Indium(III)-Catalyzed Addition of 1,3-Dicarbonyl Compounds to Alkenes

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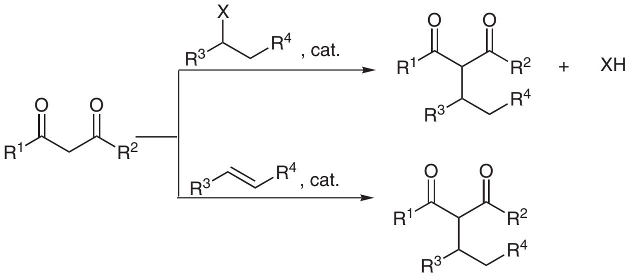
Received 14 September 2007

Abstract: A new $InCl_3$-catalyzed addition reaction of 1,3-dicarbonyl compounds to various alkenes proceeded in good yields and can be carried out in air, which provided an easy and practical procedure for carbon–carbon bond formation.

Key words: addition, indium, catalysis, alkene

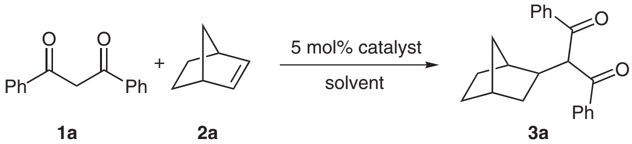
The formation of carbon–carbon bonds is one of the most important reactions for the construction of molecular frameworks in organic chemistry.[1] In recent years, much attention has been paid to the functionalization of activated methylene compounds, such as 1,3-dicarbonyl compounds, by catalytic nucleophilic substitution.[2] However, significant goals of green chemistry are to maximize the efficiency of the reaction, to minimize the creation of waste and to use environmentally benign catalysts.[3] Substitution reactions are less atom-economical than addition reactions in terms of atom efficiency, because substitution reactions invariably generate at least one byproduct (Scheme 1).[4]



Scheme 1

Consequently, the development of alternative methods, such as using Lewis acids and Brønsted acids to catalyze the addition of active methylene compounds to alkenes and alkynes, would provide a more environmentally friendly and atom-economical process. For examples, Hartwig obtained good results in the palladium-catalyzed addition of compounds with mildly acidic C–H bonds to conjugated dienes.[5] Li developed a highly effective intermolecular addition of active methylene compounds to alkenes using a mixture of $AuCl_3$–AgOTf[6] or AgOTf[7] as catalyst. Gold[8] and nickel/ytterbium[9] have also been applied to the intramolecular cyclization of δ- and ε-acetylenic 1,3-dicarbonyl compounds. The intermolecular additions of active methylene compounds to alkynes were reported by Takai[10] and Nakamura[11] using rhenium and indium Lewis acids, respectively. Recently, Wu developed the addition of activated methylene to styrene derivatives using $FeCl_3$ as the catalyst.[12] Kaneda found that the addition reaction of various 1,3-dicarbonyl compounds to alkenes in the presence of solid acid catalysts proceeded in good yield.[13] Herein, we report the use of $InCl_3$ as a catalyst to promote a highly efficient intermolecular addition of 1,3-dicarbonyl compounds to alkenes.

Table 1 Reaction of Dibenzoylmethane with Norbornene[a]



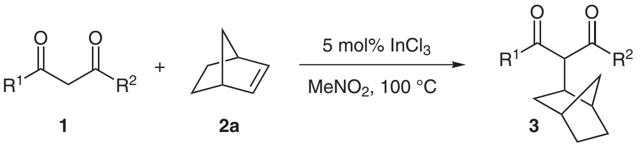
Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1	$AlCl_3$	$MeNO_2$	100	0
2	$TiCl_4$	$MeNO_2$	100	0
3	$MnCl_2$	$MeNO_2$	100	0
4	$BiCl_3$	$MeNO_2$	100	trace
5	$InCl_3$	$MeNO_2$	100	68
6	$GaCl_3$	$MeNO_2$	100	58
7	$CoCl_2{\cdot}6H_2O$	$MeNO_2$	100	10
8	$NiCl_2{\cdot}6H_2O$	$MeNO_2$	100	8
9	$CrCl_3{\cdot}6H_2O$	$MeNO_2$	100	0
10	$HAuCl_4{\cdot}4H_2O$	$MeNO_2$	100	20
11	$InCl_3$	DCE	80	32
12	$InCl_3$	CH_2Cl_2	40	trace
13	$InCl_3$	dioxane	80	0
14	$InCl_3$	$MeNO_2$	100	69[c]
15	$InCl_3$	$MeNO_2$	100	78[d]

