An Efficient Metal-Catalyzed Hydroalkylation

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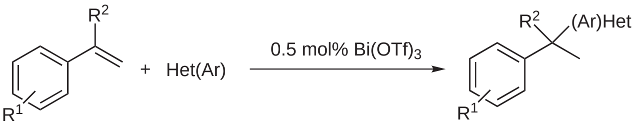
Abstract: An efficient metal-catalyzed hydroalkylation of various styrenes, norbornene, and cyclohexadiene with 1,3-dicarbonyl compounds has been developed. This new bismuth-catalyzed C–H functionalization provides the corresponding alkylated pentanediones in good to excellent isolated yields after short reaction times.

Key words: hydroalkylation, hydroarylation, benzylation, bismuth, C–H activation, catalysis, styrene, alkene

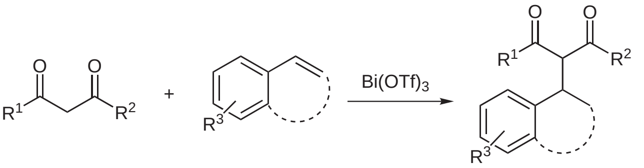
Hydroalkylation and hydroarylation reactions are of great general interest in organic chemistry. These transformations are highly atom-economic and hence represent valuable examples of green and sustainable chemistry. In view of the demand for efficient, economic and environmentally benign processes, the development of direct catalytic carbon–carbon bond-forming reactions of prior unmodified substrates is an important task. Consequently, considerable progress has been made in the development of promising metal-catalyzed C–H functionalizations, including the addition of olefins to acetophenones and aromatic imines or the inter- and intramolecular arylation of alkynes and alkenes, benzyl acetates and alcohols.[1] In this context we were recently able to successfully develop highly efficient bismuth-catalyzed reactions, such as the addition of benzyl alcohols to arenes,[2] the direct benzylation and allylic alkylation of 2,4-pentanediones[3] as well as the hydroarylation of styrenes (Scheme 1).[4]



Scheme 1 Bismuth-catalyzed hydroarylation of styrenes

Generally, these transformations can conveniently be performed in short reaction times, under mild reaction conditions with low catalyst loadings. Thus, 0.5 mol% of $Bi(OTf)_3$ is sufficient to catalyze the hydroarylation of various styrenes.[4]

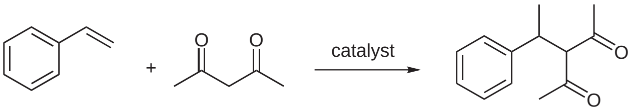
Herein, we report an extension of this procedure to the inter- and intramolecular hydroalkylation of styrenes (Scheme 2) using 1,3-dicarbonyl compounds as the nucleophile. Typically, the products obtained have been prepared by use of stoichiometric amounts of base and alkylhalides or activated alcohol derivatives leading to large amounts of salt byproducts. More recently, however, the first intra- and intermolecular addition of 1,3-dicarbonyl compounds to styrenes have been reported using palladium,[5] silver, and gold catalysts[6] or heterogeneous Brønsted acids.[7]



Scheme 2 Bismuth(III)-catalyzed hydroalkylation of styrenes

Attracted by the direct hydroalkylation of styrenes and therewith the prevention of electrophile preformation and knowing that bismuth salts are highly reactive catalysts, we started our investigations with the direct addition of 2,4-pentanedione (**2a**) to styrene (**1a**), as shown in Table 1. From these experiments we found that the reaction could best be performed in nitromethane using $Bi(OTf)_3$ as catalyst (entries 4–6). Other bismuth salts as well as trifluoromethanesulfonic acid did not result in the corresponding product (entries 1–3, 7). Reactions in nonpolar solvents such as cyclohexane led to product

Table 1 Evaluation of Different Bismuth Salts in the Hydroalkylation of Styrene with 2,4-Pentanedione[10]



1a **2a** **3a**

Entry	Catalyst	mol (%)	Time (h)	Yield (%)[a]
1	$BiCl_3$	5	8	0
2	$BiBr_3$	5	8	0
3	$Bi(NO_3)_3(H_2O)_5$	5	8	0
4	$Bi(OTf)_3(H_2O)_4$	1	2	67
5	$Bi(OTf)_3(H_2O)_4$	2	2	76
6	$Bi(OTf)_3(H_2O)_4$	5	2	81
7	TfOH	15	8	0

[a] Isolated yield after flash chromatography.

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formation, but with the generation of a byproduct.[8] In chlorinated solvents including dichloromethane and chloroform, an immediate decomposition of the styrene was observed, even at room temperature. Decreasing the catalyst loading resulted in lower yields (entries 4–6). Thus, by employing 5 mol% of $Bi(OTf)_3$ in nitromethane, the corresponding product **3a** could be isolated in 81% isolated yield after chromatography.

