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Assia Omrani, Farhat Rezgui, Elisabet Dunach, Sophie Poulain-Martini. Bi(OTf)₃-catalysed regioselective arylation of Morita-Baylis-Hillman type allylic electrophiles. *Tetrahedron Letters*, 2020, 61, pp.151758 -. 10.1016/j.tetlet.2020.151758 . hal-03489592

HAL Id: hal-03489592

<https://hal.science/hal-03489592>

Submitted on 20 May 2022

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Bi(OTf)₃-catalysed regioselective arylation of Morita-Baylis-Hillman type allylic electrophiles

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

ABSTRACT

The Friedel-Crafts reaction of a wide variety of arenes and heteroarenes was accomplished, in good to excellent yields (50-98%) and with high α -regioselectivity, using Morita-Baylis-Hillman acetates. Functionalized conjugated enones were obtained under Bi(OTf)₃ catalysis (10 mol%) in dichloroethane (DCE) at 50 °C.

Keywords:

Morita-Baylis-Hillman; Lewis superacid;

Friedel-Crafts reaction; Metal triflate;

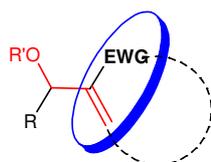
Bismuth triflate

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1. Introduction

Aromatic compounds are commonly found in various drugs[1] and are frequently employed in materials science.[2] The development of new synthetic methods for the construction of such structures has therefore gained significant attention. Among these, the Friedel-Crafts reaction is one of the oldest processes that is still attractive for the introduction of a wide range of electrophilic moieties onto aromatic rings.[3]

On the other hand, the Morita-Baylis-Hillman (MBH) adducts, considered as functionalized allylic compounds (Fig. 1), have been used as powerful electrophiles in various synthetic methods.[4] In this context, a large number of synthetic transformations have been reported under catalyst-free conditions[5] or using efficient catalysts and additives such as Brønsted or Lewis acids,[6] organocatalysts, e.g. DABCO,[7] DMAP or imidazole,[8] as well as palladium complexes.[9]



EWG = ketone, ester, nitrile, sulfoxide

R = H, alkyl, aryl

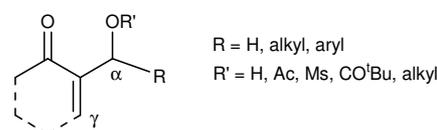
R' = H, Ac, Ms, CO^tBu, alkyl

Figure 1. MBH adducts structure.

As part of the development of the chemistry of MBH adducts, Basavaiah and co-workers have reported the stereoselective synthesis of trisubstituted olefins *via* a concentrated H₂SO₄-catalyzed Friedel-Crafts reaction of acyclic MBH alcohols with benzene.[10] Later, Kim and co-workers reported the arylation of acyclic MBH tosylamines with benzene and its derivatives, using concentrated H₂SO₄ as the additive.[11] Subsequently, numerous synthetic applications, involving the Friedel-Crafts reaction of such derivatives, allowing access to 2-benzoxepines,[12] 7*H*-benzocycloheptenes, quinoline and indene derivatives were reported.[13]

In addition, the C-3-electrophilic substitution of indoles, by acyclic MBH alcohols and acetates, was previously carried out under the catalysis of metal triflates such as Al(OTf)₃,[14] Sc(OTf)₃[15] and AgOTf,[16] as well as InBr₃[17] or palladium.[18]