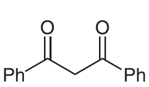
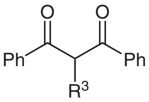
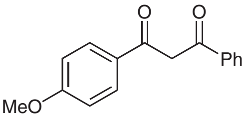
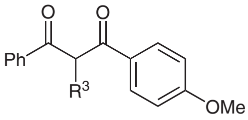
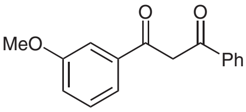
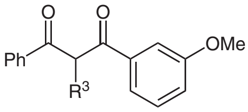
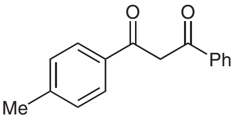
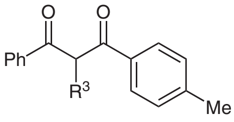
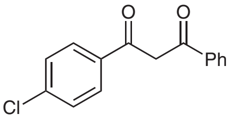
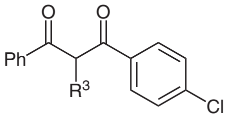
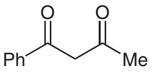
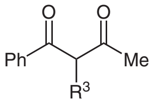
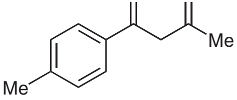
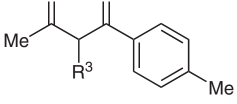
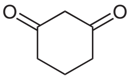
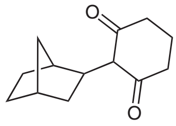
[a] Reaction conditions: dibenzoylmethane (1.0 mmol), norbornene (2.0 mmol), catalyst (5 mol%), solvent (2 mL), 12 h, argon.
[b] Isolated product yield after column chromatography.
[c] The reaction was conducted in open air.
[d] Reaction conditions: dibenzoylmethane (1.0 mmol), norbornene (4.0 mmol), catalyst (5 mol%), solvent (2 mL), 12 h, in open air.

SYNLETT 2007, No. 20, pp 3219–3223
Advanced online publication: 03.12.2007
DOI: 10.1055/s-2007-992388; Art ID: W16907ST

Our initial work focused on the screening of a variety of Lewis acids (5 mol%) as catalysts for the addition reaction of dibenzoylmethane (**1a**) to norbornene (**2**; 2.0 equiv). As shown in Table 1, the best result for this reaction was achieved using indium(III) chloride as the catalyst at 100 °C in nitromethane for 12 hours (entry 5). The effect of solvent on this addition reaction was tested subsequently. Nitromethane was found to be the most suitable solvent for the addition reaction of dibenzoylmethane to norbornene catalyzed by $InCl_3$, whereas little or no product was obtained with other solvent systems such as dichloroethane, dichloromethane or dioxane (entries 11–13). In the case of the addition reaction of alkenes catalyzed by $FeCl_3$,[12,14] the reaction was carried out in air without any loss in yield (entry 14). Increasing the amount of nor-

Table 2 Indium(III)-Catalyzed Reactions of Norbornene with 1,3-Diketones[a]



Entry	Diketone	Product[b]	Time (h)	Yield (%)[c]
1	 **1a**	 **3a**	36	94
2	 **1b**	 **3b**	30	79 (50:50)
3	 **1c**	 **3c**	30	86 (50:50)
4	 **1d**	 **3d**	36	84 (48:52)
5	 **1e**	 **3e**	36	78 (50:50)
6	 **1f**	 **3f**	32	90 (24:76)
7	 **1g**	 **3g**	32	74 (48:52)
8	 **1h**	 **3h**	32	41

[a] The reactions were carried out using diketone (1.0 mmol), norbornene (4.0 mmol), and $InCl_3$ (0.05 mmol) in anhyd $MeNO_2$ (2 mL) in open air.

