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Access to Polycyclic Derivatives by Triflate-Catalyzed Intramolecular Hydroarylation

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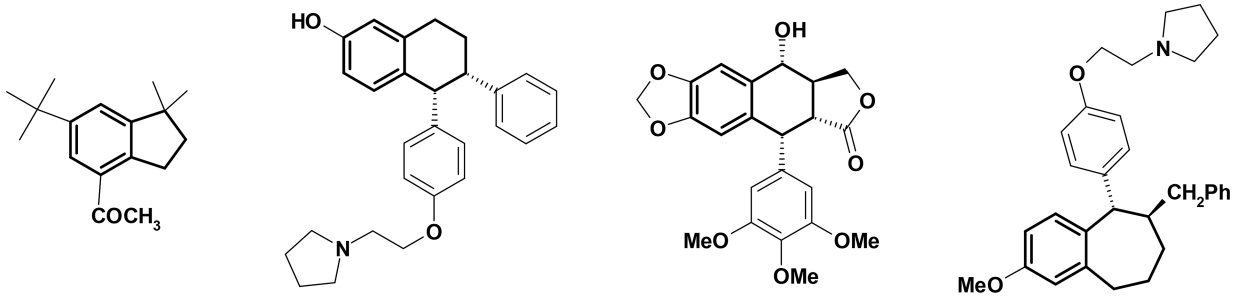
An efficient and versatile synthesis of indane, tetralin and benzosuberan derivatives has been developed; the synthesis starts from nonactivated aromatic compounds bearing unsaturated side chains and is a bismuth(III) or indium(III) trifluoromethanesulfonate-catalysed atom-economic process. A variety of polycyclic compounds have been isolated in high yields. Lactonisation could be observed for esters with 2,2-disubstituted terminal olefins through a Lewis acid catalysed reaction between the olefin and one of the ester groups.

Introduction

Indane, tetralin and benzosuberan derivatives are interesting building blocks in organic synthesis. These substructures are present in a variety of natural products, pharmaceuticals and perfumes and display a substantial range of biological and flavouring activities.

Some selected examples are presented in Scheme 1, including celestolide, a commercial perfume component with an outstanding musk odour,[1] lasofoxifene for the treatment of osteoporosis, the anticancer agent podophyllotoxin[2] and the antifertility agent *trans*-1-(2-{4-[6,7,8,9-tetrahydro-2-methoxy-6-(phenylmethyl)-5*H*-benzocyclohepten-5-yl]phenoxy}ethyl)pyrrolidine.[3] Their challenging structures have led to a permanent interest in the development of efficient and selective syntheses. Hydroarylation reactions could be considered as one interesting alternative for the construction of the indane, tetralin and benzosuberan structural frameworks through the intramolecular Friedel–Crafts cyclisation of an alkene tethered to an arene ring.

The Friedel–Crafts reaction has undergone recent improvements through the use of heterogeneous catalysis.[4] The use of Brønsted and Lewis acids[5,6] in (over)stoichiometric amounts has been reported for these reactions, generally with activated aryl substrates. The challenge of the last decade was the development of efficient Friedel–Crafts alkylations of arenes with catalytic amounts of a Lewis acid. Catalytic Friedel–Crafts reactions have been described with allylic alcohols,[7] methylenecyclopropanes,[8] allenes[9] and conjugated olefins[10] and generally require electron-



Celestolide
Musk odor
(indane)

Lasofoxifene
Treatment of osteoperosis
(tetralin)

Podophyllotoxin
Treatment of cancer
(tetralin)

Pyrrolidine derivative
Antifertility agent
(benzosuberan)

Scheme 1. Examples of indane, tetralin and benzosuberan derivatives.

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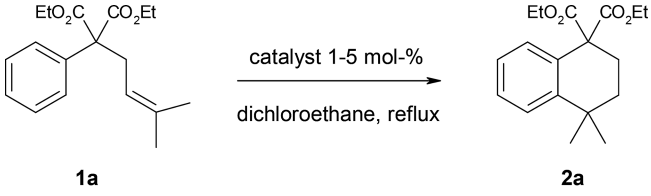
rich aromatic derivatives. Intramolecular catalytic reactions[11] have been achieved with Rh^{I} complexes,[12] In(OTf)$_3$ (OTf = triflate),[13] $InBr_3$,[14] $BiCl_3$,[15] $RuCl_3$/AgOTf[16] or performed with catalytic systems such as [PPh_3AuCl]/$AgSbF_6$[17] or $AuCl_3$/AgOTf;[18] these reactions essentially involve the aryl coupling with terminal double bonds. Very few references deal with the intramolecular hydroarylation of internal alkenes (with $AlCl_3$ or TfOH).[19] We published a preliminary report dealing with a Bi^{III} intramolecular cycloisomerisation reaction of aromatic compounds bearing side-chain olefin substituents.[20]

We report here that Bi(OTf)$_3$ or In(OTf)$_3$ are efficient catalysts for the intramolecular hydroarylation of nonactivated aromatic rings bearing highly substituted olefins in a completely atom-economic process. This eco-friendly methodology constitutes a direct and easy access to indane, tetralin, benzosuberan and other polycyclic derivatives. Coupling occurs under mild conditions with only 1–10 mol-% of catalyst. We also present some insight into the mechanism of this reaction.

Results and Discussion

1. Catalyst Screening

The reactivity of a series of commercially available metal triflates was first examined in the hydroarylation reaction of **1a** as a model substrate (Scheme 2), and substituted tetralin **2a** was isolated as the main product. Among the various catalysts investigated at 5 mol-% (Table 1, Entries 1–6), Sn(OTf)$_2$, Al(OTf)$_3$ and Fe(OTf)$_3$ catalysed the intramolecular reaction of **1a** in moderate yields (Table 1, entries 1–3). Sc(OTf)$_3$, In(OTf)$_3$ and Bi(OTf)$_3$ were the most efficient catalysts (Table 1, Entries 4–6) and led to the expected bicyclic structure **2a** in yields of 92–96%. The cyclisation of **1a** could also be observed with only 1 mol-% of Bi^{III} or In^{III} triflate to afford the tetralin **2a** in 89–94% yield after 2 h (Table 1, Entries 7 and 8).



Scheme 2. Model substrate for the hydroarylation reaction.