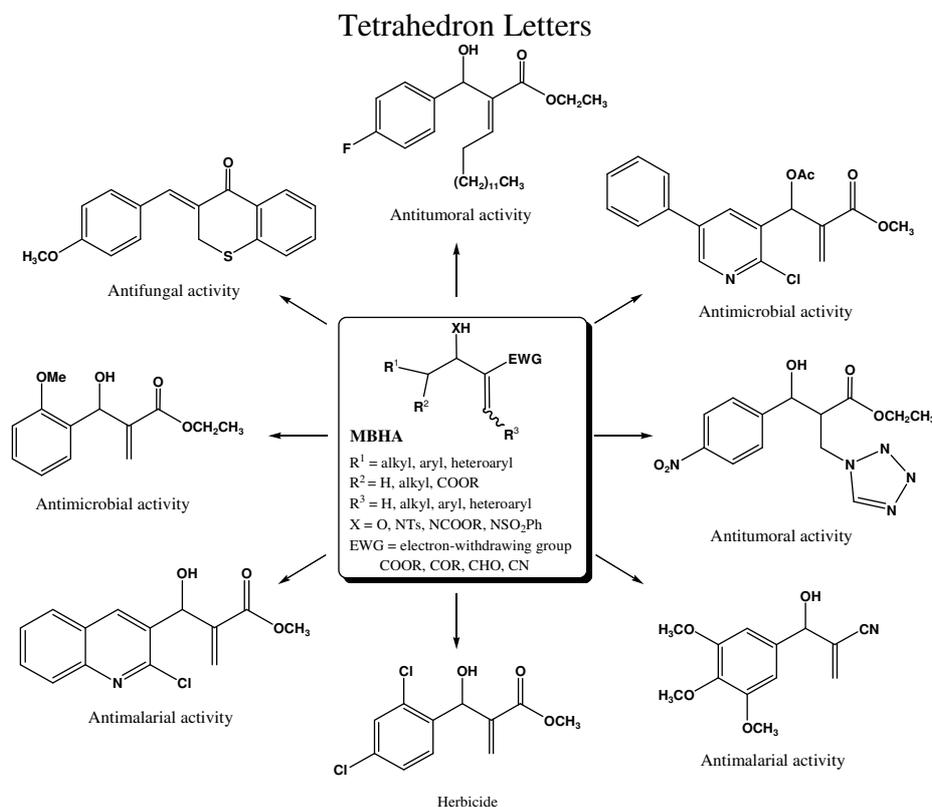
The nucleophilic allylic substitution of acyclic MBH adducts affords either, under catalyst-free conditions, mainly the γ -products *via* a S_N2' reaction[19] or the α -products under DABCO- or Pd-promoted S_N2'-S_N2' transformations.[20,21] In particular, with bulky Ph₃P as the catalyst, α -substitution of the MBH acetate occurred with 2-trimethylsilyloxyfuran derivatives as the nucleophile.[22]



R = H, alkyl, aryl

R' = H, Ac, Ms, CO^tBu, alkyl

Figure 2. α - and γ -Regioselectivity for the nucleophilic substitution of MBH adducts.



In contrast, such allylic reactions, involving cyclic MBH derivatives, generally provide the α - and/or γ -products (Fig. 2).[13,18,23] The ratio of the obtained isomers is highly dependent on the nature of the R' group (Fig. 2). Indeed, when the reaction proceeds with MBH alcohols ($R' = \text{H}$), mixtures of the α - and γ -products are obtained, and during the course of the reaction, a rearrangement from the γ - to α -products has been observed.[23] When the reaction is performed with MBH acetate as a good leaving group ($R = \text{Ac}$), α -regioselective substitution has been reported.[18] Chemical transformations of the obtained synthons can lead to potentially biologically active substances.[24] Representative examples of interesting structures are given in Scheme 1, indicating the versatility of these intermediates.

Our research group has previously reported contributions to the development of cyclic MBH chemistry and in this regard, we have been particularly interested in the nucleophilic allylic substitution of a variety of MBH derivatives, using various catalysts or additives, including DMAP or imidazole,[25] palladium[26] and $\text{Fe}(\text{OTf})_3/\text{BF}_3 \cdot \text{Et}_2\text{O}$.[27]

Taking into account the previous reports of the catalytic activation of nucleophilic allylic substitution by metal triflates[28] and other Lewis acids,[29] we decided to explore the Friedel-Crafts reaction between both acyclic and cyclic MBH acetates and a series of arenes and heteroarenes as nucleophiles, using a catalytic amount of $\text{Bi}(\text{OTf})_3$, under mild conditions.

2. Results and Discussion

Optimisation of the catalytic system was performed for the model reaction between the MBH acetate **1a** and an electron-rich aromatic compound, *i.e.* 1,3,5-trimethoxybenzene **2a** (ratio **1a/2a** = 1:2). A range of Lewis acids, including metal triflate catalysts, were screened for their catalytic activity (Table 1).

