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$Bi(OTf)_3$-Catalyzed Cycloisomerization of Aryl-Allenes

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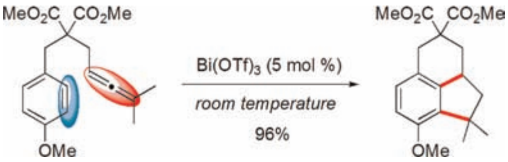
ABSTRACT



Intramolecular hydroarylation of allenes was achieved under very mild conditions using bismuth(III) triflate as the catalyst. Efficient functionalization of activated and nonactivated aromatic nuclei led to C−C bond formation through a formal Ar−H activation. A tandem bis-hydroarylation of the allene moiety was also developed giving access to various interesting polycyclic structures.

The development of catalytic, clean, efficient, and mild synthetic methods to create C−C bonds remains one of the most important topics in the field of organic chemistry. In this context, catalytic Friedel−Crafts reactions have gained particular attention.[1] The hydroarylation, namely the addition of an arene C−H bond across a multiple bond, represents the most atom-economical means to functionalize aromatic nuclei since theoretically no waste is produced during the reaction. Although the studies concerning the catalytic hydroarylation of alkynes[2] and alkenes[3] have been well-undertaken, the extension to related allenes has been less pursued.[4] Allenes have gained increasing attention during the past decades[5] and numerous transition-metal-catalyzed cycloisomerizations[6] and cycloadditions[7] involving allenes have been developed and enable access to valuable cyclic compounds usually with good selectivities.

Hydroarylation of allenes has been mainly reported using noble transition-metal catalysts based on gold[8,6c] and platinum[9] derivatives. This strategy has been elegantly used as the key step in the total synthesis of natural compounds with the functionalization of pyrrole[10] and indole[11] derivatives. Despite their efficiency, these methodologies suffer from the need to use only electron-rich arenes. For instance, Gagné has recently described the gold(I)- and silver(I)-catalyzed synthesis of substituted tetralins of highly activated aromatic derivatives.[9b]

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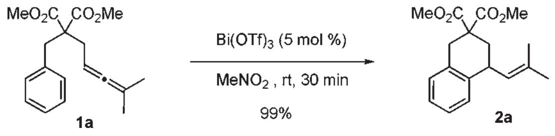
10.1021/ol3009667

Our group has been interested in the development of new cycloisomerization processes catalyzed by triflate[12] and triflimide[13] metal salts. Bismuth(III) triflate has recently emerged as a suitable and relatively inexpensive catalyst to catalyze various organic transformations[14] including Friedel–Crafts acylation,[15] benzylation,[16] and propargylation.[17] Moreover, this metal salt could be successfully employed as a π-Lewis acid to formally activate alkynes[18] and alkenes.[12d,e] We envisioned that bismuth(III) triflate could be an appropriate catalyst for the intramolecular hydroarylation of allenic substrates bearing a tethered activated and nonactivated aromatic ring.

In earlier studies, we noticed that nitromethane was an excellent solvent to perform C–C double bond activation with $Bi(OTf)_3$.[12e] By treatment with 5 mol % of this catalyst in nitromethane, the arene-allene **1a**, featuring a simple phenyl ring, was cleanly converted into tetralin **2a** after 30 min at room temperature with an excellent yield of 99% (Scheme 1). This result constitutes the first example of a catalyzed intramolecular Friedel–Crafts allylation of nonactivated phenyl rings, involving the participation of an allene under very mild conditions. Moreover, it avoids the use of noble metal complexes. Other metal triflates and metal complexes were also screened with no improvement of the efficiency.[19] Interestingly, triflic acid did catalyze this reaction with almost the same yield as $Bi(OTf)_3$; nevertheless we preferred exploring the scope and limitations of this novel cycloisomerization with the Bi(III) salt, since it gave generally better results. Moreover it is safer and easier-to-handle than corrosive and toxic triflic acid.