We focused our attention on the catalyst recycling. The commercially available Bi(OTf)$_3$ at 1 mol-% was efficient over 10 runs without loss of activity. The recycling method was based on the evaporation and drying of the aqueous layer after extraction of the crude mixture.[21]

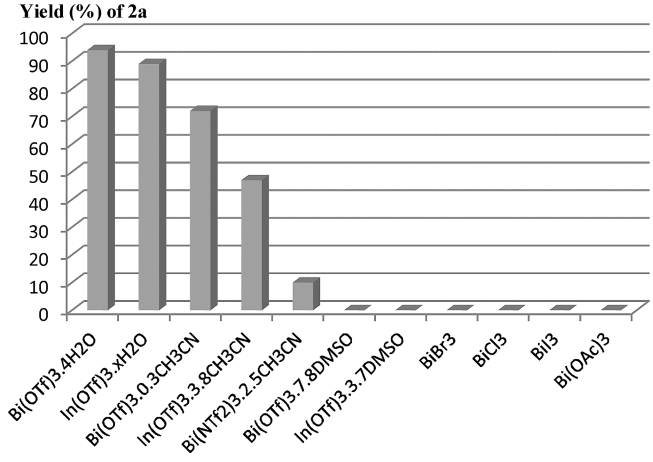
In^{III} and Bi^{III} trifluoromethanesulfonate were chosen as the best catalysts owing to their low toxicity and relatively low price. The nature of the counterion and the different metal solvation of the catalyst proved to be essential for the efficiency of the catalytic system. The catalytic activity of

Table 1. Screening of metal triflates in the intramolecular Friedel–Crafts cyclisation of **1a**.[a]

Entry	Catalyst [mol-%]	Time [h]	Isolated yield **2a** [%]
1	Sn(OTf)$_2$ [5]	2	47
2	Al(OTf)$_3$ [5]	2	63
3	Fe(OTf)$_3$ [5]	2	51
4	Sc(OTf)$_3$ [5]	2	92
5	In(OTf)$_3$ [5]	0.5	96
6	Bi(OTf)$_3$ [5]	0.5	96
7	In(OTf)$_3$ [1]	2	89
8	Bi(OTf)$_3$ [1]	2	94

[a] General conditions: **1a** (1 mmol), catalyst (1–5 mol-%) in $ClCH_2CH_2Cl$, reflux.

various bismuth salts was examined with **1a**. As shown in Scheme 3, 1 mol-% of $BiBr_3$, $BiCl_3$, BiI_3 or Bi(OAc)$_3$ in dichloroethane failed to provide the expected product **2a** after 6 h of reflux. Although Bi(NTf$_2$)$_3$·2.5CH_3CN catalysed the intramolecular hydroarylation of **1a** in 10% yield, the best catalytic activities were observed with Bi(OTf)$_3$ and In(OTf)$_3$. The order of reactivity of the different counterions was determined as follows: –OTf > –NTf$_2$ >> –Br, –Cl, –I, –OAc.



Scheme 3. Influence of the counterion and of the metal solvation of the catalyst. Conditions: MX_3 1 mol-%, $ClCH_2CH_2Cl$, reflux, 6 h.

The catalytic activities of Bi(OTf)$_3$ and In(OTf)$_3$ were also examined for different solvations of the metallic centre. Commercial Bi(OTf)$_3$ and In(OTf)$_3$ are hydrated salts. Three synthetic methods for anhydrous metallic triflates and triflimidates were used: (1) an electrochemical process,[22] (2) a sonochemical process[23] to obtain CH_3CN-solvated catalysts and (3) an oxidative process[24] to give access to dimethyl sulfoxide (DMSO) solvated salts. Accordingly, we prepared Bi(OTf)$_3$·0.3CH_3CN, In(OTf)$_3$·3.8CH_3CN, Bi(OTf)$_3$·7.8DMSO and In(OTf)$_3$·3.7DMSO to compare their activities with those of commercially available hydrated salts. The compositions of the catalysts as well as the relative amount of coordinating solvent present were determined by ^1H and ^{19}F NMR spectroscopy with 1-chloro-4-fluorobenzene as the internal standard.

$Bi(OTf)_3{\cdot}4H_2O$ catalysed the cyclisation of **1a** to **2a** in 94% yield (conditions: 1 mol-%, $ClCH_2CH_2Cl$, reflux, 6 h, Scheme 3). The hydrated indium triflate showed a slightly lower activity than the corresponding hydrated bismuth triflate. $Bi(OTf)_3{\cdot}0.3CH_3CN$ exhibited a lower activity with a 72% yield, whereas $Bi(OTf)_3{\cdot}7.8DMSO$ was inactive. It is interesting to note that the indium and bismuth triflate catalysts were less effective when solvated by CH_3CN than when solvated by H_2O, and a complete inhibition was obtained with a DMSO coordination of the salts. The inhibition of the catalyst by the DMSO could be explained by its strong coordinating effect, which lowers the Lewis acidity of the catalysts. Therefore, for the cycloisomerisation of **1a** to **2a**, the observed reactivity order for the catalysts was: $M(OTf)_3{\cdot}H_2O > M(OTf)_3{\cdot}CH_3CN >> M(OTf)_3{\cdot}DMSO$.

2. Extension of the Catalytic Hydroarylation

The intramolecular hydroarylation reaction was then extended to a variety of arylalkene derivatives **1b**–**1u** with hydrated $Bi(OTf)_3$ and $In(OTf)_3$ as the catalysts at 1 and 5 mol-% in dichloroethane or nitromethane under reflux. As illustrated in Table 2, the reactions were very efficient for the dimethyl-substituted olefin substrates **1a**–**1e**. The bicyclic structures **2a**–**2e** were isolated in high yields and selectivities. Ester and nitrile groups were compatible with the reaction conditions. The presence of a nitrile substituent induced a slight inhibition of the catalyst activity (Table 2, Entry 4), and the reaction required a higher temperature and a longer time to reach completion. The coordination of the Lewis acid to the nitrile or ester groups may explain this difference of reactivity. The presence of a diester group enhanced the substrate activity, but an efficient cyclisation was also observed in the absence of ester groups (Table 2, Entry 5). In all cases, the six-membered rings were exclusively formed, and tetralins were isolated selectively. The catalytic activities of $Bi(OTf)_3{\cdot}4H_2O$ and $In(OTf)_3{\cdot}H_2O$ were similar when 5 mol-% of catalyst was used. When the quantity of catalyst was decreased to 1 mol-%, the best results were obtained with bismuth triflate.