Table 1. Screening of Lewis acid catalysts.

Entry ^a	Catalyst (mol%)	Reaction Conditions	Time	Yield ^b 3aa (%)
1	AlCl_3 (10)	DCE, 50 °C	24 h	0
2	BiCl_3 (10)	DCE, 50 °C	24 h	0
3	$\text{Bi}(\text{OAc})_3$ (10)	DCE, 50 °C	24 h	0
4	$\text{In}(\text{OTf})_3$ (5)	DCE, 50 °C	10 min	71
5	$\text{Al}(\text{OTf})_3$ (5)	DCE, 50 °C	10 min	71
6	$\text{Bi}(\text{OTf})_3$ (5)	DCE, 50 °C	10 min	80
7	$\text{Bi}(\text{OTf})_3$ (5)	CH_3NO_2 , 50 °C	10 min	75
8	$\text{Bi}(\text{OTf})_3$ (5)	THF, 50 °C	10 min	75
9	$\text{Bi}(\text{OTf})_3$ (5)	DCE, reflux	10 min	66
10	$\text{Bi}(\text{OTf})_3$ (5)	CH_3NO_2 , reflux	10 min	57
11	$\text{Bi}(\text{OTf})_3$ (10)	DCE, 50 °C	10 min	95
12	TfOH (5)	DCE, 50 °C	10 min	50

^a General screening procedure: To a stirred solution of allylic acetate **1a** in DCE (0.3 M) and trimethoxybenzene **2a** (2 eq), at 50 °C, was added the catalyst (5-10 mol%). ^b Isolated yield.

While the conversion of **1a** was very low using AlCl_3 , BiCl_3 and $\text{Bi}(\text{OAc})_3$, in dichloroethane (DCE) at 50 °C (Table 1, entries 1-3), α -substituted compound **3aa** was formed in 71-80 % yield after ten minutes, using 5 mol% of $\text{In}(\text{OTf})_3$, $\text{Al}(\text{OTf})_3$ or $\text{Bi}(\text{OTf})_3$ (Table 1, entries 4-6). The yield was not improved when the reaction was conducted in solvents such as CH_3NO_2 or THF, or when the mixture was heated at reflux (Table 1, entries 7-10). With a catalytic loading of 10 mol% in DCE, $\text{Bi}(\text{OTf})_3$ was found to be the most effective catalyst and **3aa** was obtained in 95% yield, after only ten minutes at 50 °C (Table 1, entry 11). Interestingly, triflic acid also catalysed the formation of **3aa**, however with a decreased yield of 50% (Table 1, entry 12). In this preliminary study, in addition to the α -product **3aa**, no side-

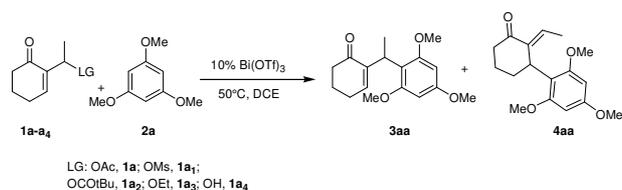
product resulting from competitive substitution at the γ -carbon of **1a** could be detected by ^1H NMR analysis of the crude reaction mixture.

On the basis of the previous study, we selected the optimized conditions involving $\text{Bi}(\text{OTf})_3$ (10 mol%) as the catalyst, in DCE at 50 °C, for further transformations of other MBH acetates with various arenes.

We first evaluated the influence of the leaving group (LG) on the steric course of the arylation reaction, using the MBH derivatives **1a**, **1a**₁₋₄ bearing various leaving groups, *i.e.* LG= OAc, OMs, OCO^tBu, OEt, OH (Table 2). We found that the arylation of allylic compounds **1a**, **1a**₁₋₄ with **2a** worked well and the corresponding final product **3aa** was obtained in 62-95% yield. The reaction selectivity was dependent on the nature of the leaving group. Indeed, in the case of LG= OAc, a clean reaction occurred, affording exclusively the α -substitution product **3aa** in a short reaction time (10 min), and in 95% yield (Table 2, entry 1). The other MBH adducts **1a**₁ and **1a**₂, possessing good leaving groups (LG= OMs, OCO^tBu, respectively), reacted similarly to acetate **1a**, affording the α -substitution product **3aa**, along with the γ -substitution derivative **4aa** as the minor product (Table 2, entries 2, 3).

