

# Evaluating Lewis acid catalyzed hydroalkylation of alkenes in neat and in ionic liquids

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## Abstract

Recent emphasis on green chemistry has called for the exploration of more environmentally friendly media such as supercritical CO<sub>2</sub> and water. Ionic liquids offer interesting alternative reaction media to volatile organic solvents due to their low vapor pressure and the possibility of recycling. Towards this end, we have explored the addition of activated methylenes to alkenes in ionic liquids and under neat conditions. These alternatives are advantageous over our previous method, which requires the use of toxic organic solvent and expensive catalysts. Our results show that 1,3-diketones can be added to alkenes in ionic liquid with the use of 10% SnBr<sub>4</sub> or under solventless conditions with 10% Cu(OTf)<sub>2</sub>. Up to 85% yield can be achieved using these new methodologies.

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## 1. Introduction

A rather common methodology in organic synthesis for the formation of a new carbon–carbon bond is the alkylation of 1,3-dicarbonyls [1]. Unfortunately, the traditional method (Fig. 1, route a) requires a stoichiometric amount of base and an organic halide, resulting in a large quantity of waste. However, a more atom-economical [2] approach entails the addition of an activated methylene of the dicarbonyl to an alkene (Fig. 1, route b). Towards this end, we [3] and others [4] have developed the highly atom-economical addition of 1,3-dicarbonyl to unsaturated molecules. While these reactions incorporate a favorable, atom-economic route to the formation of a new carbon–carbon bond, its practical application is limited due to cost of the catalyst and the environmental hazard of using methylene chloride as solvent.

The use of ionic liquid as a “greener” [5] solvent alternative has attracted considerable attention in recent years [6]. Ionic liquids are a promising extension to the library of solvents available to organic synthesis because they have negligible vapor pressure and often form biphasic systems with organic solvents and product mixtures, allowing for easy isolation of product. The use of

ionic liquids can also allow for homogeneous transition-metal catalytic reactions with remarkable improvements in yield. Furthermore, the reusability of ionic liquids reduced the amount of waste generated during synthetic processes. Herein, we describe the studies on the Lewis acid catalyzed addition 1,3-dicarbonyl compounds onto alkenes in ionic liquids and under neat conditions.

## 2. Experimental

### 2.1. General methods

All experiments were carried out under air atmosphere. Column chromatography was performed over Sorbent silica gel 30–60 μm. <sup>1</sup>H NMR spectra were acquired by Varian 400 and 100 MHz or 300 and 75 MHz, respectively, and referenced to the internal solvent signals. Starting materials and reagents were purchased from Aldrich and were used without purification.

### 2.2. Preparation of [bmim]OTf

The ionic liquid, 1-butyl-3-methylimidazolium bromide, was obtained by using the microwave method developed by Varma and Namboodiri [7] and Chan co-workers [8] with minor modifications of the protocol (Table 1). Butyl bromide (158.9 mL,

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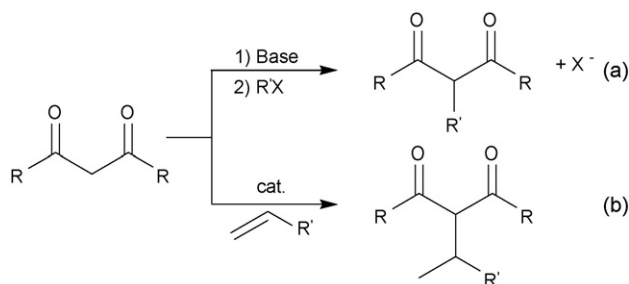


Fig. 1. Alkylation of 1,3-dicarbonyl compounds.

