Carbonyl Chemistry

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α-Alkylation of Carbonyl Compounds by Direct Addition of Alcohols to Enol Acetates**

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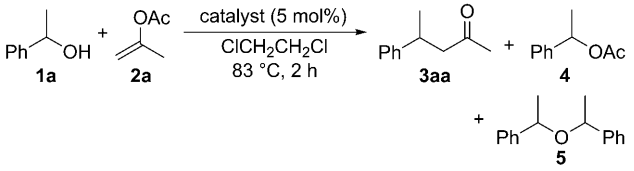
The catalytic α-alkylation of carbonyl compounds has contributed remarkably to the development of organic synthesis, and the reaction of enolate derivatives with alkyl electrophiles is a powerful alkylation method.[1] Alcohols are appealing electrophiles, as they are plentiful and readily synthesized; however, the direct use of alcohols is effectively prevented by the fact that the hydroxy group is a particularly poor leaving group, and it often tends to decomposition of catalysts and active intermediates.[2,3] The α-alkylation of monocarbonyl compounds using an alcohol remains problematic whereas many research groups have reported the direct alkylation of 1,3-dicarbonyl compounds.[4] The transfer hydrogenation method has achieved some direct α-alkylations of ketones, although this is only applicable to primary alcohols and requires a strong base to generate the enolate species.[5] Hidai, Uemura et al. published a ruthenium-catalyzed system, which was limited to the reactions of 1-arylpropargylic alcohols, in the presence of an excess of ketone.[6] Methods using metal enolates suffer from decomposition of the enolates by the hydroxy group, critically narrowing the scope of available alcohol substrates;[7] furthermore, the α-alkylation of aldehydes has not been investigated to the degree that ketones have.[8] Herein, we report a synthesis of α-alkylated carbonyl compounds from enol acetates and alcohols, catalyzed by InI_3, $GaBr_3$, or $FeBr_3$, in which the α-alkylation of not only ketones but also of aldehydes has been successfully achieved. Furthermore, the exploitation of enol acetates as readily available, stable, and easily-handled enolate reagents enhances the practicality of this α-alkylation method.[9] We employed Lewis acids to selectively activate alcohols and thereby suppress side reactions, such as transesterification.

We recently found that the moderate Lewis acidity of indium trihalide effectively promoted the direct coupling of alcohols with nucleophiles, such as allyl and alkenyl silanes;[3,4e] these results suggested that indium trihalide selectively interacts with hydroxy groups in the presence of other oxygen-containing moieties such as carbonyl groups.

As a model reaction, 1-phenylethanol (**1a**) and 2-propenyl acetate (**2a**) were heated to reflux in 1,2-dichloroethane in the presence of 5 mol% indium trihalide to afford the desired product **3aa** in satisfactory yields, of which InI_3 gave the highest (83%; Table 1, entries 1–3). By contrast, the more

Table 1: Effects of catalyst and solvent in the reaction of 1-phenylethanol (**1a**) with isopropenyl acetate (**2a**).[a]



Entry	Catalyst	Yields [%]		
		3aa	**4**	**5**
1	$InCl_3$	60	0	0
2	$InBr_3$	70	0	0
3	InI_3	83	0	0
4	$In(OTf)_3$	25	0	0
5	$GaCl_3$	62	0	0
6	$GaBr_3$	73	0	0
7	$FeBr_3$	77	0	0
8	$FeCl_3$	48	0	0
9	$FeBr_2$	38	31	31
10	$FeCl_2$	0	17	66
11	$BF_3{\cdot}OEt_2$	0	46	43
12	$AlCl_3$	0	10	27
13	$TiCl_4$	0	34	0
14	$Sc(OTf)_3$	25	0	0
15	$RuCl_3$	0	6	35
16	$Cu(OTf)_2$	7	0	0
17[b]	CH_3COOH	0	0	0
18[c]	InI_3	55	0	0
19[d]	InI_3	50	0	0
20[e]	InI_3	64	30	6

[a] Reaction conditions: **1a** (1 mmol), **2a** (2 mmol), catalyst (5 mol%), $ClCH_2CH_2Cl$ (2 mL), 83 °C, 2 h. [b] 99% recovery of **1a**. [c] $CF_3C_6H_5$ used instead of $ClCH_2CH_2Cl$. [d] Toluene used instead of $ClCH_2CH_2Cl$. [e] CH_2Cl_2 used instead of $ClCH_2CH_2Cl$; 40 °C.