In the case of poor leaving groups such as LG= OH (**1a**₃), OEt (**1a**₄), the reaction selectivity was lower, giving a *ca.* 60/40 mixture of the α - and γ -substitution products **3aa** and **4aa**, respectively, with longer reaction times (Table 2, entries 4, 5).

Table 2. Arylation of cyclic MBH adducts **1a**-**a**₄ with **2a**.



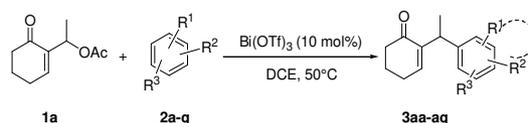
Entry ^a	LG	(1a - a ₄)	Time (min)	Yield ^b (%)	Ratio 3aa / 4aa ^c
1	OAc	(1a)	10	95	100:0
2	OMs	(1a ₁)	2	86	95:5
3	OCO ^t Bu	(1a ₂)	70	78	92:8
4	OEt	(1a ₃)	90	68	60:40
5	OH	(1a ₄)	45	62	58:42

^a General procedure: to a stirred solution of allylic acetate **1a**-**a**₄ in DCE (0.3 M) and trimethoxybenzene **2a** (2 eq), at 50 °C, was added $\text{Bi}(\text{OTf})_3$ (10 mol%). ^b Isolated yield. ^c Isomer ratios were determined by GC.

The high selectivity previously observed in the arylation of acetate **1a** prompted us to further explore the scope of this synthetic protocol with a variety of arenes and heteroarenes.

Thus acetate **1a** was reacted with various aromatic compounds **2b**-**g** to provide α -products **3ab**-**ag** (Table 3). As shown in entries 2 and 3, the arylation of cyclic MBH acetate **1a** with 1,4-disubstituted aromatic derivatives **2b** and **2c** occurred at the available *ortho*-positions. The corresponding Friedel-Crafts adducts **3ab** and **3ac** were isolated in 66% and 65% yield, respectively (Table 3, entries 2, 3).

Table 3. Arylation of MBH acetate **1a** with various arenes **2a**-**g**.

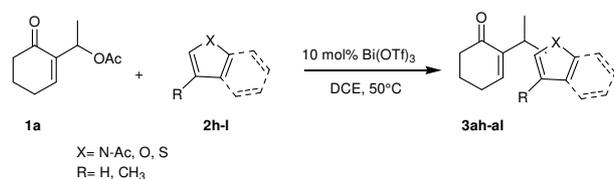


Entry ^a	Ar-H	α -Product 3aa - ag	Time	Yield ^b (%) (3 , ratio) ^c
1	2a	3aa	10 min	95% (3aa , 100)
2	2b	3ab	2.5 h	66 (3ab , 100)
3	2c	3ac	2 h	65 (3ac , 100)
4	2d	3ad , 3ad'	30 min	95 (3ad , 88) (3ad' , 12)
5	2e	3ae , 3ae' , 3ae''	3 h	80 (3ae , 60) (3ae' , 11) (3ae'' , 29)
6	2f	3af , 3af'	3 h	88 (3af , 63) (3af' , 37)
7	2g	3ag	1.5 h	76 (3ag , 100)

^a General procedure: to a stirred solution of allylic acetate **1a** in DCE (0.3 M) and arene **2a**-**g** (2 eq), at 50 °C, was added $\text{Bi}(\text{OTf})_3$ (10 mol%). ^b Isolated yields. ^c Isomer ratios were determined by ^1H NMR spectroscopy. ^d DCE at reflux.

The procedure was also shown to be successful with 1,3-trimethoxybenzene **2d**, whose electrophilic substitution at the *ortho*- and *para*-positions with the acetate **1a**, afforded predominately the less hindered regioisomer **3ad** (88%), along with **3ad'** (12%), in 95% combined yield (Table 3, entry 4).