1.476 mol) and 1-methylimidazole (64.5 mL, 0.813 mol) were combined in a 500 mL flask fitted with a drying tube. The mixture was placed in a 60 °C water bath in a standard household 1200 W microwave oven equipped with a turntable. The microwave oven was then operated under the conditions given in Table 1, swirling the contents of the flask between runs. The mixture was poured into a separatory funnel and the excess bromobutane (top layer) removed. The ionic liquid (lower layer) was washed with ether (3 × 50 mL) to give a viscous, pale yellow liquid. This was dried under reduced pressure at room temperature overnight with stirring, and then at 50 °C with stirring for 2.5 h. The liquid solidified to give a pale yellow solid upon exposure to air. Then, 1-butyl-3-methylimidazolium bromide and an equimolar amount of silver triflate were dissolved in distilled water (10 mL/g) in separate vessels [9]. The two solutions were then combined, and the mixture was refluxed with vigorous stirring at 80–90 °C for 20 min. Once cooled to room temperature, the green precipitate was filtered off through a cotton plug and the solvent removed under reduced pressure. The product was dried under high vacuum with stirring at 80 °C until a relatively anhydrous (as seen in <sup>1</sup>H NMR spectrum) pale yellow liquid was obtained.

### 2.3. General procedure [10]

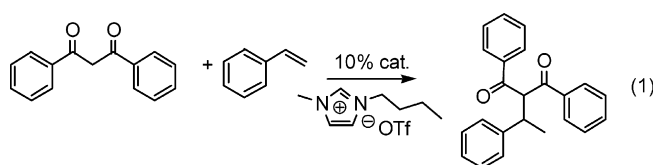
#### 2.3.1. Procedure for reactions in ionic liquid

The Lewis acid (0.025 mmol) and dibenzoylmethane (56.1 mg, 0.250 mmol) were combined in a test tube with 1 mL of [bmim]OTf ionic liquid. Styrene (43.0 μL, 0.375 mmol) was added drop-wise with stirring. The test tube was then capped and placed in an 80 °C oil bath with stirring overnight (17 h). The products of the reaction were extracted with ether (3 × 2 mL), and the solvent removed from the combined ether extracts (upper layer) under reduced pressure. The resulting yellow oil or pale yellow precipitate was diluted in chloroform-D (*ca.* 500 μL), and dichloromethane (10 μL, 0.156 mmol) was added as an internal

Table 1  
Conditions for the microwave preparation of [bmim]Br

Time (s)	Power level (%)	Power level (W)
60	10	120
180	30	360
180	30	360
180	30	360
30	30	360
50	30	360

Table 2  
Lewis acid catalyzed addition of dibenzoylmethane to styrene<sup>a</sup>



Entry	Catalyst	Yield (%) <sup>b</sup>
1	Bi(OTf) <sub>3</sub>	11
2	In(OTf) <sub>3</sub>	6
3	Ga(OTf) <sub>3</sub>	5
4	Zn(OTf) <sub>2</sub>	20
5	Cu(OTf) <sub>2</sub>	55
6	SnBr <sub>4</sub>	63
7	RuCl <sub>3</sub>	33
8	PtCl <sub>2</sub>	21
9	PdCl <sub>2</sub>	12
10	HAuCl <sub>4</sub> ·H <sub>2</sub> O	15
11	AgOTf	0

<sup>a</sup> Reactions run overnight at 80 °C.

<sup>b</sup> Yield determined by <sup>1</sup>H NMR with internal standard.

standard. <sup>1</sup>H NMR was used to calculate the percentage yield of the desired product in the crude mixture. The product was isolated using flash chromatography (60:1 hexanes:ethyl acetate to 5:1 hexanes:ethyl acetate).

#### 2.3.2. Procedure for reactions in solventless conditions

The Lewis acid (0.015 or 0.0075 mmol), diketone (0.15 mmol), and alkene (0.30 or 0.225 mmol) were combined in a small test tube and stirred for 6 h in a 50 °C (bath temperature) oil bath. The crude product mixture was diluted in a minimal amount of acetone and separated by flash chromatography (60:1 hexanes:ethyl acetate to 5:1 hexanes:ethyl acetate).

