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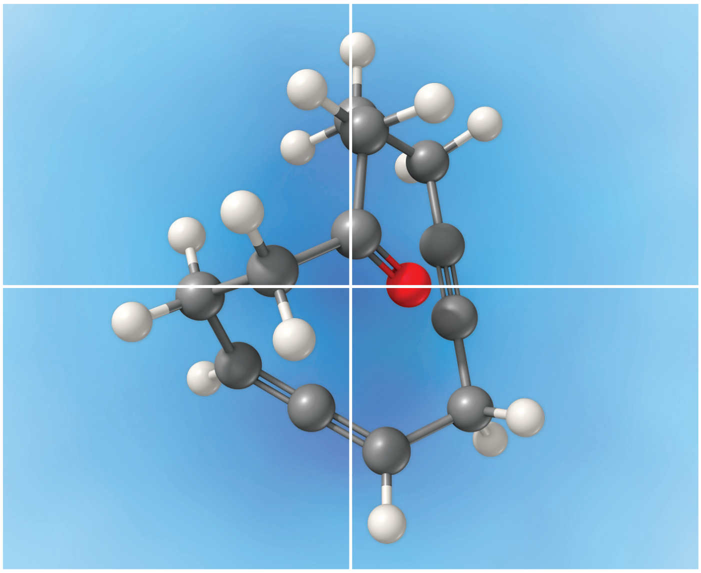

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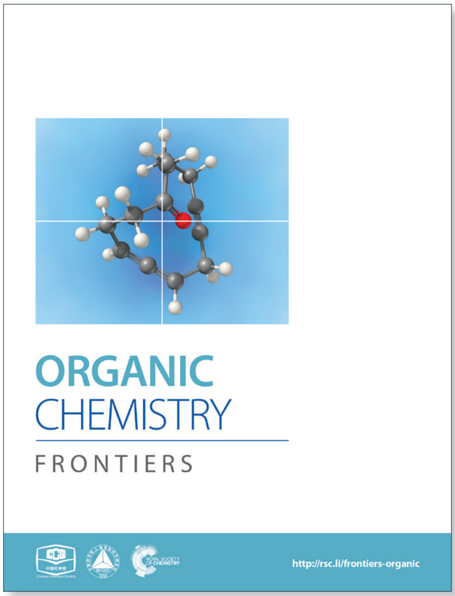

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ARTICLE TYPE

Bi(OTf)$_3$-Catalysed Synthesis of Substituted Indanes by a Double Hydroarylation of Unactivated 1,3-Dienes

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The intermolecular reaction between differently substituted electron-rich arenes and unactivated 1,3-dienes catalysed by bismuth(III) triflate is presented. This highly atom-economical process is conducted under very mild conditions and leads efficiently to substituted indane derivatives through a tandem bis-hydroarylation.

The Friedel-Crafts reaction remains a process of choice for the functionalisation of aromatic compounds through carbon-carbon bond formation.[1] Over the past century, several Lewis and Brønsted acids have been used to perform Friedel-Crafts reactions in the presence of alkyl halides. Despite the importance of this transformation, it may present some drawbacks, such as the use of toxic halide derivatives, the requirement of over-stoichiometric amounts of Lewis acids and therefore the production of non-negligible amounts of waste.

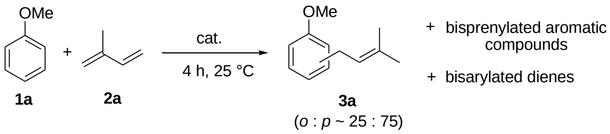
The hydroarylation reaction represents the most atom-economical way to functionalize aromatic nuclei, since no by-products are formed. Therefore, this process appears as a sustainable alternative to the original Friedel-Crafts reaction. The main reports on hydroarylation of olefins have been devoted to the addition of aromatic compounds to vinylarenes,[1e] typically styrene derivatives. The extension to conjugated dienes has been scarcely reported, possibly because of the increased difficulties to control the selectivities, avoiding polyfunctionalisation and diene polymerisation. The achievements made with 1,3-dienes in this field have been mainly focused on the synthesis of chromanes, by reaction of isoprene with phenol derivatives.[2] However, the direct allylation of non-phenolic arenes using 1,3-dienes is rare and, except for some sporadic reports,[3] it usually offers limited results in terms of yields and selectivities.[4]