Table 4. Arylation of the MBH acetate **1a** with various heteroarenes **2h**-**l**.



Entry ^a	Ar-H	α -Product 3	Time (h)	Yield ^b (%) (3, ratio) ^c
1 ^d		 	2	83 (3ah, 72) (3ah', 28)
2		 	2	72 (3ai, 66) (3ai', 22) (3ai'', 12)
3		 	1.5	50 (3aj, 90) (3aj', 10)
4		 	0.5	82 (3ak, 80) (3ak', 20)
5			0.3	61 (3al, 100)

^a General procedure: to a stirred solution of allylic acetate **1a** in DCE (0.3 M) and arene **2h-I** (2 eq), at 50 °C, was added Bi(OTf)₃ (10 mol%). ^b Isolated yield. ^c Isomer ratios were determined by ¹H NMR spectroscopy. ^d Ratio **1a/2i** = 1:10.

In addition, the arylation of **1a** with 1-methoxy-3-methylbenzene **2e**, provided a mixture of three regioisomers in which the less hindered derivative **3ae** is the main compound (60%), along with **3ae'** (11%) and **3ae''** (29%), in 80% combined yield (Table 3, entry 5).

Table 5. Arylation of various MBH acetates **1a-g** with arenes.

We also examined the reaction of anisole **2f** with acetate **1a**, and found that it mostly afforded the less hindered *para*-regioisomer **3af**, along with the *ortho*-product **3af'** (*para/ortho* = 63:37), in 88% combined yield (Table 3, entry 6).

Finally, we investigated the Friedel-Crafts reaction of mesitylene that provided the corresponding compound **3ag** in 76% yield (Table 3, entry 7).

In order to explore the scope and the limitations of this strategy, we have also investigated the reaction of acetate **1a** with common electron-deficient arenes such as bromobenzene, acetophenone, methyl benzoate, benzonitrile and pyridine, under the optimized conditions. In all of these cases, the reaction failed, and the starting material was recovered within 6-8 h, suggesting that these electron-deficient arenes are not sufficiently reactive to be used in this protocol. In this regard, a literature survey showed that electron-deficient (hetero)arenes could alternatively be functionalized *via* C-H amination[30] or allylation[31] using copper catalysts, as well as Pd- or Rh-catalyzed C-H olefination[32] and arylation.[33,34]

We successfully extended the arylation of acetate **1a** with a variety of electron-rich heteroarenes **2h-I**, under the optimized conditions (Table 4). In this regard, the reactions of **1a** with thiophene **2h**, methylthiophene **2i**, benzothiophene **2j** and benzofuran **2k**, gave the corresponding the 2- and/or 3-disubstituted arenes **3**, resulting from the expected electrophilic substitution. The arylation products were obtained within 0.3-2 h in satisfactory to good yields (Table 4, entries 1-4).

Moreover, the reaction of the protected indole derivative **2l** with the MBH acetate **1a**, selectively gave 3-substituted indole **3al** in 61% yield (Table 4, entry 5).

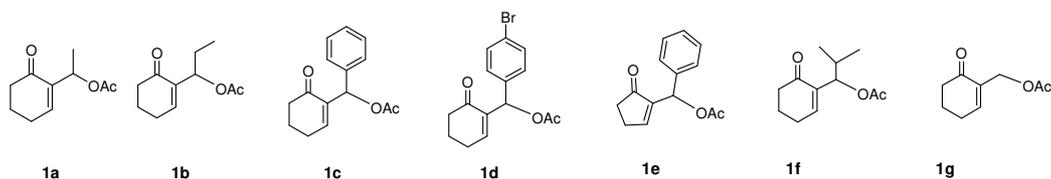
The full conversion of acetate **1a**, in the presence of thiophene **2h** and its derivatives **2i-j**, within 1.5-2 h (Table 4, entries 1-3), is slower than that using the more reactive benzofuran **2k** (0.5 h) or indole derivative **2l** (0.3 h) (Table 4, entries 4,5).

