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Efficient Metal-Catalyzed Direct Benzylation and Allylic Alkylation of 2,4-Pentanediones

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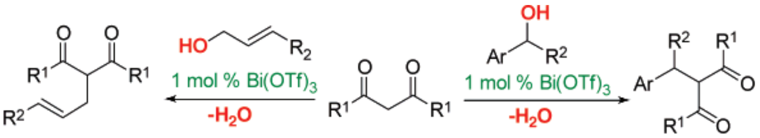
ABSTRACT



A highly effective metal-catalyzed benzylation and allylic alkylation of 2,4-pentanediones has been developed. This new bismuth-catalyzed direct carbon–carbon bond forming reaction provides the corresponding monoalkylated dicarbonyl compounds in high yields after short reaction times using the lowest amounts of catalyst (1 mol %) and the free alcohol. In addition, a new route to substituted indenes is presented.

The functionalization of activated methylene units, such as 1,3-dicarbonyl compounds, is one of the most utilized types of carbon−carbon bond forming reactions. Generally, these transformations are performed using alkyl halides, and at least equimolar amounts of base or Lewis acid are required, resulting in large amounts of salt byproducts. Additionally, the need of electrophile preformation and coproduction of hydrogen halides may lead to undesired side reactions which can be a significant drawback. Thus, in view of the demand for efficient, economic, and ecologically valuable processes, the development of direct catalytic carbon−carbon bond forming reactions of prior unmodified substrates is an important task. Recently, interesting examples of such reactions have been reported, including the direct functionalization of benzyl alcohols with the generation of water as the single byproduct. In this context, considerable progress has been made in the metal-catalyzed Friedel−Crafts-type alkylations of arenes using benzyl alcohols as the electrophilic component resulting in products containing a diarylmethane moiety commonly found in biologically active compounds and pharmaceuticals.[1] Recently, we were able to demonstrate that bismuth salts are highly efficient catalysts for this transformation, and the use of 0.5−1 mol % of $Bi(OTf)_3$ was sufficient to catalyze the addition of benzyl alcohol and derivatives to arenes and heteroarenes.[2,3]

However, so far, C nucleophiles other than arenes have not been investigated. Hence, we herein report the first direct bismuth-catalyzed benzylation of 2,4-pentanediones using benzyl alcohol and its derivatives.[4] Furthermore, we describe an extension of this procedure to a new bismuth-catalyzed allylic alkylation using the corresponding free allylic alcohols.

Bismuth(III) salts have been used as a catalyst for various transformations, including acylations, sulfonylations, phosphonylations, desilylations, Diels−Alder reactions, oxidations, halogenations, and rearrangements.[5] Among the bismuth-

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[1] (a) ElGihani, M. T.; Heaney, H.; Shuhaibar, K. F. *Synlett* **1996**, 871−872. (b) Shimizu, I.; Khien, K. M.; Nagatomo, M.; Nakajima, T.; Yamamoto, A. *Chem. Lett.* **1997**, 851−852. (c) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S. *J. Org. Chem.* **1997**, *62*, 6997−7005. (d) Shiina, I.; Suzuki, M. *Tetrahedron Lett.* **2002**, *43*, 6391−6394. (e) Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. *J. Org. Chem.* **2003**, *68*, 9340−9347. (f) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 238−242. (g) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913. (h) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691−695.

[2] Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W. *Adv. Synth. Catal.* **2006**, *348*, 1033−1037.

[3] For a metal-catalyzed hydroarylation of styrenes, see: Rueping, M.; Nachtsheim, B. J.; Scheidt, T. *Org. Lett.* **2006**, *8*, 3717−3719.

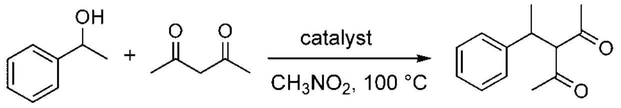
[4] During our investigations, Baba and co-workers described a similar indium-catalyzed transformation: Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793−796.

10.1021/ol063048b CCC: $37.00

(III) derivatives, $Bi(OTf)_3$ belongs to the most reactive and used catalyst with Lewis acid properties comparable to other metal triflates such as $Sc(OTf)_3$, $Yb(OTf)_3$, or $Y(OTf)_3$.