The intramolecular hydroarylation was extended to various differently substituted olefins **1f**–**1i** (Table 3). The reaction was very efficient with cinnamyl derivatives **1f** and **1g** in the presence of 1 or 5 mol-% of indium or bismuth triflate (Table 3, Entries 2 and 3). The tetralin derivatives **2f** and **2g** were isolated in good yields of 75–97%. The mono- and disubstituted olefins **1h** and **1i** allowed the formation of the expected bicyclic structures **2h** and **2i** with 5 mol-% of $Bi(OTf)_3$, though moderate yields of 33 and 42% were obtained for **2h** and **2i**, respectively (Table 3, Entries 4 and 5).

Trisubstituted alkenes presented a higher reactivity than terminal and disubstituted olefins. The observed reactivity suggests that the intramolecular hydroarylation was facilitated with highly substituted double bonds through a mechanism involving carbocationic-type intermediates formed from the alkene in the presence of the strong Lewis acid.

Table 2. Intramolecular Friedel–Crafts cyclisation of dimethyl-substituted olefin substrates **1a**–**1e**.

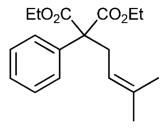
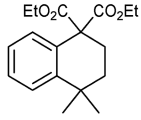
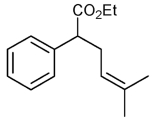
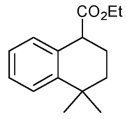
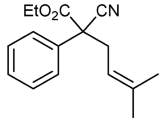
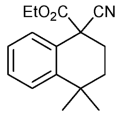
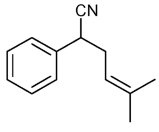
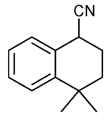
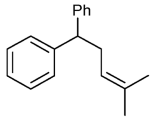
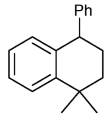
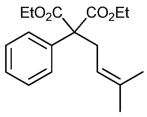
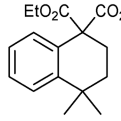
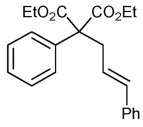
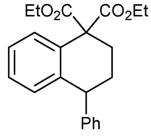
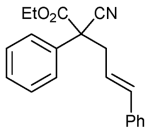
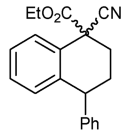
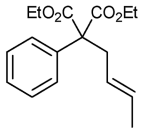
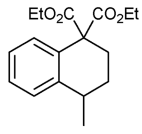
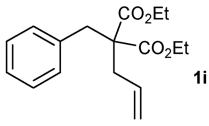
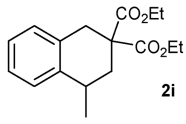
Entry	Substrate	Conditions	Product	$Bi(OTf)_3{\cdot}4H_2O$ 5 mol-%	$Bi(OTf)_3{\cdot}4H_2O$ 1 mol-%	$In(OTf)_3{\cdot}H_2O$ 5 mol-%	$In(OTf)_3{\cdot}H_2O$ 1 mol-%
				% isolated yield			
1	 **1a**	$Cl(CH_2)_2Cl$, reflux, 2 h	 **2a**	96	94	96	89
2	 **1b**	$Cl(CH_2)_2Cl$, reflux, 2 h	 **2b**	95	91	94	86
3	 **1c**	CH_3NO_2, reflux, 4 h	 **2c**	94	82	92	75
4	 **1d**	CH_3NO_2, reflux, 6 h	 **2d**	72	65	68	58
5	 **1e**	$Cl(CH_2)_2Cl$, reflux, 2 h	 **2e**	95	95	94	91

Table 3. Influence of the olefin substitution on the intramolecular hydroarylation.

Entry	Substrate	Conditions	Product	$Bi(OTf)_3 \cdot 4H_2O$ 5 mol-%	$Bi(OTf)_3 \cdot 4H_2O$ 1 mol-%	$In(OTf)_3 \cdot H_2O$ 5 mol-%	$In(OTf)_3 \cdot H_2O$ 1 mol-%
				% isolated yield			
1	 **1a**	$Cl(CH_2)_2Cl$, reflux, 2 h	 **2a**	96	94	96	89
2	 **1f**	$Cl(CH_2)_2Cl$, reflux, 2 h	 **2f**	97	92	97	84
3	 **1g**	CH_3NO_2, reflux, 2 h	 **2g**	97 (*dr* 65:35)[a]	86 (*dr* 65:35)[a]	92 (*dr* 65:35)[a]	75 (*dr* 65:35)[a]
4	 **1h**	CH_3NO_2, reflux, 6 h	 **2h**	33	–	15	–
5	 **1i**	CH_3NO_2, reflux, 6 h	 **2i**	42	–	27	–

[a] Ratio of diastereoisomers.

Substrate **1h** (Table 3, Entry 4) offered the possible formation of five- or six-membered rings. The selective formation of the tetralin structure **2h** indicates that the six-membered ring was favoured in these bicyclic structures.

The reaction was then extended to 2-substituted terminal olefins **1j**–**1o** in the presence of 1–10 mol-% of indium or bismuth triflate catalyst. Surprisingly, the mono- and diester derivatives **1j** and **1k** led to the preferential and selective formation of the γ-lactones **3j** and **3k** (Table 4, Entries 1 and 2), which were isolated in excellent yields of 96–97%. The cyano-substituted olefin substrate **1l** also led to the corresponding lactone **3l** in a moderate yield of 46–48% (Table 4, Entry 3). The use of other metallic triflates (Fe^{III}, Al^{III}, Sn^{II}) or protic acids (TfOH, Tf_2NH) did not allow the formation of the expected five-membered carbocyles **2j**–**2l**. The formation of lactones **3j**–**3l** results from the Lewis acid catalysed reaction between the olefin and one of the ester groups. This dealkylative lactonisation process has already been observed for other examples,[25] and high selectivity was observed for the lactonisation of 4-methylpentenoates via alkyloxonium intermediates, which were observable by NMR spectroscopy.[26]

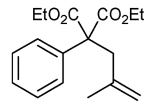
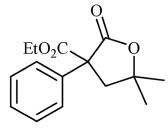
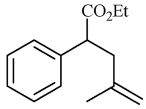
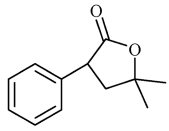
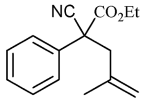
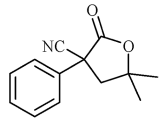
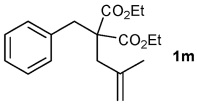
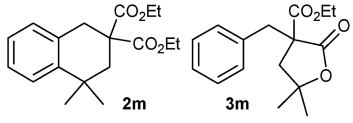
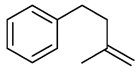
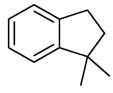
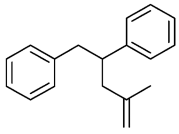
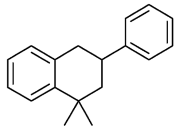
In contrast with the results for **1j**–**1l**, the analogous olefin **1m** underwent carbocyclisation to form the fused six-membered ring **2m** in yields of 53 and 35% with the Bi^{III} and In^{III} catalysts, respectively (Table 4, Entry 4). The lactone **3m** was also formed as a byproduct (Bi^{III}) or as the main product (In^{III}). When it is possible to form a γ-lactone, there is a competition between the hydroarylation and lactonisation reactions. However, if the hydroarylation should lead to a fused five-membered ring carbocycle, then the lactonisation is selectively observed.