## 3. Results and discussion

Early efforts to carry out the catalyzed hydroalkylation of 1,3-diketones (Eq. (1)) in the prepared ionic liquid indicated that the AuCl<sub>3</sub>/AgOTf combined catalyst used previously was not effective in [bmim]OTf ionic liquid. Therefore, the procedure was repeated in [bmim]OTf with a variety of other Lewis acid catalysts (Table 2). Tin(IV) bromide and copper(II) triflate

Table 3  
Lewis acid catalyzed addition of dibenzoylmethane to styrene in various solvents

Entry <sup>a</sup>	Solvent	Catalyst	Molar ratio (1:2)	Yield (%) <sup>b</sup>
1	[bmim]OTf	SnBr <sub>4</sub>	1.0/1.5	63
2	[bmim]OTf	Cu(OTf) <sub>2</sub>	1.0/1.5	55
3	[bmim]BF <sub>4</sub>	SnBr <sub>4</sub>	1.0/1.5	0
4	[bmim]BF <sub>4</sub>	Cu(OTf) <sub>2</sub>	1.0/1.5	0
5	Water	Cu(OTf) <sub>2</sub>	1.0/2.0	0
6 <sup>c</sup>	Neat	Cu(OTf) <sub>2</sub>	1.0/2.0	88

<sup>a</sup> Reactions were run overnight at 80 °C with 10 mol% catalyst.

<sup>b</sup> Yield determined by <sup>1</sup>H NMR with internal standard.

<sup>c</sup> Reaction was run overnight at 50 °C with 10 mol% catalyst.

Table 4  
Metal catalyzed addition of 1,3-diketones to alkenes



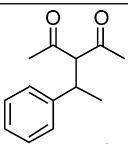

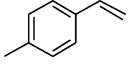
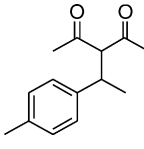

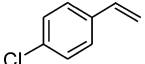
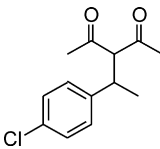


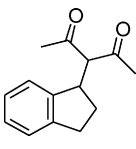


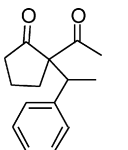
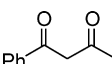
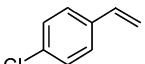
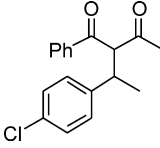
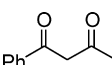

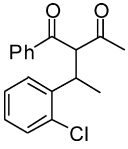
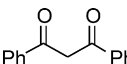

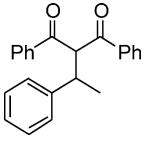
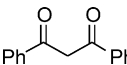
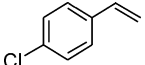
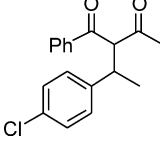
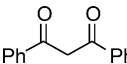

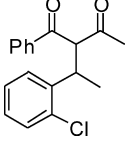
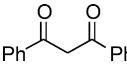
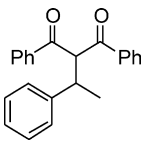
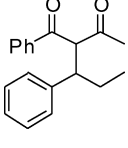
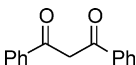

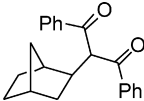
Entry	1,3-Diketone	Alkene	Product	Yield (%) <sup>a</sup>	Yield (%) <sup>b</sup>
1				32	19
2				58	0
3				49	20
4				20	9
5				15 (1:1)	10 (1:1)
6				50 (1:1)	41 (1:1)
7				8 (1:1)	11 (1:1)
8				85	60
9				85	61
10				24	11
11				5	0

Table 4 (Continued)

Entry	1,3-Diketone	Alkene	Product	Yield (%) <sup>a</sup>	Yield (%) <sup>b</sup>
12				54	31

<sup>a</sup> Isolated yield under neat conditions using 10% Cu(OTf)<sub>2</sub> at 50 °C for 6 h.

<sup>b</sup> Isolated yield using 10% SnBr<sub>4</sub> in ionic liquid at 50 °C for 6 h.