The above synthetic protocol was also tested on a series of cyclic allylic acetates **1a-g**, which were differently substituted at the β' -position (R=H, Et, *i*-Pr, Ph) (Table 5), in order to determine the possibly effect of steric hindrance on the arylation reaction course.

The results, given in Table 5, show that the six-membered derivatives **1b** (R= Et), **1c** (R= Ph), **1d** (R= 4-BrPh), as well as the five-membered compound **1e** (R= Ph), were efficiently arylated with **2a**, affording exclusively the corresponding α -products **3** in 67-88% yield (Table 5, entries 2-5).

Similarly, the allylic acetate **1c** (R= Ph) was fully converted, in 86-91% yield and with excellent selectivity, into the α -products **3cd**, **3cd'** and **3cg** using 1,3-dimethoxybenzene **2d** and mesitylene **2g**, respectively (Table 5, entries 6, 7). In addition, upon the treatment of nucleophilic heteroarenes **2h** and **2k** with **1c** (R= Ph), we also observed the formation of only the α -products **3ch** and **3ck** in 65% and 98% yields, respectively (Table 5, entries 8, 9).

Once again, we explored the electrophilic substitution of 1,3,5-trimethoxybenzene **2a** with the acetates **1f** (R= *i*-Pr) and **1g** (R= H), as they would be respectively the most and the least sterically hindered derivatives at the β' -position, in the series of acetates **1a-e**. We observed that their behavior in the arylation



Entry ^a	Reactant	Product	Time (min)	Yield ^b (%) (products, ratio) ^c
1	1a/2a		10	95 (3aa , 100)
2	1b/2a		30	67 (3ba , 100)
3	1c/2a		10	88 (3ca , 100)
4	1d/2a		1	75 (3da , 100)
5	1e/2a		25	87 (3ea , 100)
6	1c/2d		10	91 (3cd , 85) (3cd' , 15)

Entry ^a	Reactant	Product	Time (min)	Yield ^b (%) (products, ratio) ^c
7	1c/2g		30	86 (3cg , 100)
8	1c/2h		10	65 (3ch , 55)
9	1c/2k		10	98 (3ck , 100)
10	1f/2a		30	69 (3fa , 75) (4fa , 25)
11	1g/2a		4h 45min	87 (3ga , 36) (5ga , 64)

^a General procedure: to a stirred solution of allylic acetate **1a-1g** in DCE (0.3 M) and arene **2a-k** (2 eq), at 50 °C, was added Bi(OTf)₃ (10 mol%). ^b Isolated yields. ^c Isomer ratios were determined by ¹H NMR spectroscopy.

reaction was different from that of the acetates **1a-e**. Indeed, the acetate **1f** was totally converted within 30 min, in 69% yield, into a mixture of the α -product **3fa** (75%) and γ -product **4fa** (25%) (Table 5, entry 10).^[13,18,23]

In contrast, the electrophilic substitution of the primary acetate **1g** with **2a**, was significantly slower (4 h 45 min), affording mostly the α -product **3ga**, along with the 2,3-dialkylated cyclohexanone **5ga**, resulting from bis- β,β' -1,4-addition of **2a** onto **1g** (Table 5, entry 11).^[35]

The arylation of β' -diversely substituted acetates **1a-f** with aromatic derivatives **2a-f** was rapid (10 min-30 min, Table 5,

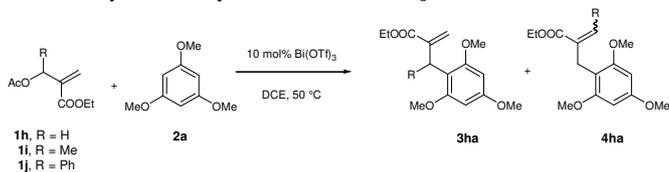
entries 1-10), whereas the conversion of the primary acetate **1g** into **3ga** and **5ga** was significantly slower (4 h 45 min, Table 5, entry 11). We believe that this electrophilic substitution should follow a reaction path that might be different from that of the secondary acetates **1a-f** (Scheme 3, *vide infra*).