Attracted by the direct functionalization of alcohols and therewith the prevention of electrophile preformation or coproduction of hydrogen halides and the fact that certain bismuth salts are compatible with air and moisture, we investigated various bismuth salts and Brønsted acids in the reaction of 1-phenylethanol with acetylacetone (Table 1).

Table 1. Evaluation of Bismuth(III) Salts and Brønsted Acids

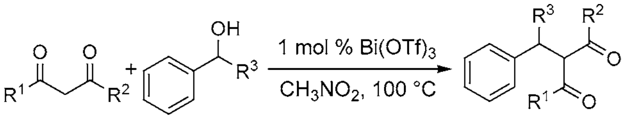


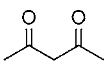
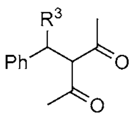
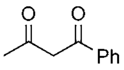
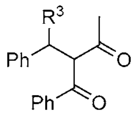
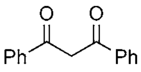
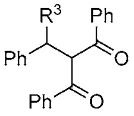
entry	catalyst	mol %	time (h)	yield (%)[a]
1	$BiCl_3$	5	3	87
2	$BiBr_3$	5	3	90
3	$Bi(NO_3)_3(H_2O)_5$	5	3	68
4	$Bi(OTf)_3$	5	3	93
5	$Bi(OTf)_3$	1	3	91
6	$Bi(OTf)_3$	0.1	6	83
7	TfOH	3	3	0
8	HCl	10	4	0
9	none	-	4	0

[a] Isolated yield after column chromatography.

From these experiments, $Bi(OTf)_3$, $BiCl_3$, and $BiBr_3$ emerged as the best catalysts and the corresponding products were obtained in 87−93% yield after column chromatography (Table 1, entries 1−4).[6] Brønsted acids, such as trifluoromethanesulfonic acid or hydrochloric acid (Table 1, entries 7 and 8), did not show catalytic activity. The catalyst loading could be decreased to 1 mol % without loss of reactivity, and even with 0.1 mol % of $Bi(OTf)_3$ catalyst the product could be isolated in 83% yield (Table 1, entries 4−6).

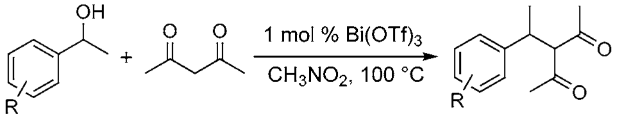
Table 2. Variation of the 1,3-Dicarbonyl Scaffold

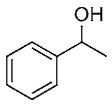
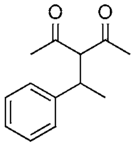
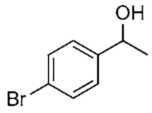
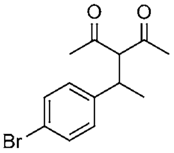
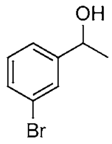
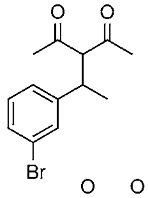
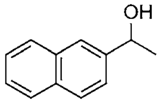
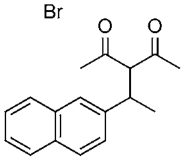
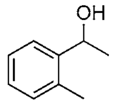
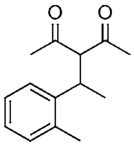
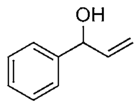
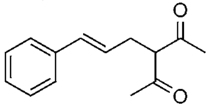
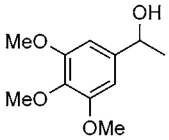
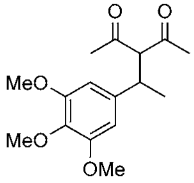
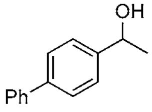
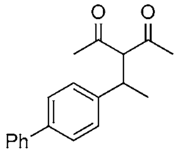


entry	pentanedione	product	R^3	cat. (mol %)	time (h)	yield (%)[a]
1			H	1	18	58
2			Me	1	3	91
3			H	1	8.5	72
4			Me	5	5	93[b]
5			H	1	6	84
6			Me	5	3	96