Lewis acidic $In(OTf)_3$ was less effective, giving only a 25% yield of the α-alkylated product (Table 1, entry 4). Examination of various Lewis acids revealed that gallium and iron halides also had high catalytic abilities (Table 1, entries 5–10); however, representative strong Lewis acids such as $BF_3{\cdot}OEt_2$, $AlCl_3$, and $TiCl_4$ all promoted transesterification (**4**) and/or dimerization (**5**) of the parent alcohol, with no formation of

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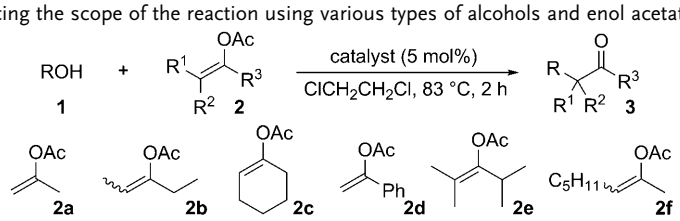
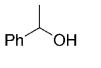
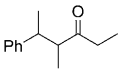
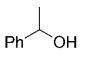
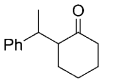
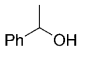
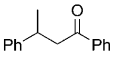
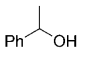
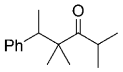
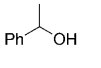
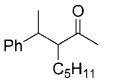
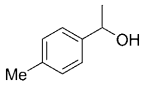
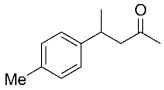
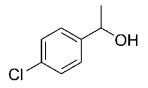
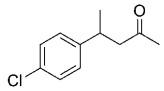
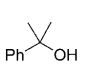
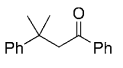
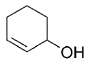
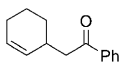
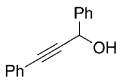
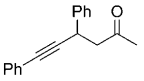
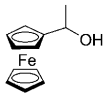
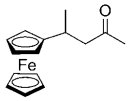
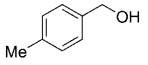
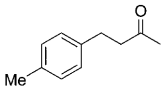
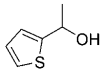
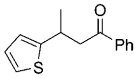
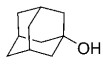
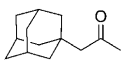
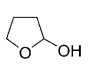
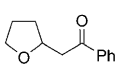
the desired product **3aa** (Table 1, entries 11–13). $Sc(OTf)_3$, $RuCl_3$, and $Cu(OTf)_2$, which are known to catalyze the coupling reaction of alcohols with 1,3-dicarbonyl compounds, was a poor catalyst (Table 1, entries 14–16);[4n] acetic acid, generated in situ, resulted in no reaction (Table 1, entry 17). Trifluorotoluene, toluene, and dichloromethane were also tested as the solvent and gave satisfactory results (Table 1, entries 18–20).[10] After analyzing these results, InI_3, $GaBr_3$, and $FeBr_3$ were taken forward as promising catalysts for further investigations.

We then assessed the scope and limitations of the alcohols **1** and enol acetates **2** (Table 2). In almost all cases, InI_3, $GaBr_3$, and $FeBr_3$ showed similar catalytic activity. Enol acetates **2b**, **2c**, and **2d**, bearing one or no substituents at the 2-position, gave high yields (Table 2, entries 1–3); disubstituted acetate **2e** afforded ketone **3ae**, including formation of a new quaternary carbon center, although the yields were poorer because of steric hindrance (Table 2, entry 4). Enol acetate **2f**, which was derived from an unsymmetrical ketone, afforded the corresponding product **3af** with no isomerization of the enol acetate (Table 2, entry 5). These results showed that the reaction system had a wide scope of applicable enol acetates. Various types of alcohols were also examined and found to be exploitable. Secondary benzylic alcohol **1b**, bearing an electron-donating group, gave the product **3ba** almost exclusively, whereas the electron-withdrawing chloro substituent decreased the yield (ca. 40%; Table 2, entries 6 and 7). Tertiary benzylic alcohol **1d** was found to react at room temperature, furnishing **3dd** in 74–792% yield (Table 2, entry 8). Allylic, propargylic, and ferrocenyl alcohols **1e**–**1g** (Table 2, entries 9–11) gave satisfying results, except in the cases of propargylic alcohol **1f** and ferrocenyl alcohol **1g** catalyzed by $FeBr_3$ (Table 2, entries 10, 11). By contrast, primary benzylic alcohol **1h** was catalysed solely in the presence of