Compounds **1n** and **1o** were prepared to further examine the five-membered versus six-membered ring formation in the absence of ester groups. The cyclisation of **1n** led to the aryl-fused five-membered ring derivative **2n** in excellent yields under Bi^{III} or In^{III} catalysis (Table 4, Entry 5). For **1o**, the carbocyclisation could lead to the formation of a fused five- or six-membered ring: in the presence of 5 mol-% of $Bi(OTf)_3$, the six-membered cyclisation product **2o** was selectively isolated in an excellent yield of 98%. This reaction allows us to conclude that the six-membered ring cyclisation is largely preferred over the formation of five-membered rings for these bicyclic structures.

The order of the reactivity for this class of compounds is six-membered ring Friedel–Crafts hydroarylation > five-membered ring lactonisation >> five-membered ring Friedel–Crafts hydroarylation.

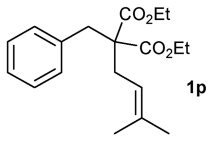
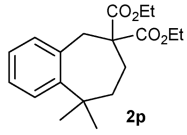
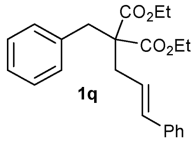
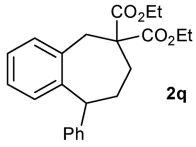
The Bi^{III}- or In^{III}-catalysed procedure also provides alternative access to aryl-fused seven-membered ring derivatives such as benzosuberan-type structures (Table 5). Thus, the cyclisation of the terminal dimethyl-substituted olefin **1p** afforded the expected benzosuberan compound **2p** in 47–50% yield (Table 5, Entry 1). This reaction also involved the formation of a six-membered lactone byproduct. The reaction of the disubstituted olefin **1q** also led to the aryl-fused

Table 4. Intramolecular hydroarylation of 2-methyl-substituted terminal olefins.

Entry	Substrate	Conditions	Product(s)	$Bi(OTf)_3 \cdot 4H_2O$ mol-%			$In(OTf)_3 \cdot H_2O$ mol-%		
				10	5	1	10	5	1
				% isolated yield					
1	 **1j**	$Cl(CH_2)_2Cl$, reflux, 4 h	 **3j**	97	96	–	97	96	–
2	 **1k**	$Cl(CH_2)_2Cl$, reflux, 4 h	 **3k**	96	–	–	96	–	–
3	 **1l**	CH_3NO_2, reflux, 4 h	 **3l**	48	–	–	46	–	–
4	 **1m**	CH_3NO_2, reflux, 2 h	 **2m** **3m**	–	53/44[a]	53/42[a]	–	35/59[a]	35/59[a]
5	 **1n**	$Cl(CH_2)_2Cl$, reflux, 2 h	 **2n**	–	97	97	–	96	96
6	 **1o**	$Cl(CH_2)_2Cl$, reflux, 2 h	 **2o**	–	98	–	–	–	–

[a] Isolated yields of **2m** and **3m**, respectively.

Table 5. Catalytic cyclisations to seven-membered ring carbocycles (conditions: CH_3NO_2, reflux, 4 h).

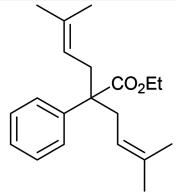
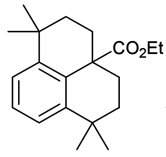
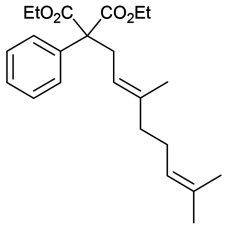
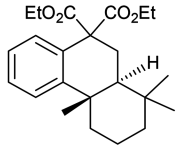
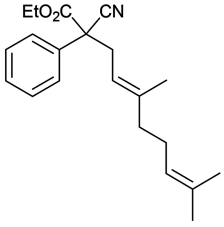
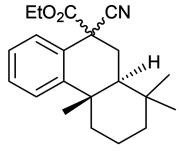
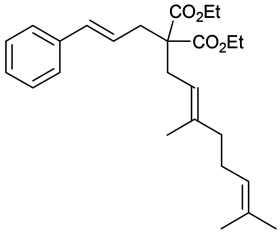
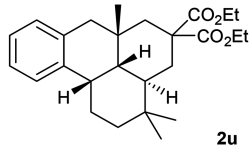
Entry	Substrate	Product(s)	$Bi(OTf)_3 \cdot 4H_2O$		$In(OTf)_3 \cdot H_2O$	
			mol-%	% isolated yield	mol-%	% isolated yield
1	 **1p**	 **2p**	10	50	10	47
2	 **1q** Ph	 **2q** Ph	10	80	10	78

seven-membered ring derivative **2q** in good yields of 78–80% (Table 5, Entry 2). The lactone was not observed in this case, probably on account of the steric hindrance of the phenyl group.

The methodology was also extended to double functionalisation reactions, as illustrated in Table 6. These tandem reactions to afford tricyclic structures occurred in the presence of 5 mol-% of $Bi(OTf)_3$ or $In(OTf)_3$. Diprenyl phenyl acetate **1r** selectively afforded a double *ortho,ortho'*-cyclisation to **2r** in up to 68% yield (Table 6, Entry 1).

Sequential double cyclisations were also obtained for derivatives **1s**–**1u** with diene side chains (Table 6, Entries 2–4). Polyene cyclisations have already been described under $Bi(OTf)_3$ catalysis.[27] The cyclisation of the geranyl deriva-

Table 6. Catalytic double and tandem Friedel–Crafts reactions.