Recently, our group described a mild and efficient intramolecular hydroarylation of olefins[5] and allenes[6] catalysed by relatively non-expensive and easily available Bi(OTf)$_3$,[7] giving rise to interesting aromatic carbocycles. This prompted us to study the more challenging Lewis acid-catalysed intermolecular reaction between 1,3-dienes and aromatic compounds, aiming at opening a straightforward access to diversely polysubstituted indanes through a tandem allylation/cyclisation process. Some related exemples have been attempted using a large excess of sulfuric acid as the catalyst, however with limited successes.[8] We herein report results concerning the catalytic, efficient and particularly atom-economic synthesis of indanes carried out under mild conditions.

We initiated our study by examining the coupling of anisole **1a** and isoprene **2a** in the presence of various metal triflate catalysts.

We rapidly grasped the difficulty of achieving this intermolecular reaction with a good selectivity in favour of a single coupling product. Monoprenylated anisole **3a** was usually obtained as a mixture of *para* and *ortho* regioisomers as a 75:25 ratio. A slight double bond isomerisation was also observed. Besides this desired monocoupling compound, anisole polyprenylation, diene polyarylation and polymer formation were competitive reactions occurring concomitantly, as observed by GC-MS analysis.

Table 1: Prenylation of anisole**1a** catalysed by metal triflate



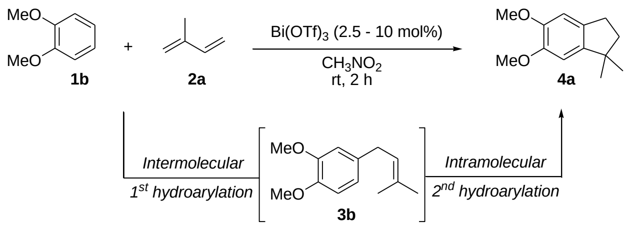
Entry[a]	Cat. (mol%)	Ratio **1a**:**2a**	Solvent	Yield of **3a**[b]
1	**In(OTf)$_3$** (10)	1:1	CH_3NO_2	6%
2	**Cu(OTf)$_2$** (10)	1:1	CH_3NO_2	5%
3	**Al(OTf)$_3$** (10)	1:1	CH_3NO_2	4%
4	**Bi(OTf)$_3$** (10)	1:1	CH_3NO_2	32%
5	**AgOTf** (10)	1:1	CH_3NO_2	–
6	**Zn(OTf)$_2$** (10)	1:1	CH_3NO_2	5%
7	**Yb(OTf)$_3$** (10)	1:1	CH_3NO_2	–
8	**Sn(OTf)$_2$** (10)	1:1	CH_3NO_2	49 %
9	**Sn (OTf)$_4$** (10)	1:1	CH_3NO_2	3%
10	**Sc(OTf)$_3$** (10)	1:1	CH_3NO_2	12%
11	Sn(OTf)$_2$ (10)	1:1	**$(CH_2Cl)_2$**	22%
12	Sn(OTf)$_2$ (10)	1:1	**CH_2Cl_2**	10%
13	Sn(OTf)$_2$ (10)	**2:1**	–	31%
14	Sn(OTf)$_2$ (10)	**5:1**	–	45%
15	Sn(OTf)$_2$ (10)	**10:1**	–	62%
16	Bi(OTf)$_3$ (10)	**10:1**	–	53%
17	Sn(OTf)$_2$ **(5)**	10:1	–	15%
18	Sn(OTf)$_2$ **(1)**	10:1	–	15%
19	Bi(OTf)$_3$ **(5)**	10:1	–	55%
20	**Bi(OTf)$_3$ (1)**	**10:1**	**–**	**94%**
21[c]	Bi(OTf)$_3$ (1)	10:1	–	52%
22[d]	Bi(OTf)$_3$ (1)	10:1	–	24%

a) To a solution of anisole **1a** in solvent (0.5 M), isoprene **2a** was added followed by $M(OTf)_n$ (1-10 mol%) at room temperature. The solution was stirred for 4 h and monitored by GC. b) GC yields using dodecane as internal standard. c) The reaction was conducted at 40 °C. d) The reaction was conducted at 10 °C.