[b] R^3 = norbornanyl.

[c] Isolated yield after column chromatography. The ratio of diastereomers is given in parentheses.

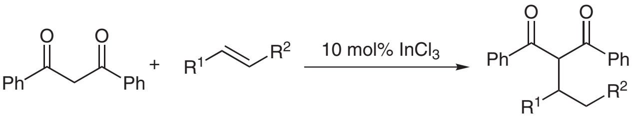
bornene used (4.0 equiv), improved the yield of the adduct (entry 15).

To examine the substrate scope of the addition reaction, various 1,3-dicarbonyl compounds were reacted with norbornene under the optimized conditions. In the presence of 5 mol% of $InCl_3$, all substituted dibenzoylmethane and 1-benzoylacetone compounds reacted well with norbornene to give the corresponding addition products in good yields in acceptable times (Table 2). However, only moderate yields were observed when acetylacetone (not shown in Table 2) or 1,3-cyclohexadione were used as the substrate under the same reaction conditions. It was determined that the phenyl group in the active methylene compounds was very important for the reaction to proceed in good yield. This could be due to the 1,3-allylic strain in the enol form that could increase the substrate's reactivity.[9,15]

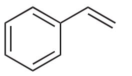
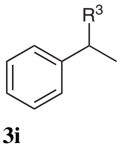
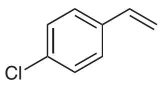
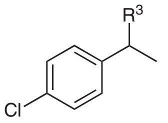
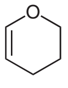
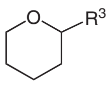
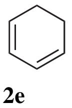
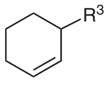
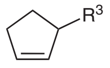
Next, we investigated the scope of alkene substrates compatible with the $InCl_3$-catalyzed addition reaction of dibenzoylmethane (**1a**, Table 3). The catalyst loading of $InCl_3$ was increased to 10 mol% because only poor yields (less than 20%) of the addition of **1a** to dienes were obtained with 5 mol% of catalysts. Here, the yields obtained were only moderate in comparison with the addition reaction of dibenzoylmethane to norbornene. GC–MS analysis of the crude reaction mixtures showed that this was due to the formation of alkene dimers and oligomers in the presence of the catalyst.[12,16] Interestingly, the yield of the addition product was found to be dependent on the solvent used for the different alkenes. For examples, nitromethane was the best solvent for the addition of styrene-type alkenes as less oligomer was formed (entries 1 and 2). On the other hand, addition reaction of dienes and dihydropyran was most efficient when conducted in CH_2Cl_2 (entries 3–5).

It has previously been shown in the literature that phenols, carboxylic acids, amines and aryl compounds add to alkenes in the presence of several Lewis and Brønsted acid catalysts.[17] Therefore our attention next turned to the scope of nucleophiles that could be applied to the addition reaction to alkenes. Hence, reaction of 4-methylbenzoic acid with norbornene in the presence of 5 mol% of $InCl_3$ gave 2-(4-methyl)benzoyloxynorbornane in 97% yield when nitromethane was used as solvent. The reactions using 4-chlorophenol and tosylamine were found to be equally effective. Hence, $InCl_3$ was shown to be a general catalyst for the addition reaction of nucleophiles to alkenes in good yields (Scheme 2).