[a] Isolated yield after column chromatography. [b] dr: 1:1

Table 3. Reaction of Various 1-Phenylethanol Derivatives



entry	alcohol	product	time (h)	yield (%)[a]
1			3	91
2			4	84
3			4	65
4			4	87
5			3	85
6			2	54[b]
7			3[c]	76[d]
8			3	90

[a] Isolated yield after column chromatography. [b] 10% of branched product observed. [c] Reaction performed at rt. [d] Additionally, 16% of indene derivative was obtained.

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(5) For reviews see: (a) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373−8397. (b) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517−2532.

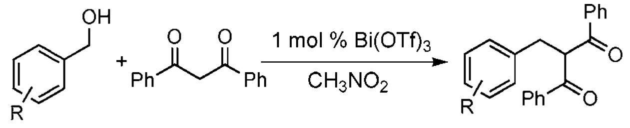
Further experiments concentrated on the evaluation of the 1,3-dicarbonyl scaffold (Table 2). As expected, the use of different 2,4-pentanediones resulted in the corresponding products in good yields irrespective of whether a primary or secondary benzyl alcohol was applied (Table 2).

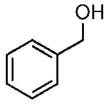
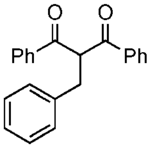
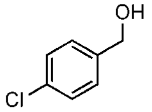
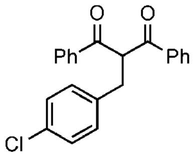
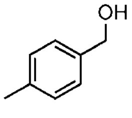
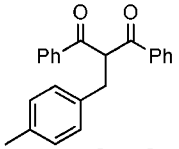
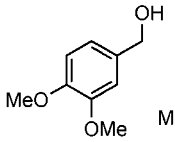
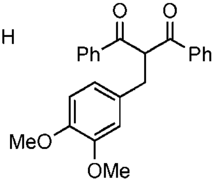
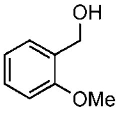
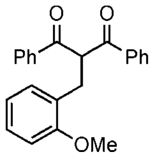
However, the reaction with 1-phenylethanol proceeded generally more readily, which is in agreement with a more stabilized carbocation intermediate.

Hence, we applied various 1-phenyl ethanol derivatives in the direct alkylation reaction of acetyl acetone using 1 mol % of Bi(OTf)$_3$ as catalyst (Table 3). In general, a range of differently substituted benzyl alcohols with electron-donating or -withdrawing groups are tolerated and the corresponding products were isolated after short reaction times (2−4 h) in good to excellent yields. Interestingly, if 1-phenylallyl alcohol was employed (Table 3, entry 6), the linear styrene derivative was obtained as the main product, together with the generation of 10% of the branched isomer.

In further experiments, we investigated the bismuth-catalyzed alkylation of dibenzoylmethane by employing various primary benzyl alcohol derivatives (Table 4). Again, differently substituted benzyl alcohols could be applied, and the products were isolated in good to excellent yields.

Table 4. Reaction with Various Benzyl Alcohol Derivatives

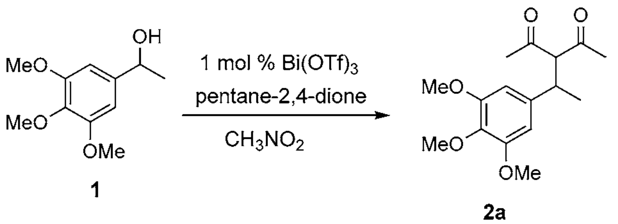


entry	alcohol	product	temp (°C)	time (h)	yield (%)[a]
1			100	6	84
2			80	10	69
3			60	7	91
4			40	6	61
5			60	11	70

[a] Isolated yield after column chromatography.

During our investigations of the bismuth-catalyzed alkylation with 1-trimethoxyphenylethanol as the electrophile (Table 3, entry 7), we observed that product formation proceeds already at room temperature with generation of a second product (Scheme 1).