Entry	Substrate	Conditions	Product	$Bi(OTf)_3 \cdot 4H_2O$ mol-%	$Bi(OTf)_3 \cdot 4H_2O$ % isolated yield	$In(OTf)_3 \cdot H_2O$ mol-%	$In(OTf)_3 \cdot H_2O$ % isolated yield
1	 **1r**	CH_3NO_2, reflux, 2 h	 **2r**	5	68	5	60
2	 **1s**	CH_3NO_2, reflux, 2 h	 **2s**	5	93[a]	5	90[a]
3	 **1t**	CH_3NO_2, reflux, 2 h	 **2t**	5	92 (*dr* 65:35)[b]	5	89 (*dr* 65:35)[a,b]
4	 **1u**	CH_3NO_2, reflux, 2 h	 **2u**	5	83[a]	–	–

[a] One diastereoisomer. [b] Ratio of diastereoisomers.

tive **1s** proceeded in excellent yields and selectivities under Bi^{III} or In^{III} catalysis. A single diastereoisomer with a *trans*-fused stereochemistry was isolated for **2s**.

The tandem cyclisation of the diene **1t** was efficiently performed under the same conditions and led selectively to a *trans* configuration for the ring junction and a 65:35 mixture of diastereoisomers.

The cyclisation of derivative **1u** with a triene side chain (Table 6, Entry 4) under Bi^{III} catalysis led to the aryl-fused six-membered ring derivative **2u**. Compound **2u** was isolated as a single diastereoisomer in 83% yield. This diastereocontrolled reaction allowed the formation of three carbon–carbon bonds and the control of four stereogenic centres in a single step. It is interesting to note that the migration of a methyl group could be observed during the cycloisomerisation process.

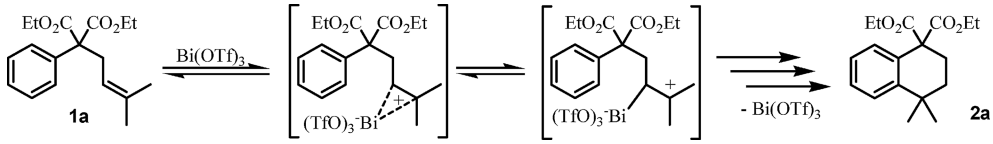
3. Mechanistic Aspects

As Lewis acids, the metallic triflates possess an empty electronic gap that can generate a carbon–metal bond with the π electrons of the double bond. This could lead to the formation of carbocationic-type species, which are able to initiate the intramolecular cyclisation (Scheme 4).

Recently, DFT computations of a 1,6-diene cycloisomerisation catalysed by tin(IV) triflimide suggested that the mechanism should not involve the direct addition of the tin(IV) cation to a double bond (as in Scheme 4), as the catalyst regeneration step would not be energetically feasible.[28] A hydrated triflimide salt was proposed to be the active catalyst; this leads to the hypothesis of a hidden Brønsted acid catalysis.

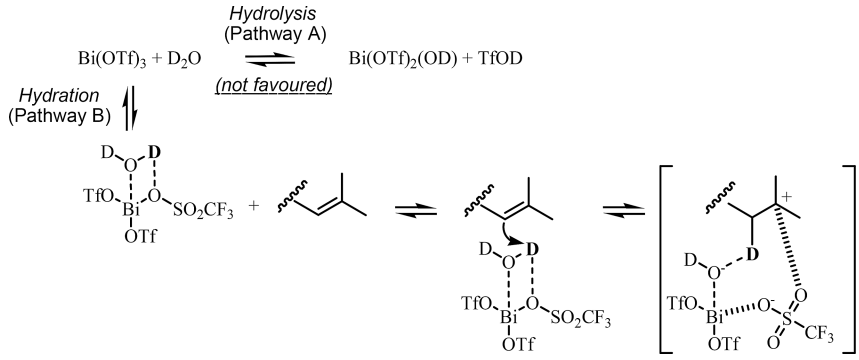
The active role of a proton generated by the hydrolysis of the Lewis acid has also been proposed.[29] For the cyclisation of **1a** with TfOH as the catalyst (5 mol-%, $ClCH_2CH_2Cl$, reflux), complete conversion was attained after 1 h, and the yield of **2a** was 72% with some degradation of the starting material. Interestingly, in the presence of 1 mol-% of 2,6-di-*tert*-butylpyridine as a proton scavenger, the reaction of **1a** was inhibited [$Bi(OTf)_3 \cdot 4H_2O$ 1 mol-%, $ClCH_2CH_2Cl$, reflux]; this seems to suggest a mechanism involving a proton species in one of the steps.

From a mechanistic viewpoint, the catalytic role of a metal ion versus the activity of a proton is still under de-

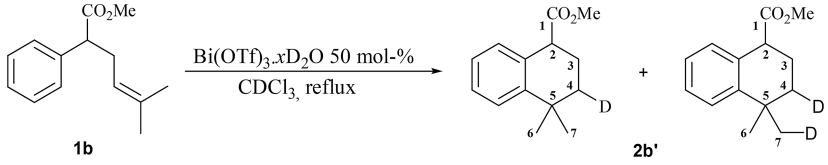


Scheme 4. Activation of an olefin by a Lewis acid catalyst.