Optimization of the reaction conditions have been carried out in order to limit these undesired side-reactions. Results are summarized in Table 1. The screening of catalysts (10 mol%) in nitromethane (Table 1, entries 1-10) highlighted $Sn(OTf)_2$ and $Bi(OTf)_3$ as promising intermolecular hydroarylation candidates (Table 1, entries 4 and 8). The reaction proved to be less efficient in dichloroethane and dichloromethane as compared to nitromethane which is a low-coordinating polar solvent favouring the stabilisation of cationic intermediates (Table 1, entries 8, 11 and 12). To limit the diene polymerisation and polyarylation, anisole was used in excess (entries 13-16). A 10:1 ratio of anisole over isoprene without additional solvent allowed to increase the selectivity in favour of **3a** with $Sn(OTf)_2$ and $Bi(OTf)_3$ to 62% and 53%, respectively (entries 15 and 16). Lowering the $Sn(OTf)_2$ loading to 1-5 mol% had a bad effect on the conversion (entries 17 and 18). Remarkably, the yield of **3a** could be increased to an excellent yield of 94% by performing the reaction with only 1 mol% of $Bi(OTf)_3$ indicating its higher catalytic activity (entry 20).

On the other hand, $Bi(OTf)_3$ has been reported as a good catalyst for the intramolecular hydrarylation of olefins. Being interested in performing two hydroarylations in a one step, we turned our attention to the coupling of isoprene **2a** with more electron-rich arenes. A better control of the regioselectivity and a favoured cyclisation process was expected. In the presence of 5 mol% of $Bi(OTf)_3$ and a slow addition (over 1 hour) of isoprene **2a**, 1,2-dimethoxybenzene **1b** reacted at room temperature in nitromethane (initial concentration of the arene: 0.25 $mol.L^{-1}$) to afford the desired indane **4a** as a single regioisomer with 54% yield. The other products detected by GC-MS analysis corresponded to a mixture of aromatic derivatives with two and three isoprene units (Table 2, entry 1). Surprisingly, the same reaction carried out at a higher initial arene concentration enabled to limit the aromatic polyfunctionnalization and improved the yield of indane **4a** to 79% (Table 2, entry 3).

Table 2: Optimisation of the reaction conditions for the coupling between 1,2-dimethoxybenzene and isoprene catalysed by $Bi(OTf)_3$



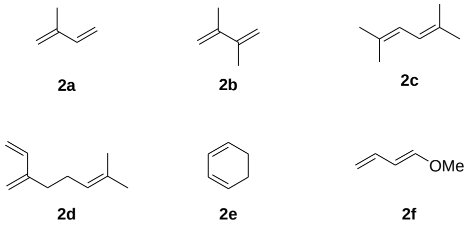
Entry[a]	Catalyst loading (mol%)	Initial conc. of **1b** ($mol.L^{-1}$)	Yield of **4a** (%)[b]
1	5	0.25	54
2	5	0.5	61
3	**5**	**1**	**79**
4	2.5	1	42
5	10	1	33
6[c]	5	1	44

a) General procedure : To a solution of 1,2-dimethoxybenzene (0.25-1 mmol) and $Bi(OTf)_3$ (2.5-10 mol%) in CH_3NO_2 (1 mL) was added isoprene (1.5 mmol) in CH_3NO_2 (1 mL) over 1 hour at rt and the solution was further stirred for 1 h. b) Isolated yields. c) The reaction was conducted at 40 °C.

Further variations of the reaction parameters such as the catalyst loading, and the temperature were carried out without enhancement of the yield (Table 2, entries 4-6).

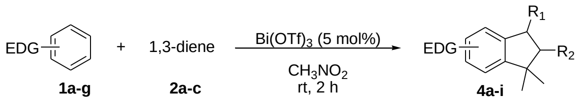
We then extended this novel catalytic sequential transformation to the synthesis of other indane derivatives with a variation of the arene and diene partners. Six commercially available and variously substituted dienes were tested (Figure 1).