Table 3 Indium(III)-Catalyzed Reactions of Alkenes with Dibenzoylmethane[a]



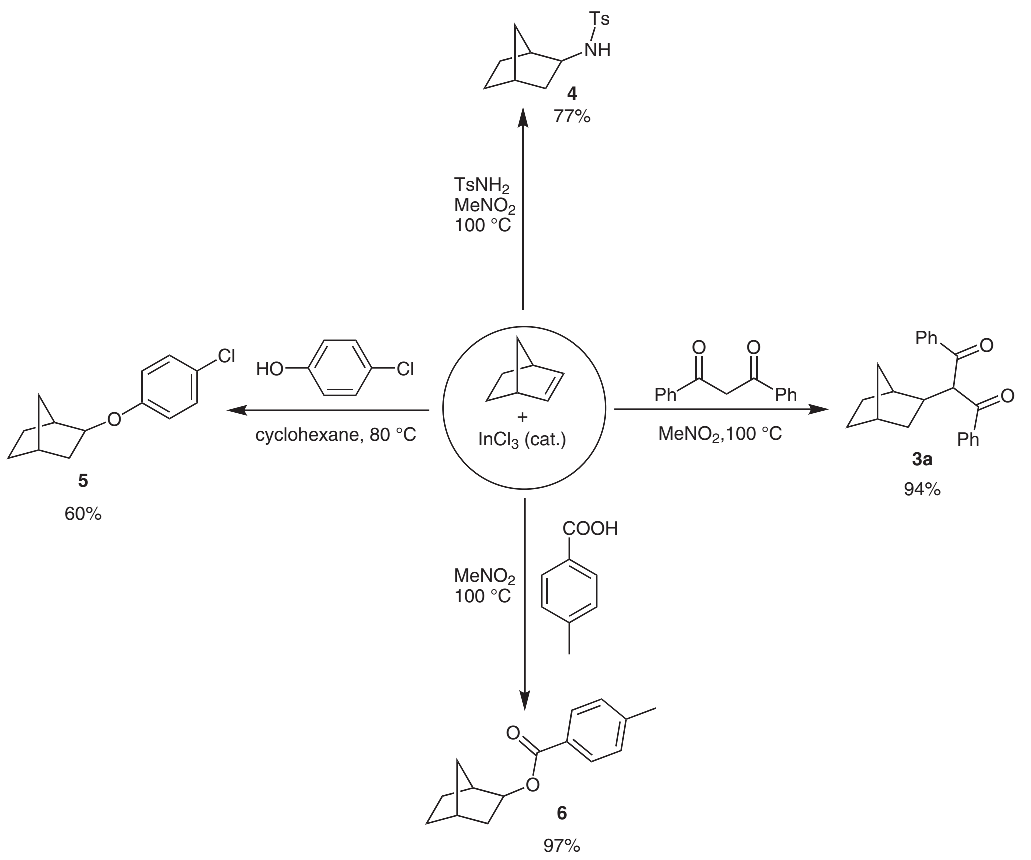
1a 2 3

Entry	Alkene	Product[b]	Solvent	Temp. (°C)	Time (h)	Yield (%)[c]
1	 **2b**	 **3i**	$MeNO_2$	100	15	65
2	 **2c**	 **3j**	$MeNO_2$	100	15	73
3	 **2d**	 **3k**	CH_2Cl_2	40	20	48
4	 **2e**	 **3l**	CH_2Cl_2	40	20	58
5	 **2f**	 **3m**	CH_2Cl_2	40	20	40

[a] Unless otherwise noted, the reactions were carried out using β-diketone (1.0 mmol), alkene (4.0 mmol), and $InCl_3$ (0.1mmol) in anhyd solvent (2 mL), in open air.

[b] R^3 = dibenzoylmethyl.

[c] Isolated yield after column chromatography.



Scheme 2

In summary, we have developed a new $InCl_3$-catalyzed addition reaction of 1,3-dicarbonyl compounds to various alkenes.[18] The reaction proceeded in good yields and can be carried out in air. It provides an easy and practical procedure for carbon–carbon bond formation because of the readily availability of the catalyst and simple reaction conditions. Furthermore, the reaction can also be applied to carbon–heteroatom bond formation using alternative nucleophiles. Mechanistic studies on this reaction are in progress.

Acknowledgment

We are grateful for the financial support from the National Natural Science Foundation of China (20702043), Jiangsu Provincial Natural Science Foundation (BK2006549) P. R. of China, and Program for New Century Excellent Talents in Yangzhou University.