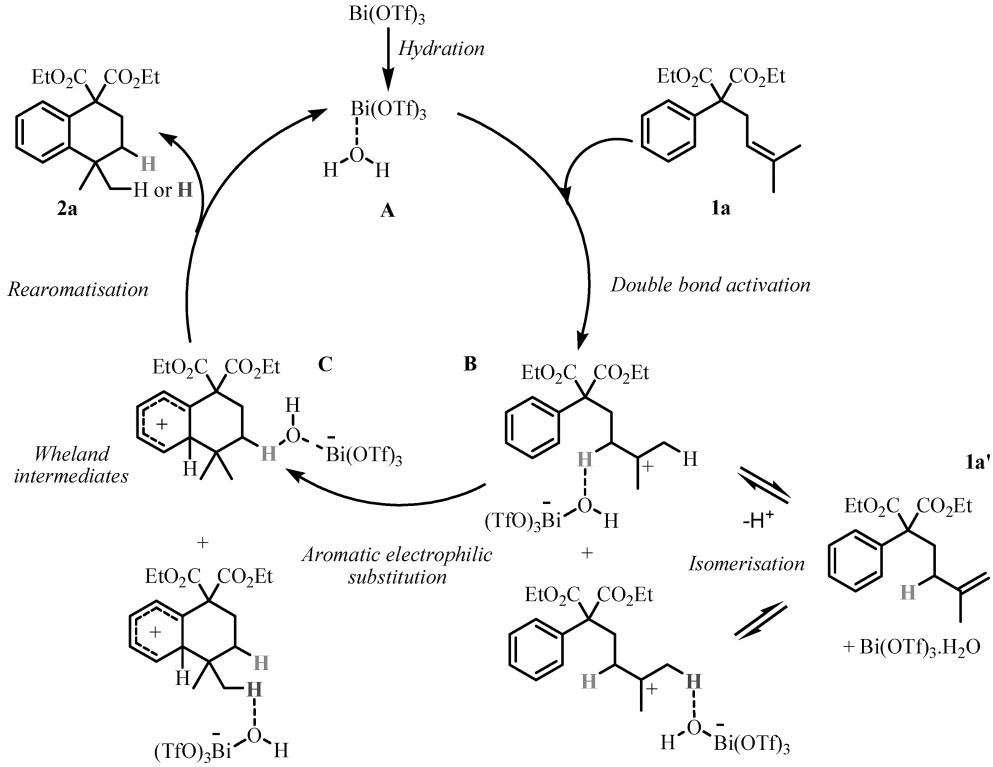
bate.[30] However, recent calculations energetically favoured the hydration of Bi^{III} over its hydrolysis, without the apparent formation of TfOH.[31] Hydrated metal triflates could act as active catalysts in a Lewis acid assisted Brønsted acid



Scheme 5. Proposed hydrated $Bi(OTf)_3$-catalysed mechanism.



Scheme 6. Incorporation of deuterium to **1b** from the coordination sphere of the catalyst.



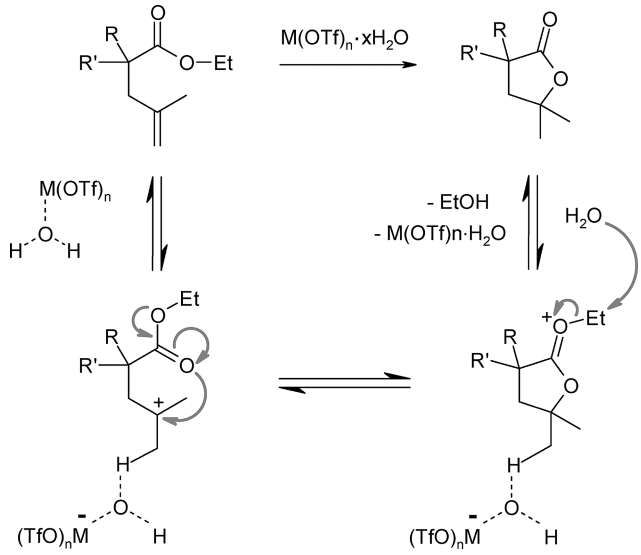
Scheme 7. Proposed mechanism for the hydroarylation of **1a** to **2a**.

(LBA) type activation.[32] Considering such activation, the water molecules coordinated to $Bi(OTf)_3$ could present a strong acidity, enhanced by the coordination to the metal centre. This could lead to a carbocationic-type intermediate, in which the proton added to the double bond is supplied by a Bi^{III}-activated water molecule.

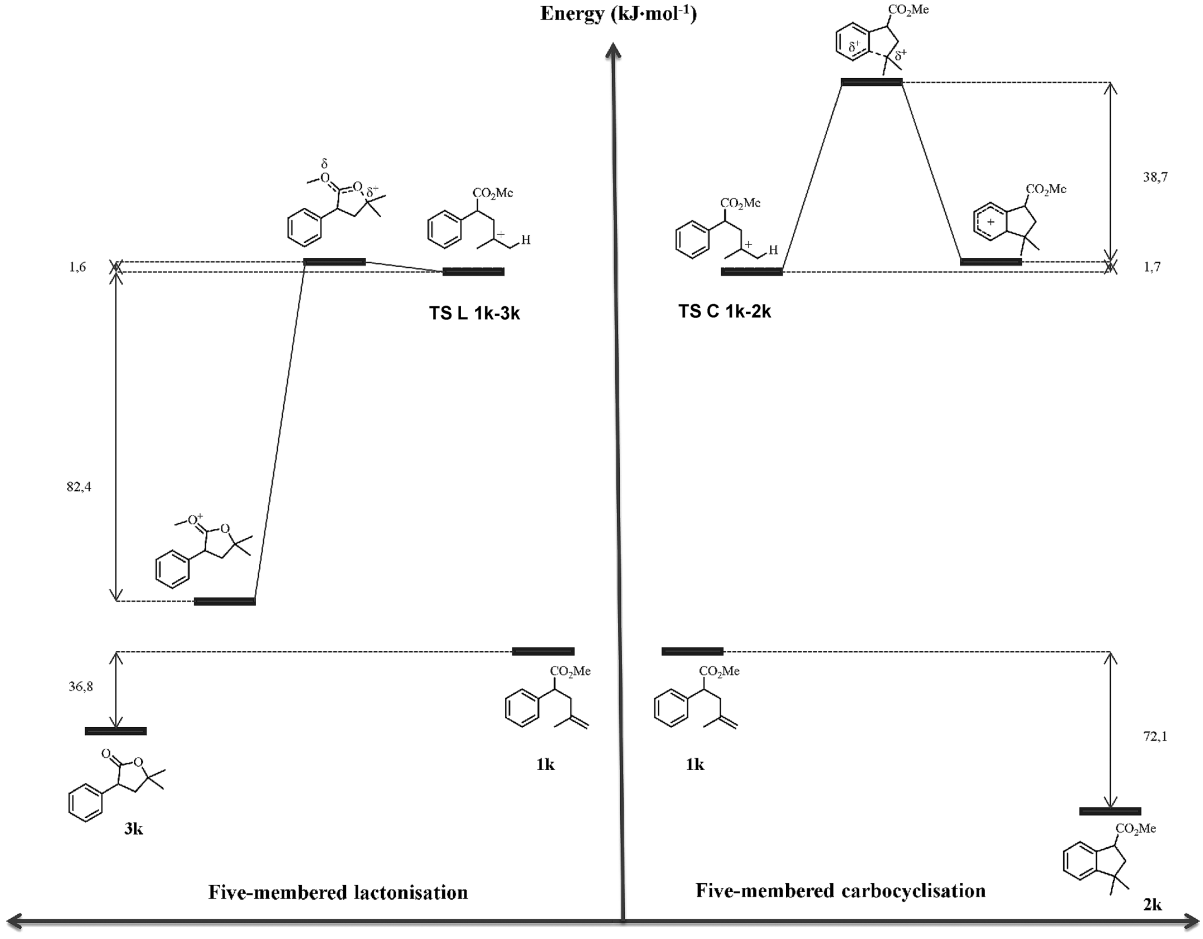
To obtain some experimental evidence that the proton involved in the activation of the double bond results from a water molecule coordinated to the metal centre of the catalyst, we prepared the deuterated catalyst $Bi(OTf)_3{\cdot}nD_2O$ from anhydrous $Bi(OTf)_3{\cdot}0.3CH_3CN$ and D_2O (Scheme 5). According to theoretical calculations, the proposed hydration pathway B should be preferred over the hydrolysis pathway A.