Using these optimized conditions, we explored the scope of the bismuth-catalyzed hydroalkylation by varying the styrene as well as the 1,3-carbonyl components (Table 2). Generally different styrene derivatives **1a**–**f** and 2,4-pentanediones **2a**–**c** can be employed and the corresponding products **3a**–**h** could be isolated in good yields after short reaction times (Table 2, entries 1–8). With regard to the styrene derivatives electron-donating, as well as electron-withdrawing substituents (entries 4–8) are tolerated and even indene resulted in the cyclic 3-substituted dihydroindene **3i**, though only in moderate yield (entry 9). Furthermore, we were able to extend the scope of this transformation to other substrates, including norbornene (**1h**) and cyclohexadiene (**1i**). For instance, bismuth-catalyzed hydroalkylation of **1h** with the more reactive dibenzoylmethane **2c** gave the corresponding alkylated norbornene **3j** in 90% yield after 90 minutes (entry 10). Surprisingly, cyclohexadiene was also successfully transformed to the alkylated cyclohexene **3k**, although the reaction was performed at ambient temperature (entry 11).[9]

Table 2 Scope of the Intermolecular Hydroalkylation of Different Styrene Derivatives with 2,4-Pentanediones[10,11]

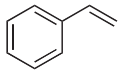
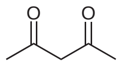
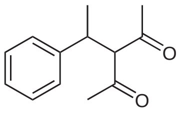
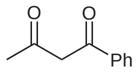
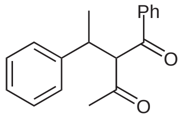
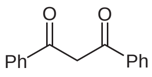
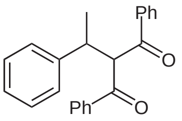
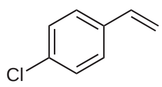
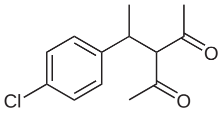
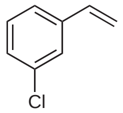
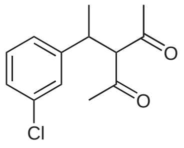
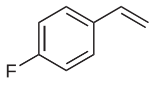
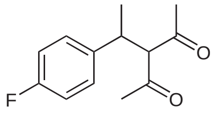
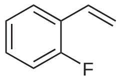
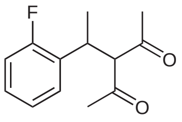
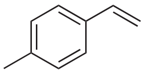
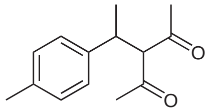
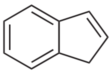
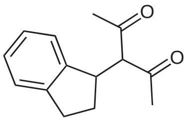
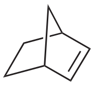
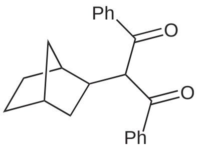
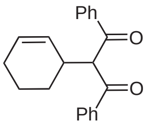
Entry	Electrophile **1**	Pentanedione **2**	Cat. (mol%)	Temp (°C)	Time (h)	Product **3**	Yield (%)[a]
1	 **1a**	 **2a**	5	80	2	 **3a**	81
2	**1a**	 **2b**	5	100	4.5	 **3b**	88[b]
3	**1a**	 **2c**	5	50	2	 **3c**	89
4	 **1b**	**2a**	5	100	5	 **3d**	78
5	 **1c**	**2a**	5	100	20	 **3e**	41
6	 **1d**	**2a**	5	100	4	 **3f**	89
7	 **1e**	**2a**	5	100	4	 **3g**	71

Table 2 Scope of the Intermolecular Hydroalkylation of Different Styrene Derivatives with 2,4-Pentanediones[10,11] (continued)

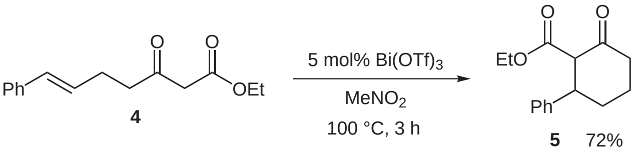
Entry	Electrophile **1**	Pentanedione **2**	Cat. (mol%)	Temp (°C)	Time (h)	Product **3**	Yield (%)[a]
8	 **1f**	**2a**	5	100	3	 **3h**	86
9	 **1g**	**2a**	5	90	5	 **3i**	41[c]
10	 **1h**	**2c**	5	90	1.5	 **3j**	90
11	 **1i**	**2c**	5	r.t.	4	 **3k**	45

[a] Isolated yield after flash chromatography.

[b] Diastereomeric ratio = 1:1

[c] 2,4-Pentanedione (1 mL) was used as solvent.

