudolph and Sons Inc. Model 63 polarimeter using the sodium D line with benzene as the solvent.

Examination of Possible Elimination–Addition Mechanism. The "triacetoxyborane" catalyzed esterification of *tert*-butyl chloride (10 mmol) was run exactly as indicated above with styrene (20 mmol) added. A 31% yield of *tert*-butyl acetate was observed and no α-phenethyl acetate was evident. In a similar manner α-phenethyl chloride (10 mmol) was esterified in the presence of isobutylene (60 mmol). A 30% yield of α-phenethyl acetate was obtained and no *tert*-butyl acetate was observed.

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