Figure 1 Commercial 1,3-dienes tested

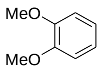
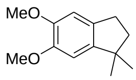
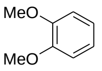
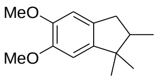
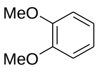
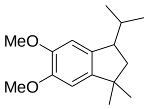
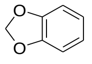
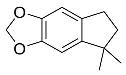
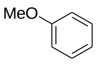
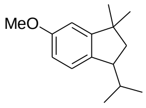
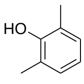
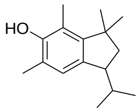
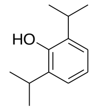
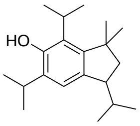
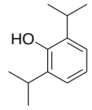
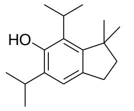
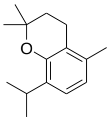
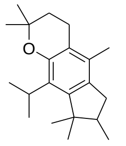


Likewise isoprene **2a**, 2,3-dimethyl-1,3-butadiene **2b** reacted efficiently under the same conditions (Table 2, entry 3) with 1,2-dimethoxybenzene **1b** to afford the desired indane product **4b** with an excellent yield of 95 % (Table 2, entry 2). Interestingly, the same arene efficiently coupled as well with a more hindered 1,3-diene such as 2,5-dimethyl-2,4-hexadiene **2c** (Table 2, entry 3). In this case, the substituted indane **4c** was obtained with 71 % yield and a total control of the regioselectivity through the tandem allylation/cyclisation process. It is worth to mention that the other 1,3-dienes tested were not effective in this reaction. Myrcene **2d** was prone to polymerisation and cyclohexadiene **2e** afford a mixture of polyallylated compounds. In addition, no coupling products could be detected with the (*E*)-1-methoxybuta-1,3-diene **2f**. Therefore, we turned our attention to the coupling of dienes **2a-c** with other electron-rich aromatic derivatives. 1,3-Benzodioxole **1c** reacted cleanly with isoprene **2a** to lead to polycyclic compound **4d** with 91 % yield (entry 4). Under the same conditions, less activated anisole **1a** was found to react selectively with the tetrasubstituted 1,3-diene **2c** at room temperature (entry 5). The lower polymerisation ability due to the higher hindrance of this diene in comparison to isoprene **2a** allowed the regioselective monofonctionalisation of anisole at the *para* position. Increase of the temperature after total consumption of the starting diene **2c** afforded the cyclised product **4e** with 79 % yield. 2,6-Dimethylphenol **1d** and more hindered 2,6-diisopropylphenol **1e** efficiently reacted regioselectively with 2,5-dimethyl-2,4-hexadiene **2c** to afford substituted indanes **4f** and **4g**, respectively, with excellent yields (entries 6 and 7).Isoprene **2a** could also be coupled to phenol derivative **1e** giving rise to indane **4h**, known as the artificial musk HDDI, which possess a very strong musk odour (entry 8).[9] This catalytic procedure represents an efficient access to this artificial fragrance compound under very mild reaction conditions. Fully substituted aromatic compound **4i** was also selectively obtained by reaction of 2,3-dimethylbuta-1,3-diene **2b** and the corresponding chromane derivative **1f** with a nearly quantitative yield (entry 9).

Table 2: Tandem hydroarylations of 1,3-dienes



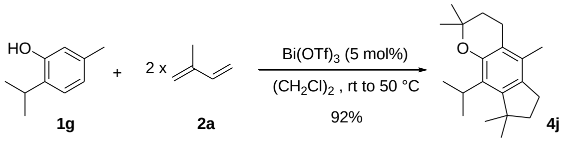
1a-g **2a-c** **4a-i**

Entry^a	Arene		Diene	Product		Yield^b
1		**1b**	**2a**		**4a**	79 %
2		**1b**	**2b**		**4b**	95 %
3		**1b**	**2c**		**4c**	71 %
4		**1c**	**2a**		**4d**	91 %
5		**1a**	**2c**		**4e**	79%^{c}
6		**1d**	**2c**		**4f**	93%^{c}
7		**1e**	**2c**		**4g**	94%
8		**1e**	**2a**		**4h**	82%
9		**1f**	**2b**		**4i**	97%^{c}