(Table 2, entries 5 and 6) appeared to be the most promising catalysts among those tested. In an effort to optimize the conditions of the copper and tin catalyzed reactions in ionic liquids, the reaction time, the amount of catalyst, and the molar ratios of the reactants were varied. Optimal yield was obtained with 10 mol% catalyst in an overnight (17 h) reaction. It was found that a 50% molar excess of styrene was necessary to limit the dimerization of styrene as a competing side reaction. Combination of the isolated product with 10 mol% catalyst in ionic liquid resulted in the formation of some starting material, indicating the reversibility of the reaction. Under these same reaction conditions, the reaction in [bmim]BF<sub>4</sub> gave no desired product with either the Tin(IV) or Cu(II) catalyst (Table 3, entries 3 and 4). In order to explore other green solvent options, we investigated the reaction in water and under neat conditions. Whereas water did not prove to be a successful solvent, the solventless condition was very promising, returning 88% yield of the desired product (Table 3, entry 6). The neat reaction with copper(II) triflate and the ionic liquid reaction with tin(IV) bromide became the focus of subsequent investigation in order to follow its “green” aims. The temperature, reaction time, and molar ratios of the reactants were varied in an effort to optimize the reaction conditions. Good yields were obtained with a 6 h reaction at 50 °C with a 50% molar excess of styrene.

These reaction conditions were applied to a variety of substrates (Table 4). The acidity of the C–H bond of the activated methylene was found to have an effect on the yield of the product. Indeed, the addition of 2,4-pentanedione to various styrenes (entries 1–4) generally gave lower yield than the addition of a more active methylene, such as 1-benzoylacetone or dibenzoyl-

methane (entries 5–12). Steric interactions also play a key role for the alkene; the addition of 2-chlorostyrene 1-benzoylacetone (entry 7) or dibenzoylmethane (entry 11) is considerably less successful than the addition of 4-chlorostyrene, which has similar electronics, to these same alkenes (entries 6 and 9). The use of electron-donating alkene (such as 4-methoxystyrene) did not lead to any conversion at all. Interestingly, the high reactivity of norbornene results in a reasonable yield of the endo product when combined with dibenzoylmethane (entry 12).

Considering trends in addition to the reversibility of the reaction, the proposed mechanism of the reaction entails the coordination of the electron-rich alkene to the metal ([Sn] or [Cu]) centre. The diketone then adds to the metal coordinated alkene at the more substituted end to give the alkylmetal intermediate. Protonolysis of the carbon–metal bond then generates the final product (Fig. 2).

#### 4. Conclusion

In summary, the copper triflate-catalyzed reaction in neat and the tin bromide-catalyzed reaction in ionic liquid are promising “green” alternatives for the addition of dibenzoylmethane onto styrene. These conditions eliminate the use of halogenated solvent. In applying these conditions to a variety of other substrates, it appears that the overall versatility of the reaction is limited at this stage. Consequently, the search for a more effective catalyst to further optimize such a hydroalkylation both in neat and in ionic liquids is in progress.

#### Acknowledgments

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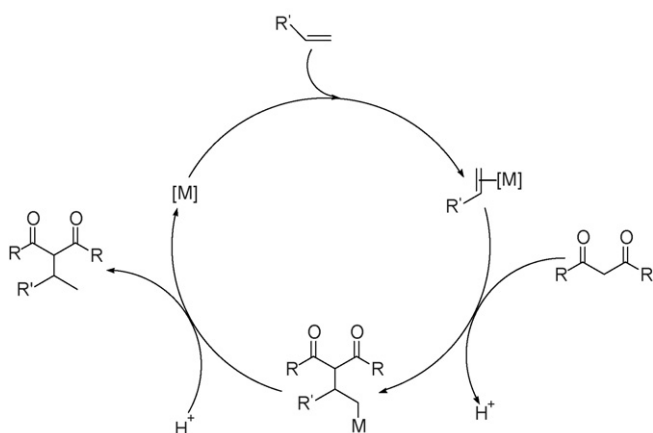


Fig. 2. Proposed mechanism for the addition of 1,3-diketones to alkenes.

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