The reaction of **1b** catalysed by $Bi(OTf)_3{\cdot}nD_2O$ in $CDCl_3$ led to a mixture of deuterated derivatives **2b′** (Scheme 6). ^1H NMR spectroscopy indicated two sites of deuteration, that is, carbon atoms C-4 and C-6/C-7. The deuteration at C-4 occurred at 100%; this indicates that the water molecule in the coordination sphere of the catalyst supplies the proton that initiates the hydroarylation reaction. The deuteration at C-6/C-7 occurred in 33% through the same mechanism (see Schemes 5 and 6) after an isomerisation of the double bond.

The different data favour a mechanism that involves a hydrated Lewis acid catalysis. The mechanism proposed for



Scheme 8. Proposed mechanism for the lactonisation reaction (R = Ph; R′ = H, CN, COOEt; M = In or Bi).



Scheme 9. Five-membered carbocyclisation versus five-membered lactonisation for **1k**.

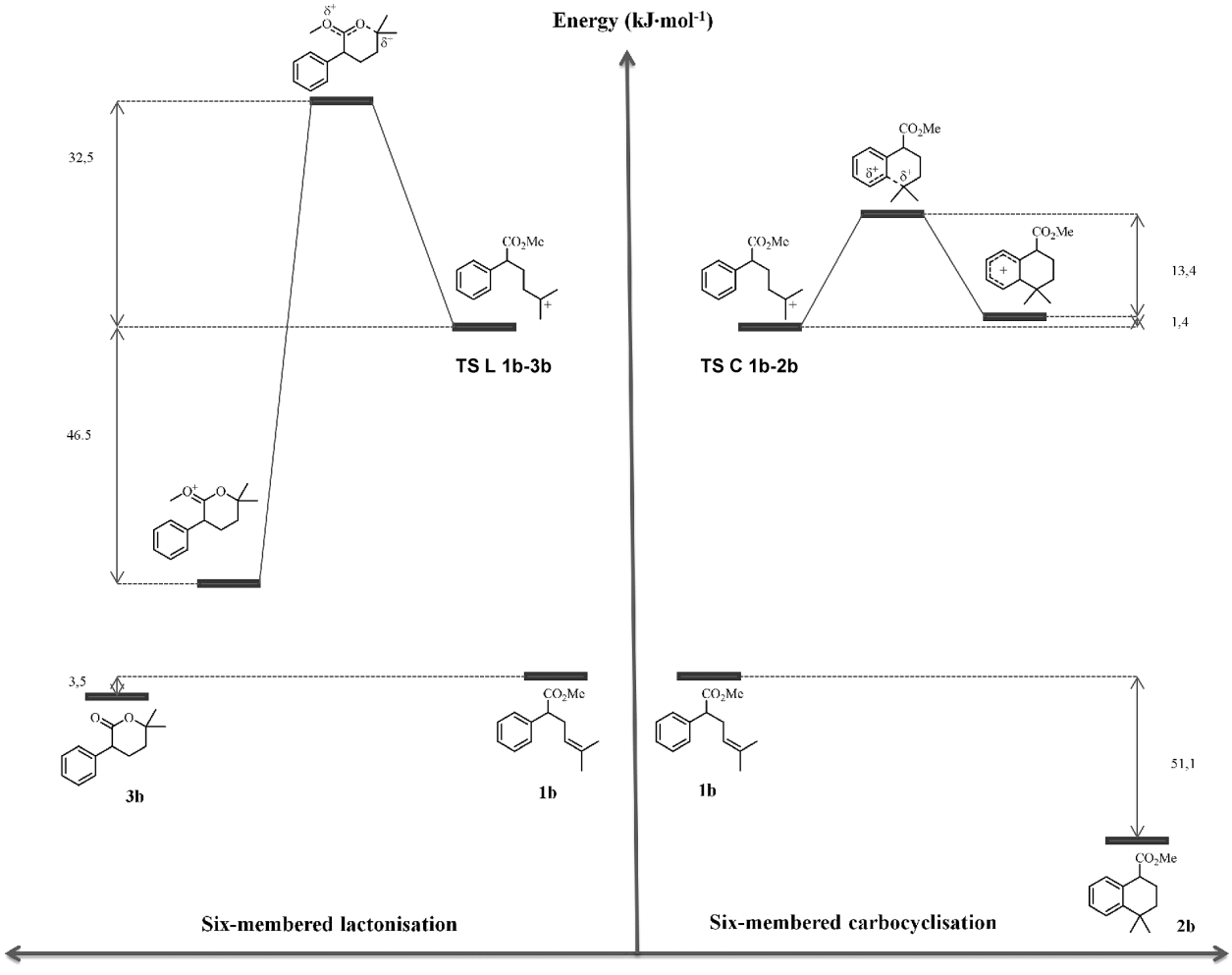
the hydroarylation of **1a** to **2a** is shown in Scheme 7. The commercially available $Bi(OTf)_3$ is already hydrated. Otherwise, traces of water are necessary to activate the catalyst. The hydration of the bismuth triflate by a molecule of water allows the in situ formation an acid species **A**, which is able to activate the double bond of **1a**. The carbocationic intermediate **B** undergoes aromatic electrophilic substitution to form intermediate **C**. Intermediate **B** can also undergo some isomerisation with deprotonation to **1a′**, in agreement with the deuteration experiment. After a rearomatisation step from **C** and the loss of a proton, the target molecule **2a** is formed, and the hydrated bismuth triflate is regenerated.