a) General procedure: To a solution of arene (1 mmol) and Bi(OTf)$_3$ (0.05 mmol) in CH_3NO_2 (1 mL) was added the diene (1.5 mmol) in CH_3NO_2 over 1 h at room temperature. The reaction was further stirred at rt for 1 h. b) Isolated yields. c) The temperature was increased to reflux after the total consumption of the diene (GC monitoring).

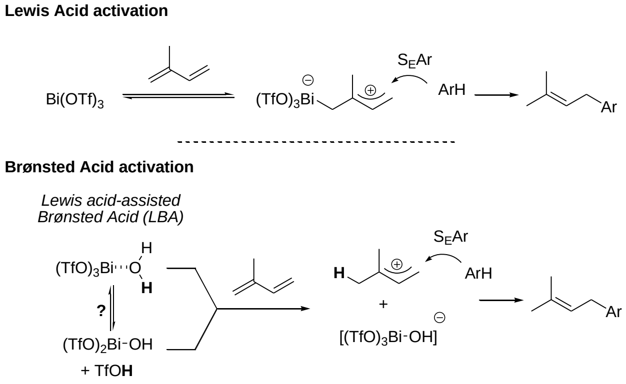
As an extension of this methodology, we were able to perform an efficient double tandem allylation/cyclization by the reaction of thymol **1g** with two isoprene units **2a** and a catalytic amount of Bi(OTf)$_3$ (Scheme 1). The first isoprene unit reacted with the phenolic part to form a chromane sub-structure. The second equivalent gave a regioselective access to the fully substituted benzene **4j** with an excellent total yield of 92%. This unprecedented transformation, involving four bond formation steps in a one-pot reaction was very efficient at room temperature in dichloroethane with a heating at 50 °C after the diene addition at room temperature, to facilitate the final intramolecular hydroarylation.

Scheme 1: Efficient synthesis of tricyclic compound **4j** from commercially available thymol and isoprene



From a mechanistic point of view, two activation modes of the 1,3-diene can be suggested (Scheme 2). The first pathway invokes the formation of an allylic cation generated by the direct activation of the diene by Bi(OTf)$_3$. Trapping of this cationic intermediate by the aromatic derivative through an S_EAr type reaction furnishes the allylated arene. This possibility has already been proposed for the Bi(OTf)$_3$-catalysed hydroamination of 1,3-dienes.[10] The alternative pathway involves a Brønsted acid catalysis. Even though the first Lewis acid activation pathway cannot be entirely ruled out, the experimentally observed activation of highly hindered diene **2c** suggests that a Brønsted-type acid catalysis could be preferred. In this case, the acid species would be produced either by hydrolysis or by hydration of the triflate salt. The first possibility would liberate triflic acid whereas the latter one would form an acidic hydrated metal which could act as a Lewis acid-assisted Brønsted acid (LBA)-type catalyst.[11] The activity of triflate salts is still a matter of debate[12] but theoretical calculations tend to suggest that hydration of triflate and trifimidate salts is much favored over their hydrolysis.[13] Finally, the second catalysed intramolecular hydroarylation[5] gives rise to the indane procucts.

Scheme 2: Mechanistic aspects



In conclusion, we have developed an efficient Bi(III)-catalysed regioselective condensation of 1,3-dienes with arenes. This highly atom-economical process generally using 5 mol% of catalyst leads to substituted indane derivatives through a sequential intermolecular hydroarylation of the diene followed by an intramolecular hydroarylation of the resulting tethered olefin. The control of the reaction parameters such as the addition rate, the solvent, the concentration of the substrate and the reaction temperature have to be finely tuned, in order to limit side-reactions and diene polymerisation. Moreover, the regioselectivity of these transformations is excellent and can be predicted by the analysis of the electronic and steric contributions of the different groups present on the starting arene.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

†† This work is dedicated to Professor Max Malacria on the occasion of his 65th birthday.

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