Scheme 1. $Bi(OTf)_3$-Catalyzed Transformation of **1a**



A subsequent exemplification of the reaction with arene-substituted analogues of **1a** was undertaken. Allene **1b** substituted in the *para* position with an *i*-Pr group underwent smooth cyclization to the corresponding carbobicycle **2b** with an excellent yield (Table 1, entry 2).

We next examined the influence of the nature of the linker by introducing an ether function. Oxygen-containing heterocycles are of particular interest, and the development of new reactions to access substituted and functionalized chromanes, an important class of naturally occurring and bioactive compounds,[20] is highly sought after. Satisfyingly, readily available phenol derivative **3a** was converted into the isobutenyl chromane **4a** at room temperature with an excellent yield of 93% (Table 1, entry 3). In this case, the catalyst loading could be reduced to only 1 mol % without a decrease in catalytic activity. Allenic substrate **3b**, easily obtained from vanillin and bearing additional methyl ether and aldehyde functions on the aromatic ring, was transformed into polysubstituted chromane **4b** in good yield, despite the presence of the aldehyde (entry 4). Chromane **4c** with a 4-MeO substituent could be obtained from allene **3c** with a low catalyst loading of 1 mol % (entry 5). Gratifyingly, the less electron-rich *para*-Cl derivative **3d** underwent a clean and efficient cyclization to **4d** within a short reaction time (entry 6). Interestingly, under the same reaction conditions, chiral-racemic substrate **3e** provided the bicyclic compound **4e** with the *trans* configuration, as the only diastereoisomer (Table 1, entry 7). Tetrahydroquinoline **6** was also obtained from tosylamide **5**, demonstrating good functional group tolerance and the broad applicability of this novel bismuth(III)-catalyzed transformation (entry 8). In addition, the catalyst could be recovered quantitatively by aqueous extraction and solvent evaporation and recyled in a second run with no loss of catalytic activity.[20]

One interesting feature of this reaction is that the products obtained after the cyclization still contain a C–C double bond which can be further functionalized. We wondered whether, at higher temperature, the same $Bi(OTf)_3$ catalyst could allow a subsequent hydroarylation of the generated olefin, to produce appealing tricyclic frameworks.

Gratifyingly, when the previous hydroarylation reaction was performed at a higher temperature, i.e. at refluxing nitromethane, arene-allene **1a** was directly converted into the tricyclic compound **9a** in 98% yield (Table 2, entry 1). This new tandem reaction was then extended to other allenic substrates. Allene **1b** bearing an *i*-Pr substituent easily underwent the double cyclization to afford the polycycle **9b** (entry 2). The oxygen-containing tricyclic product **10c** could be obtained from **3c** in 69% yield (entry 3). The reactivity of the allenic precursor **1c** linked

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(19) See Supporting Information for more details.

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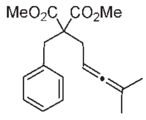
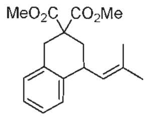
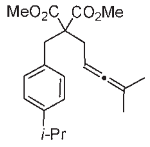
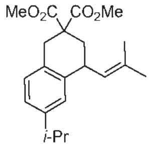
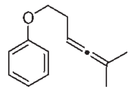
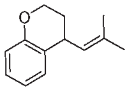
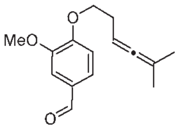
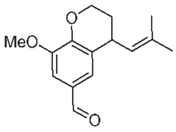
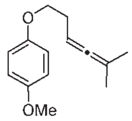
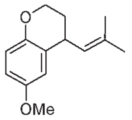
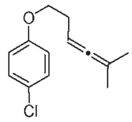
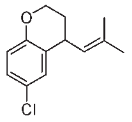
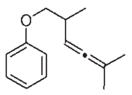
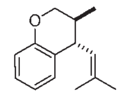
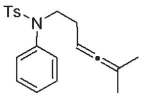
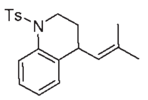
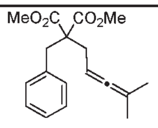
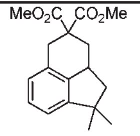
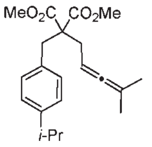
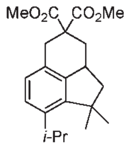
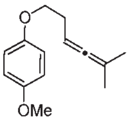
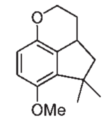
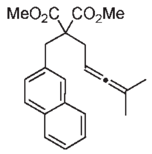
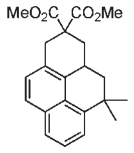
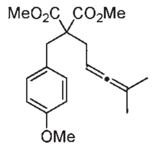
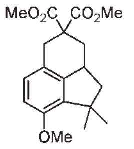
(24) Baes, C. F., Jr.; Mesmer, R. E. *The Hydrolysis of Cations*; Wiley-Interscience: 1976.