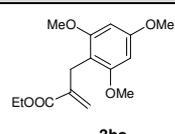
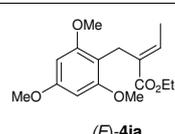
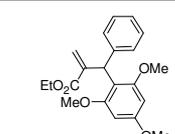
The arylation protocol was also extended to acyclic MBH acetates **1h-j** (Table 6). The acetate **1h** (R= H) was arylated with 1,3,5-dimethoxybenzene **2a**, as an electron-rich aromatic compound, to afford α -substituted product **3ha**, in 87% yield within 6 h (Table 6, entry 1).

The aromatic electrophilic substitution was also efficiently performed with **2a** using compound **1i** (R= Me), leading, *via* attack of the less hindered allylic site (S_N2' reaction), to the (*E*)- γ -product **4ia**, in 50% yield and with excellent regioselectivity (Table 6, entry 2).[19]

In the case of the compound **1j** (R= Ph), the Friedel-Crafts reaction provided almost an equimolar mixture of α - and (*E*)- γ -products **3ja** and **4ja**, in 56% combined yield (Table 6, entry 3).

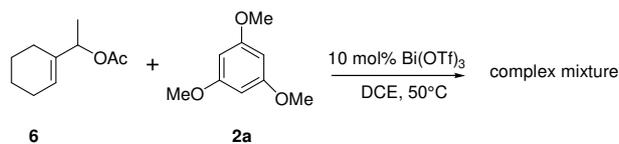
Table 6. Arylation of acyclic MBH acetates **1h-j** with **2a**.



Entry ^a	R	Product	Time	Yield ^c (%)	Selectivity (Regioisomer, ratio) ^b
1	H (1h)		6 h	87	(3ha , 100)
2	Me (1i)		8 h	50	(<i>E</i> - 4ia , 100)
3	Ph (1j)	 	15 min	56	(3ja , 49) (<i>E</i> - 4ja , 51)

^a General procedure: to a stirred solution of allylic acetate **1h-j** in DCE (0.3 M), and arene **2a** (2 eq), at 50 °C, was added Bi(OTf)₃ (10 mol%). ^b Isomer ratios were determined by ¹H NMR spectroscopy. ^c Isolated yields.

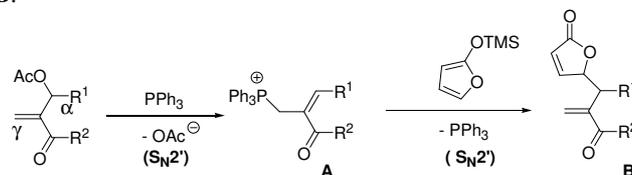
In order to disclose the possible role played by the carbonyl group of MBH acetates in the Friedel-Crafts reaction, some complementary experiments were carried out. For this purpose, we examined, under the optimized conditions, the behavior of cyclic allylic acetate **6**, towards 1,3,5-trimethoxybenzene **2a** as a nucleophile, as it does not possess the ketone group, but has the same skeleton and the same allylic moiety as **1a**. An inseparable complex mixture was obtained within 5 min, suggesting the crucial role played by the carbonyl group in the arylation of MBH acetates **1** by various arenes and heteroarenes **2** (Scheme 2).[18,23,27]



Scheme 2. Arylation attempts of allylic acetate **6** with **2a**.

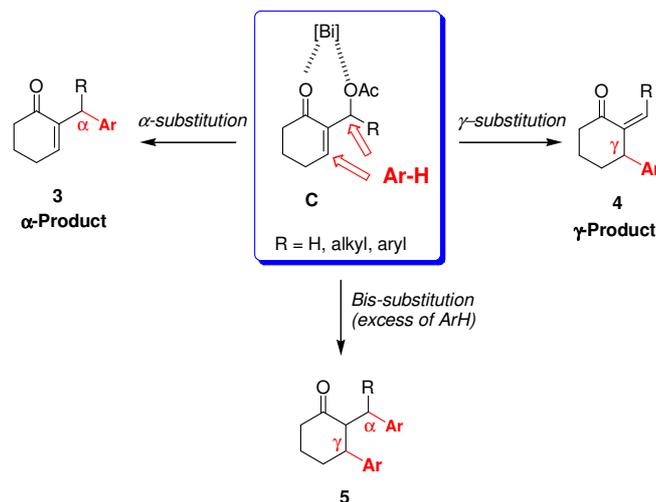
We then became interested in the mechanistic study of this reaction. The allylic substitution, described by Krische and co-workers,[22] starts with an S_N2' reaction, involving PPh₃ as a