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(18) All the products have been fully characterized by ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) and the analyses were in agreement with published data. Data that were not found in the literature are as follows: Product **3b**: ^{1}H NMR [600 MHz, CDCl$_3$; diastereomeric mixture (50:50)]: δ = 8.03–8.05 (m, 4 H), 7.93–7.96 (m, 4 H), 7.36–7.56 (m, 6 H), 6.85–6.94 (m, 4 H), 4.95 (d, J = 3.6 Hz, 1 H), 4.93 (d, J = 3.0 Hz, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 2.67–2.73 (m, 2 H), 2.24 (s, 2 H), 1.94 (s, 2 H), 1.55–1.64 (m, 2 H), 1.40–1.47 (m, 6 H), 1.25–1.30 (m, 2 H), 1.17–1.20 (m, 4 H), 1.07–1.12 (m, 2 H). ^{13}C NMR [150 MHz, CDCl$_3$; diastereomeric mixture (50:50)]: δ = 196.22, 196.63, 194.31, 193.68, 163.89, 163.72, 137.27, 137.18, 133.44, 133.25, 131.42, 131.28, 130.26, 130.12, 128.94, 128.81, 128.77, 128.72, 114.12, 113.95, 64.57, 64.49, 55.57, 55.52, 43.62, 43.59, 39.84, 39.52, 37.48, 37.00, 36.77, 36.76, 36.05, 36.03, 30.10, 28.60, 28.58. HRMS: *m/z* calcd for $C_{23}H_{24}O_3$: 348.1725; found: 348.1720. Product **3c**: ^{1}H NMR [600 MHz, CDCl$_3$; diastereomeric mixture (50:50)]: δ = 7.93–8.04 (m, 4 H), 7.28–7.65 (m, 12 H), 7.04–7.12 (m, 2 H), 5.02 (d, J = 11.4 Hz, 2 H), 3.81 (s, 3 H), 3.73 (s, 3 H), 2.68–2.72 (m, 2 H), 2.24 (s, 2 H), 1.95 (s, 2 H), 1.61–1.65 (m, 2 H), 1.48 (m, 6 H), 1.29 (m, 2 H), 1.20–1.21 (m, 4 H), 1.09–1.11 (m, 2 H). ^{13}C NMR [150 MHz, CDCl$_3$; diastereomeric mixture (50:50)]: δ = 195.92, 195.69, 195.27, 195.00, 160.08, 159.94, 138.61, 138.55, 137.33, 137.25, 133.55, 133.35, 129.89, 129.74, 128.97, 128.82, 121.52, 121.40, 120.42, 120.31, 112.95, 112.73, 64.33, 55.47, 55.39, 43.81, 43.79, 39.74, 39.65, 37.39, 37.28, 36.78, 36.13, 30.13, 28.61. HRMS: *m/z* calcd for $C_{23}H_{24}O_3$: 348.1725; found: 348.1720. Product **3d**: ^{1}H NMR [600 MHz, CDCl$_3$; diastereomeric mixture (48:52)]: δ = 7.77–7.96 (m, 8 H), 7.29–7.48 (m, 6 H), 7.10–7.19 (m, 4 H), 4.91 (d, J = 10.8 Hz, 2 H), 2.64 (m, 2 H), 2.33 (s, 3 H), 2.18 (s, 3 H), 2.16 (s, 2 H), 1.87 (s, 2 H), 1.53–1.56 (m, 2 H), 1.40 (m, 6 H), 1.19–1.22 (m, 2 H), 1.11–1.14 (m, 4 H), 1.03 (m, 2 H). ^{13}C NMR [150 MHz, CDCl$_3$; diastereomeric mixture (48:52)]: δ = 196.06, 195.49, 195.46, 194.88, 144.57, 144.32, 137.27, 137.18, 134.77, 134.65, 133.48, 133.28, 129.66, 129.49, 129.15, 129.01, 128.95, 128.89, 128.78, 128.74, 64.39, 64.33, 43.70, 