Following a successful bismuth-catalyzed hydroalkylation of various styrenes, norbornene, and cyclohexadiene, we decided to examine an intramolecular variant of this transformation. Thus, starting from cinnamyl bromide and ethyl 3-oxobutanoate, we prepared the substituted β-ketoester **4** and carried out the intramolecular hydroalkylation reaction. Although β-ketoesters did not show efficient reactivity in the intermolecular reaction with styrene derivatives, in the intramolecular case, the substituted cyclohexanone **5** could be isolated in 72% yield after three hours (Scheme 3).



Scheme 3 Intramolecular hydroalkylation of β-ketoester **4**

In summary we have developed an efficient bismuth-catalyzed hydroalkylation of various styrenes, norbornene, and cyclohexadiene derivatives with different 2,4-pentanediones. The short reaction times, simplicity and practicability as well as the use of small amounts of reactive, cheap, non-moisture-sensitive, and nontoxic $Bi(OTf)_3$ catalyst renders this hydroalkylation procedure an interesting alternative to previous methods. Additionally, an intramolecular hydroalkylation of β-ketoesters has been developed resulting in the corresponding substituted cyclohexanone in excellent yield.

Acknowledgment

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References and Notes

(1) For reviews, see: (a) Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1699. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

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(8) 1,3-Diarylbut-1-enes were observed as the major byproducts.

(9) For other metal-catalyzed hydroalkylation procedures of dienes and 1,3-dicarbonyl compounds, see: (a) Jolly, P. W.; Kokel, N. *Synthesis* **1990**, 771. (b) Trost, B. M.; Zhi, L. *Tetrahedron Lett.* **1992**, *33*, 1831. (c) Goddard, R.; Hopp, G.; Jolly, P. W.; Kruger, C.; Mynott, R.; Wirtz, C. *J. Organomet. Chem.* **1995**, *486*, 163. (d) Leitner, A.; Larsen, J.; Steffens, C.; Hartwig, J. F. *J. Org. Chem.* **2004**, *69*, 7552.

(10) **Typical Procedure: Preparation of 3-[1-(4-fluorophenyl)ethyl]pentane-2,4-dione (3f)**
A two-necked round-bottom flask charged with $Bi(OTf)_3(H_2O)_4$ (0.036 g, 0.05 mmol) and 2,4-pentanedione (400 mg, 4 mmol) dissolved in $MeNO_2$ (3 mL) was heated to 100 °C. 4-Fluorostyrene (1 mmol) dissolved in 1 mL of $MeNO_2$ was added dropwise via syringe for 4 h and stirred at this temperature for 1 h. After cooling the reaction mixture to r.t. the crude reaction mixture was directly purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to give 198 mg (89%) of the product as a pale yellow oil which solidified upon standing. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.19–7.09 (m, 2 H, ArH), 7.03–6.91 (m, 2 H, ArH), 3.97 (d, *J* = 11.3 Hz, 1 H, CH), 3.58 (dq, *J* = 11.3, 6.9 Hz, 1 H, CH), 2.25 (s, 3 H, CH_3), 1.84 (s, 3 H, CH_3) 1.18 (d, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 203.8, 203.7, 162.2 (d, *J* = 245.4 Hz), 139.4 (d, *J* = 3.4 Hz), 129.4 (d, *J* = 7.9 Hz), 116.24 (d, *J* = 21.3 Hz), 77.4, 40.2, 30.4, 30.2, 21.5. IR (neat): ν = 3441, 3260, 2925, 2845, 1647, 1385, 1076, 698, 466 cm^{-1}. ESI-MS: *m/z* (%) = 240.0(100) $[M + NH_4]^+$. Anal. Calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 70.53; H, 6.76.

(11) **Spectroscopic Data for 3-[1-(2-fluorophenyl)ethyl]pentane-2,4-dione (3g)**
^1H NMR (250 MHz, $CDCl_3$): δ = 7.34–6.95 (m, 4 H, ArH), 4.24 (d, *J* = 11.3 Hz, 1 H, CH), 3.89 (dq, *J* = 11.3, 6.9 Hz, 1 H, CH), 2.28 (s, 3 H, CH_3), 1.94 (s, 3 H, CH_3) 1.23 (d, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 203.13, 202.98, 160.5 (d, *J* = 245.7 Hz), 129.7 (d, *J* = 14.0 Hz), 129.2 (d, *J* = 4.9 Hz), 128.6 (d, *J* = 8.4 Hz), 124.5 (d, *J* = 3.5 Hz), 116.0 (d, *J* = 22.6 Hz), 74.86, 34.6, 30.2, 28.9, 19.48. IR (neat): ν = 3441, 2980, 1699, 1493, 1452, 1360, 1281, 1228, 1246, 761 cm^{-1}. ESI-MS: *m/z* (%) = 239.9 (100) $[M + NH_4]^+$, 462.3 (90) $[2 M + NH_4]^+$. Anal. Calcd for $C_{13}H_{15}FO_2$: C, 70.25; H, 6.80. Found: C, 70.51; H, 6.78.