Table 1. Bi(III)-Catalyzed Cyclohydroarylation of Allenes

entry	substrate[a]	time	product	yield[b]
1	 **1a**	30 min	 **2a**	99%
2	 **1b**	30 min	 **2b**	97%
3	 **3a**	1 h	 **4a**	93%[c]
4	 **3b**	10 min	 **4b**	67%[d]
5	 **3c**	45 min	 **4c**	92%[c]
6	 **3d**	20 min	 **4d**	95%
7	 **3e**	10 min	 **4e**	91%[e]
8	 **5**	4 h	 **6**	82%

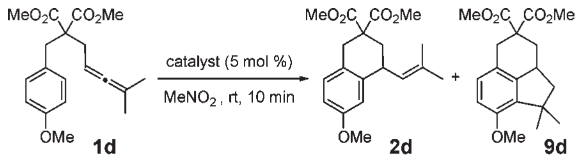
[a] Reaction conditions: allenic substrate in CH$_3$NO$_2$ (0.2 M) at room temperature with 5 mol % of Bi(OTf)$_3$. [b] Isolated yields. [c] 1 mol % of catalyst was used. [d] The reaction was conducted at reflux. [e] Only the *trans*-diastereoisomer was obtained.

Table 2. Bi(III)-Catalyzed Tandem Intramolecular Cyclizations

entry	substrate[a]	time (temp)	product	yield[b]
1	 **1a**	30 min (101 °C)	 **9a**	98%
2	 **1b**	30 min (101 °C)	 **9b**	87%
3	 **3c**	5 min (101 °C)	 **10c**	69%
4	 **1c**	24 h (20 °C)	 **11c**	97%
5	 **1d**	10 min (20 °C)	 **9d**	96%

[a] Reaction conditions: allenic substrate in CH$_3$NO$_2$ (0.2 M) at the indicated temperature with 5 mol % of Bi(OTf)$_3$. [b] Isolated yields.

Scheme 2. Selective Formation of **2d** and **9d**



1d → **2d** + **9d**

	2d	9d
Bi(OTf)$_3$	0%	**96%**
TfOH	**97%**	traces

to a 2-naphthyl group was also investigated. In the presence of 5 mol % Bi(OTf)$_3$ at room temperature, the tandem reaction proceeded smoothly and afforded regioselectively the tetracyclic product **11c** in 97% yield (entry 4). The tetrahydropyrene structure was confirmed by X-ray crystallographic analysis.[19] Methyl ether derivative **1d** could be cleanly cyclized into tricyclic compound **9d** in only 10 min at room temperature in almost quantitative yield (Table 2, entry 5).