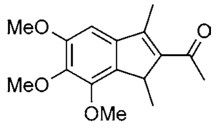
Scheme 1



1

2a

temp (°C)	2a	2b
25	76%	16%
60	46%	28%
100	0%	70%

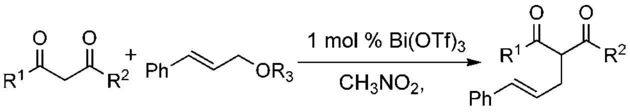


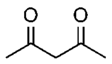
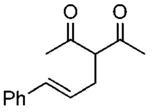
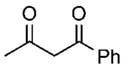
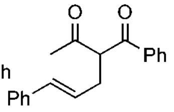
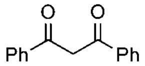
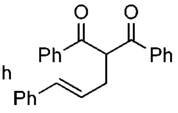
2b

This byproduct was identified to be the indene derivative **2b** and is the result of the benzylation of acetyl acetone followed by an intramolecular arylation. When performing the reaction at higher temperature, we were able to shift the product formation from the alkylated product **2a** toward the indene **2b**, and at 100 °C only indene formation was observed.

Following a successful bismuth-catalyzed direct benzylation of 2,4-pentanediones, we decided to examine cinnamyl alcohols as the electrophile in this reaction (Table 5). The allylic alkylation represents an important transformation, and

Table 5. Allylic Alkylation of Cinnamyl Alcohol Derivatives



entry	pentanedione	product	R^3	temp (°C)	time (h)	yield (%)[a]
1			H	60	5	62
2			Ac	25	4	55
3			H	25	5	73
4			Ac	25	5	70
5			H	25	5	62
6			Ac	25	4	78

[a] Isolated yield after column chromatography.

various metal-catalyzed processes, using predominantly palladium[7] but also copper,[8] tungsten,[9] nickel,[10] ruthenium,[11] molybdenum,[12] iridium,[13] indium,[14] and iron[15] complexes, have been described.

Most of these reactions have been performed with activated C nucleophiles or with acylated allyl alcohols leading to the corresponding α-branched products. Here, we present our investigations on the first bismuth-catalyzed direct allylic alkylation using a free allylic alcohol as the electrophile. Reactions were performed with different 1,3-dicarbonyl compounds and cinnamyl alcohol in the presence of 1 mol % of $Bi(OTf)_3$ catalyst (Table 5, entries 1, 3, and 5). Again the products were obtained in good isolated yields in short reaction times. Surprisingly, no significant improvement on the reactivity was observed when cinnamyl acetate was employed (Table 5, entries 2, 4, and 6).

Mechanistically, we believe that the alcohol is activated by the oxophilic bismuth catalyst, resulting in a better leaving group for the C nucleophile displacement.

In summary, we have developed a new and efficient bismuth-catalyzed direct benzylation of 2,4-pentanediones using various free benzyl alcohols and dicarbonyl compounds. The corresponding products of this direct C−C bond forming reaction have been isolated in good to excellent yields (Tables 2−4). Furthermore, we were able to extend this procedure to a direct allylic alkylation of 2,4-pentanediones resulting in the linear, unbranched products (Table 5). Compared to previous alkylations with preformed or activated electrophiles and the use of stoichiometric amounts of base and/or metal salts, this method requires remarkably small amounts of reactive, inexpensive, and nontoxic $Bi(OTf)_3$ catalyst (1 mol %) and the free benzylic or allylic alcohol. Furthermore, the mild reaction conditions, operational simplicity, practicability, and applicability to various substrates render this approach an interesting alternative to previously applied procedures. Additionally, a first extension of this procedure to highly functionalized indene derivatives was accomplished.

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Supporting Information Available: A general experimental procedure and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) In the case of benzyl alcohol as the electrophile and $BiCl_3$ or $BiBr_3$ as the catalyst, (1-((benzyloxy)methyl)benzene) was obtained as the major product. For a $BiBr_3$-promoted etherification using benzyl alcohols, see: Boyer, B.; Keramane, E. M.; Roque, J. P.; Pavia, A. A. *Tetrahedron Lett.* **2000**, *41*, 2891−2894.

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