nucleophilic catalyst, which attacks the less substituted sp²-carbon(γ), affording the phosphonium salt **A**. Further, 2-(trimethylsilyloxy) furan, as a moderate sterically hindered nucleophile, reacts with this intermediate in an S_N2' manner at the less hindered sp²-carbon(α), leading finally to γ -butenolides **B**.



Scheme 3. Synthesis of γ -butenolides described by Krische and co-workers.

In view of our results on the arylation of MBH acetates, because Bi(OTf)₃ is a Lewis acid catalyst, we propose that there is an initially preformed bismuth-chelate complex **C**, involving both the carbonyl and leaving group of the substrates **1**. This involves an activation of the carbonyl group as well as the allylic C(α), which enhances both the reactivity and selectivity of acetates **1** towards nucleophilic attack.[36,37] Hence, the complex **C** could be further attacked, at the α - and/or γ -position, by an aromatic compound, affording, respectively, after elimination of the leaving group, the α -product **3** and/or γ -product **4** (Scheme 4).[23]



Scheme 4. Possible mechanism for the reaction of (hetero)arenes **2** with MBH acetates **1**.

This step of the reaction depends not only on the steric hindrance of the R group, but also on the nature of the leaving group. Indeed, when R is a moderately bulky substituent such as Me, Et and Ph, α -products **3** are selectively observed *via* isomerisation of the corresponding γ -products **4** (Scheme 4 and Table 5, entries 1-9). On the other hand, in the case of acetate **1f**, the relatively bulkier R= isopropyl group partially hinders α -attack, and leads to a (75:25) mixture of the α - and γ -products **3fa** and **4fa**, respectively (Scheme 4, Table 5, entry 10). It is interesting to note that, when the compound **4fa** is subjected to the reactions conditions, we did not observe its isomerization to **3fa**. Moreover, when a mixture of **3fa/4fa** of known ratio is put into reaction, this ratio does not change. These results suggest that the compounds **3fa** and **4fa** are obtained *via* two parallel or competing reactions.

Moreover, the nature of the leaving group is also an important parameter. When the reaction is performed with -OAc, -OMs, or -OCOR₂ as good leaving groups, α -regioselective substitution is

observed, whereas with poor leaving groups, such as -OH or -OEt, a mixture of the α - and γ -products is obtained.

In the case of the arylation of the primary acetate **1g**, we believe that the corresponding bis arylated derivative **5ga** is resulting from a further β^{\prime} -1,4-addition onto the γ -product **4ga** (Scheme 4).

3. Conclusion

We have developed a general and efficient Bi(OTf)₃-catalysed Friedel-Crafts reaction of arenes and heteroarenes with a series of primary and secondary cyclic or acyclic MBH acetates, differently substituted at the carbon bearing the leaving group.[38] This synthetic protocol was found to be general with moderately hindered groups R attached to the α -carbon (i.e R= Me, Et, Ph), affording the α -arylation products generally in short reaction times, high yields and with excellent α -selectivity.

4. References and Notes

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- [38] General procedure : To a stirred solution of Morita-Baylis-Hillman acetate **1a-j** (0.3 M) in 1,2-dichloroethane, and 2 equiv. of arene or heteroarene **2a-l**, was added 10 mol% of Bi(OTf)₃. The mixture was stirred at 50 °C until full conversion was reached. The reaction was quenched by the addition of saturated NaHCO₃ aqueous solution and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The resulting product was purified by column chromatography eluting with a PE-Et₂O mixture. For further details see the ESI.

Graphical Abstract

Bi(OTf)₃-catalysed regioselective arylation of Morita-Baylis-Hillman type allylic electrophiles

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