Remarkably, when the reaction was conducted with TfOH (5 mol %) under the same conditions, only the olefin intermediate **2d** was formed with an excellent yield (Scheme 2). This result clearly points out a difference of behavior between TfOH and bismuth(III) triflate for this transformation. The few examples of gold(I)-catalyzed intermolecular hydroarylation of allenes with electron-rich arenes did not allow further participation of the remaining pendant double bond.[21] Remarkably, in the presence of Bi(OTf)$_3$, trisubstituted allene **12** reacted cleanly with

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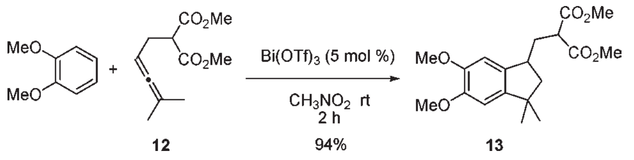
(25) (a) Williams, D. B. G.; Lawton, M. *J. Mol. Catal. A: Chem.* **2010**, *317*, 68. (b) Coulombel, L.; Rajzmann, M.; Pons, J.-M.; Olivero, S.; Duñach, E. *Chem.—Eur. J.* **2006**, *12*, 6356.

1,2-dimethoxybenzene at room temperature to form the functionalized Indane **13** in 94% yield, through an intermolecular regioselective tandem Friedel–Crafts allylation/alkylation (Scheme 3).

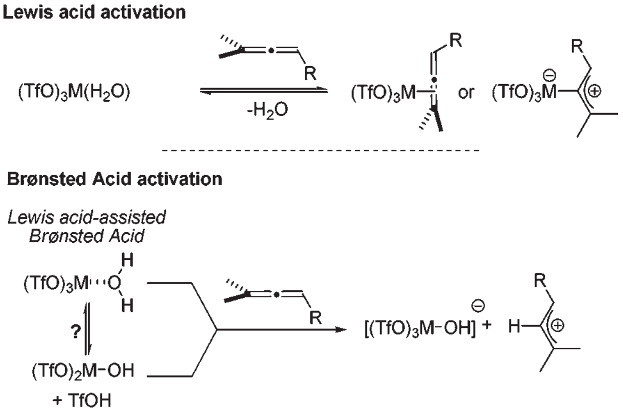
Scheme 3. Intermolecular $Bi(OTf)_3$-Catalyzed Tandem Reactions



Mechanistically, two general distinctive activation modes of the allene can be proposed for these cycloisomerizations. The first one is a purely metallic-based pathway in which the initial allene activation arises from a η^1 or η^2 sigma-type interaction between the electrophilic metal center and the allene moiety as previously established for gold catalysis (Scheme 4).[22]

The second possibility would involve a Brønsted acid catalysis. Many metal triflate mediated transformations have been described proceeding *via* proton transfer, but the nature of the catalytic species is still under debate.[23] Metal cations such as Bi^{3+} and Al^{3+} in water exhibit strong acidic properties because of the acidification through coordination of water molecules present in the "inner-sphere" of the cation.[24] Lewis acids are therefore prone to induce Brønsted acidity by coordination of a protic species (e.g., R–OH) to the metal center in organic solvents,[25] and some elegant stoichiometric and catalytic enantioselective protonation systems have been designed based on the concept of a Lewis acid assisted Brønsted acid (LBA).[26] Bismuth(III) triflate[27] is generally obtained and used as its hydrate form and therefore presents indubitably a strong induced Brønsted acidity. By treatment of a stoichiometric amount of commercial $Bi(OTf)_3$, 2,6-di-*tert*-butylpyridine, a proton scavenger, was instantly and totally displaced to its pyridinium salt as indicated by ^1H NMR monitoring in CD_3NO_2. The resulting mixture failed to promote cyclization in the presence of allene **1a**, which suggests that an LBA-type catalysis is presumably involved.

Scheme 4. Mechanistic Aspects: Plausible Activation Modes of the Allene by Metal Triflates



In conclusion we report here that commercially available and nontoxic bismuth(III) triflate is a suitable catalyst to successfully promote the hydroarylation of substituted allenes under very mild conditions. This reaction is quite general and has been used to synthesize carbocycles and heterocycles without using noble metals and additional ligands. Moreover, a new tandem reaction with a low catalyst loading has been developed in both intra- and intermolecular versions to form polycyclic structures. Some mechanistic investigations are in progress in order to devise appropriate enantioselective approaches to this unprecedented transformation.

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Supporting Information Available. Synthetic experimental details, spectroscopic data of all new compounds, and X-ray structure of **11c**. This material is available free of charge via Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.