Table 2: Testing the scope of the reaction using various types of alcohols and enol acetates.[a]



Entry	1		2	Product 3		Catalyst	Yield [%][b]
1		**1a**	**2b** (69:31)		**3ab**	InI_3 $GaBr_3$ $FeBr_3$	80 (60:40) 86 (60:40) 92 (62:38)
2		**1a**	**2c**		**3ac**	InI_3 $GaBr_3$ $FeBr_3$	86 (55:45) 75 (59:41) 80 (53:47)
3		**1a**	**2d**		**3ad**	InI_3 $GaBr_3$ $FeBr_3$	92 98 92
4		**1a**	**2e**		**3ae**	InI_3 $GaBr_3$ $FeBr_3$	28 47 45
5		**1a**	**2f** (67:33)		**3af**	InI_3 $GaBr_3$ $FeBr_3$	86 (58:42) 94 (57:43) 81 (56:44)
6		**1b**	**2a**		**3ba**	InI_3 $GaBr_3$ $FeBr_3$	97 97 82
7		**1c**	**2a**		**3ca**	InI_3 $GaBr_3$ $FeBr_3$	43 38 37
8[c]		**1d**	**2d**		**3dd**	InI_3 $GaBr_3$ $FeBr_3$	75 79 74
9		**1e**	**2d**		**3ed**	InI_3 $GaBr_3$ $FeBr_3$	82 89 77
10[d]		**1f**	**2a**		**3fa**	InI_3 $GaBr_3$ $FeBr_3$	96 74 0
11[e]		**1g**	**2a**		**3ga**	InI_3 $GaBr_3$ $FeBr_3$	82 77 26
12		**1h**	**2a**		**3ha**	InI_3 $GaBr_3$ $FeBr_3$	40 0 0
13[f]		**1i**	**2d**		**3id**	InI_3 $GaBr_3$ $FeBr_3$	64 69 67
14[g]		**1j**	**2a**		**3ja**	InI_3 $GaBr_3$ $FeBr_3$	99 99 99
15[h]		**1k**	**2d**		**3kd**	InI_3 $GaBr_3$ $FeBr_3$	62 63 68

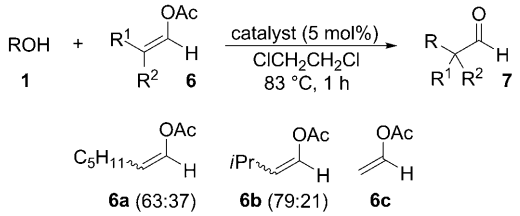
[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), catalyst (5 mol%), $ClCH_2CH_2Cl$ (2 mL), 83 °C. [b] Diastereomeric ratio is shown in parentheses. [c] CH_2Cl_2 (2 mL), room temperature, **2d** (3 mmol) was slowly added over 30 min. [d] MeCN (2 mL) used instead of $ClCH_2CH_2Cl$; room temperature. [e] **2a** (5 mmol), MeCN (2 mL) used instead of $ClCH_2CH_2Cl$; 81 °C. [f] **2d** (5 mmol), MeCN (2 mL) used instead of $ClCH_2CH_2Cl$; room temperature. **1i** was added slowly over 30 min. [g] 10 mol% catalyst used. [h] MeCN (2 mL) used instead of $ClCH_2CH_2Cl$; 30 min, 81 °C.

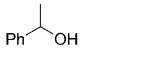
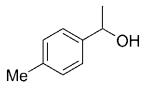
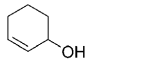
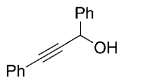
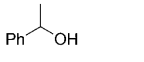
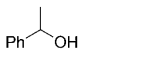
InI_3 to afford the adduct **3ha** in 40% yield (Table 2, entry 12). These results suggested that the mechanism went via a carbocation intermediate, and that InI_3 could be a more general catalyst than either $GaBr_3$ or $FeBr_3$. The reaction of alcohol **1i**, which bears a thiophene moiety, proceeded successfully without deactivation of the metal halide catalyst by the sulfur atom (Table 2, entry 13). 1-Adamantanol **1j** gave the desired product **3ja** in quantitative yield (Table 2, entry 14), although the simple aliphatic alcohol, 2-methyl-4-phenyl-2-butanol, gave no product. Hemiacetal **1k** was effectively transformed into the desired ketone **3kd** without ring cleavage (Table 2, entry 15).