43.65, 39.78, 39.55, 37.45, 37.12, 36.76, 36.07, 30.11, 30.10, 28.60, 28.58, 21.73, 21.67. Anal. Calcd for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28. Found: C, 82.84; H, 7.42. Product **3e**: ^{1}H NMR [600 MHz, CDCl$_3$; diastereomeric mixture (50:50)]: δ = 7.88–8.04 (m, 8 H), 7.35–7.60 (m, 10 H), 4.93 (d, J = 11.4 Hz, 2 H), 2.69–2.72 (m, 2 H), 2.25 (s, 2 H), 1.94 (s, 1 H), 1.91 (s, 1 H), 1.60–1.62 (m, 2 H), 1.47 (m, 6 H), 1.27–1.29 (m, 2 H), 1.21–1.98 (m, 2 H), 1.06–1.10 (m, 2 H). ^{13}C NMR [150 MHz, CDCl$_3$; diastereomeric mixture (50:50)]: δ = 195.84, 195.22, 194.77, 194.20, 140.17, 139.94, 137.11, 136.99, 135.44, 135.35, 133.75, 133.54, 130.40, 130.24, 129.27, 129.11, 129.02, 128.97, 128.86, 128.82, 64.95, 64.93, 43.60, 39.72, 39.67, 37.29, 37.22, 36.76, 36.05, 36.04, 30.09, 28.55. Anal. Calcd for $C_{22}H_{21}ClO_2$: C, 74.89; H, 6.00. Found: C, 74.50; H, 6.06. Product **3g**: ^{1}H NMR [600 MHz, CDCl$_3$; diastereomeric mixture (48:52)]: δ = 7.90–7.93 (m, 4 H), 7.26–7.29 (m, 4 H), 4.26 (d, J = 11.4 Hz, 1 H), 4.20 (d, J = 11.4 Hz, 1 H), 2.50–2.57 (m, 2 H), 2.42 (s, 3 H), 2.41 (s, 3 H), 2.27 (s, 1 H), 2.19 (s, 1 H), 2.13 (s, 3 H), 2.10 (s, 3 H), 1.94 (s, 1 H), 1.81 (s, 1 H), 1.09–1.52 (m, 15 H), 0.86–0.88 (m, 1 H). ^{13}C NMR [150 MHz, CDCl$_3$; diastereomeric mixture (48:52)]: δ = 204.65, 204.43, 196.00, 196.54, 144.82, 144.79, 134.93, 134.87, 129.62, 129.57, 70.66, 70.11, 42.53, 42.43, 40.19, 39.03, 37.25, 36.88, 36.72, 35.79, 35.72, 35.33, 30.11, 30.08, 28.60, 28.58, 27.33, 27.12, 21.75. HRMS: *m/z* calcd for $C_{18}H_{22}O_2$: 270.1620; found: 270.1620. Product **3h**: ^{1}H NMR (600 MHz, CDCl$_3$): δ = 5.30 (s, 1 H), 4.02 (d, J = 6.6 Hz, 1 H), 2.40–2.41 (m, 1 H), 2.30–2.36 (m, 5 H), 1.05–1.98 (m, 10 H). ^{13}C NMR (150 MHz, CDCl$_3$): d = 199.91, 176.84, 103.79, 81.35, 40.98, 39.81, 36.76, 35.38, 35.34, 29.36, 28.21, 24.21, 21.31. HRMS: *m/z* calcd for $C_{13}H_{18}O_2$: 206.1307; found: 206.1307. Product **6**: ^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.90 (d, J = 7.8 Hz, 2 H), 7.22 (d, J = 7.8 Hz, 2 H), 4.83 (d, J = 6.6 Hz, 1 H), 2.44 (d, J = 4.8 Hz, 1 H), 2.40 (s, 3 H), 2.33 (br s, 1 H), 1.82 (ddd, J = 2.4, 7.2, 13.8 Hz, 1 H), 1.45–1.65 (m, 4 H), 1.15–1.23 (m, 3 H). ^{13}C NMR (150 MHz, CDCl$_3$): δ = 166.36, 143.35, 129.56, 129.03, 128.21, 77.98, 41.63, 39.74, 35.50, 28.28, 24.37, 21.70. HRMS: *m/z* calcd for $C_{15}H_{18}O_2$: 230.1307; found: 230.1307.