We then focused on the reaction of an aldehyde-derived enol acetate because the reported precedent was crucially limited to a combination of highly reactive 1,1-diarylmethanols.[8] The reaction of heptanal-derived enol acetate **6a** with 1-phenylethanol **1a** provided the α-alkylated aldehyde **7aa** in high yields (Table 3, entry 1). Other benzylic, allylic, and propargylic alcohols smoothly furnished their corresponding aldehydes, **7ba**, **7ea**, and **7fa** (Table 3, entries 2–4). As for the scope of enol acetates, the reactions using isovaleraldehyde and acetaldehyde-derived enol acetates **6b** and **6c** proceeded successfully (Table 3, entries 5,6). Furthermore, direct isolation of the aldehyde products is indicative of the mildness of these Lewis acid catalysts.

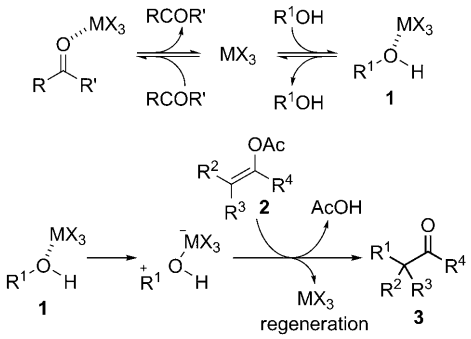
A plausible reaction mechanism is given in Scheme 1. In the cases of InI_3, $GaBr_3$, and $FeBr_3$, the metal halides (MtX_3) are weakly coordinated by oxygen atoms on either the alcohol

Table 3: Reactions using aldehyde-derived enol acetates **6**.[a]



Entry	1		6	Product	Catalyst	Yield [%]
1		**1a**	**6a**	**7aa**	InI_3	91 (55:45)
					$GaBr_3$	75 (60:40)
					$FeBr_3$	84 (61:39)
2		**1b**	**6a**	**7ba**	InI_3	78 (60:40)
					$GaBr_3$	79 (63:37)
					$FeBr_3$	78 (66:34)
3		**1e**	**6a**	**7ea**	InI_3	76 (55:45)
					$GaBr_3$	59 (54:46)
					$FeBr_3$	57 (58:42)
4[b]		**1f**	**6a**	**7fa**	InI_3	74 (54:46)
					$GaBr_3$	88 (53:47)
5		**1a**	**6b**	**7ab**	InI_3	28 (58:42)
					$GaBr_3$	54 (56:44)
					$FeBr_3$	49 (62:38)
6		**1a**	**6c**	**7ac**	InI_3	47
					$GaBr_3$	16
					$FeBr_3$	40

[a] Reaction conditions: **1** (1 mmol), **6** (5 mmol), catalyst (5 mol%), $ClCH_2CH_2Cl$ (2 mL), 83 °C, 1 h. [b] MeCN was used instead of $ClCH_2CH_2Cl$.



Scheme 1. Proposed reaction mechanism.

(**1**) or carbonyl moieties (enol acetate **2**, product **3**, or acetic acid). When MtX_3 interacts with alcohol **1**, a carbocation (R^+) is generated.[11] The electrophilic R^+ is subsequently attacked by enol acetate **2** to afford product **3** with the expulsion of acetic acid and regeneration of MtX_3.[12] By contrast, Lewis acids which have a high oxophilicity, such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $TiCl_4$, and $In(OTf)_3$, are too strongly coordinated by some oxygen moieties to act as a catalyst. Therefore, tolerance of protic conditions and a moderate Lewis acidity of MtX_3 are the particularly important factors in this system.

In summary, we have developed a new procedure for the α-alkylation of aldehydes and ketones that involves the direct use of alcohols and enol acetates in the presence of either InI_3, $GaBr_3$, or $FeBr_3$ catalysts. This reaction is applicable to various types of alcohols and enol acetates, and the synthesis of α-alkylated aldehydes is particularly noteworthy. Further investigation to elucidate the reaction mechanism is underway.

Experimental Section

Typical procedure for the reaction of **1a** with **2a** (Table 1): **1a** (1 mmol) was added to a mixture of catalyst (0.05 mmol) and **2a** (2 mmol) in 1,2-dichloroethane (2 mL) under an inert nitrogen atmosphere. The reaction mixture was stirred at 83 °C for 2 hours, then allowed to cool before diethyl ether (10 mL) and saturated $NaHCO_3$aq (10 mL) were added. The solution was extracted with diethyl ether, the organic layer dried over $MgSO_4$, and the solvent removed under reduced pressure to afford the crude product, which was analyzed by NMR spectroscopy.

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