Interestingly, the reaction of 2-substituted terminal olefins bearing an ester group led to the formation of γ-lactones in the presence of bismuth or indium triflate catalysts (Scheme 8). The activation of the double bond with the metal triflate should allow the formation of a carbocationic intermediate, which could undergo a nucleophilic attack of the ester to form the lactone with the loss of a molecule of alcohol. This mechanism suggests again the important role of a water molecule in the coordination sphere of the catalyst.

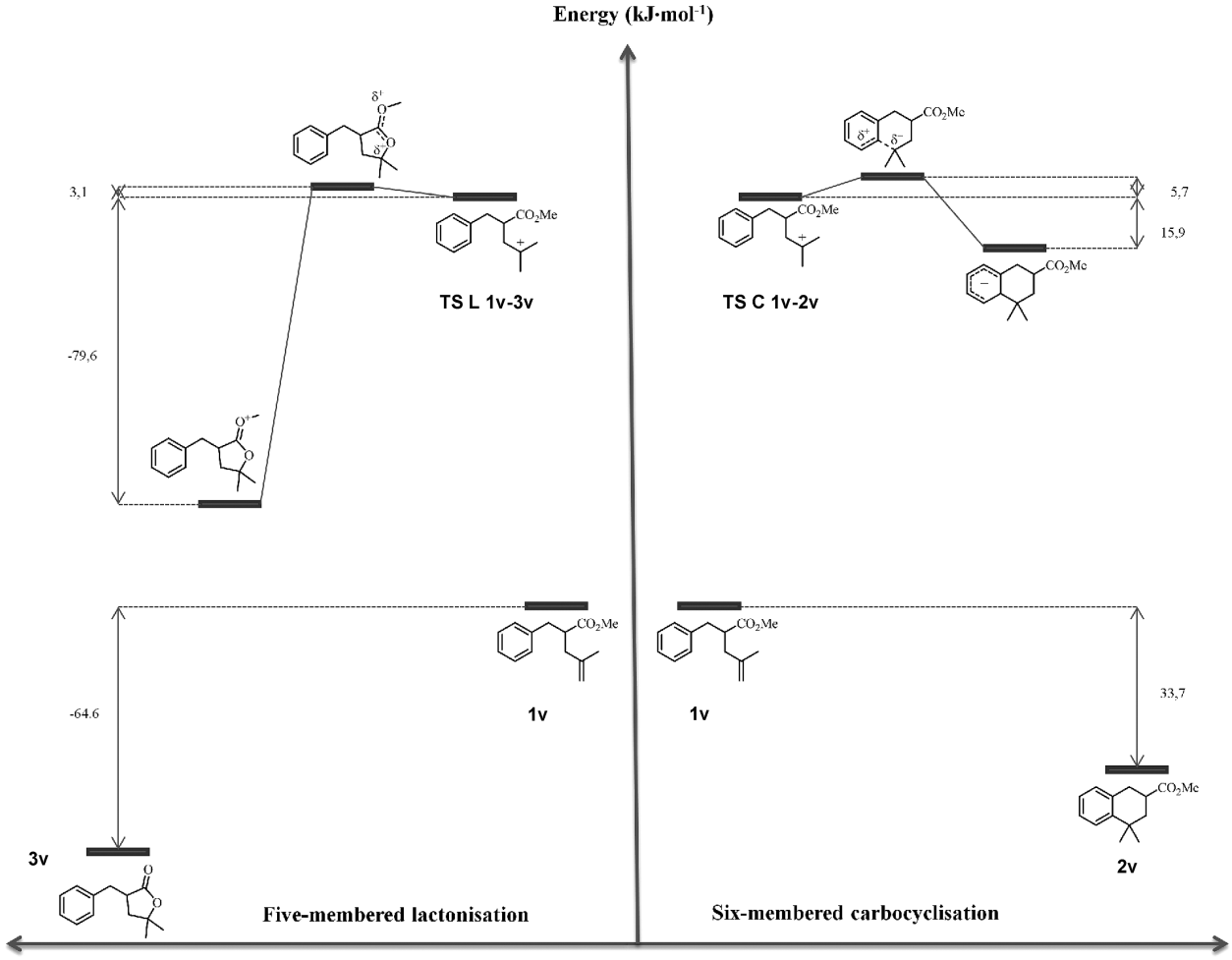
To better understand the competition between the hydroarylation and lactonisation reactions, further theoretical calculations were performed with the GAUSSIAN 09 software by using density functional theory (DFT) methods at the B3LYP/6-31+G(d,p) level of theory with the polarisable continuum model for nitromethane (Schemes 9, 10 and 11).[33] The intermediates and transition states (TS) of the proposed mechanisms correspond to stationary points on the potential-energy surface and were characterised by their calculated vibrational frequencies.

For **1k** (Scheme 9), although the five-membered carbocycle is thermodynamically favoured over the five-membered lactone ring, the reaction intermediates formed in the lactonisation of **1k** are thermodynamically more stable than those calculated for the hydroarylation reaction. Moreover, the transition state for lactone formation is reached with a low energy demand of 1.6 kJ mol^{-1}, whereas the transition state for the fused five-membered ring carbocycle requires a much higher energy of 40.4 kJ mol^{-1}. Thus, the lactonisation of **1k** is kinetically favoured, in agreement with the experimental results.

The prenyl group of **1b** exhibited a different selectivity compared with that of the methallyl substituent of **1k** for the competition between the six-membered carbocyclisation and the six-membered lactonisation (Scheme 10). The theoretical calculations confirm that the six-membered carbo-



Scheme 10. Six-membered carbocyclisation versus six-membered lactonisation for **1b**.



Scheme 11. Six-membered carbocyclisation of **1v** to **2v** versus five-membered lactonisation to **3v**.

cycle **2b** was favoured according to both kinetic and thermodynamic criteria. These data agree with the experimental observations.

We also compared the six-membered ring hydroarylation to the five-membered ring lactonisation for an analogue of **1m** (**1v**, Scheme 11). Both processes presented comparable thermodynamic profiles for the expected products. Experimentally, the lactone **3m** and the carbocyle **2m** were obtained in an almost equimolar ratio under the reaction conditions of Table 4.

Conclusions

We have developed a Lewis acid catalysed intramolecular cycloisomerisation reaction of nonactivated aromatic compounds bearing olefin substituents. The process uses only 1 mol-% of $In(OTf)_3$ or $Bi(OTf)_3$ as the catalysts in most of the cases and operates under mild conditions. The reaction allowed the preparation of a large series of indane, tetralin and benzosuberan structures in good-to-excellent yields. It also allowed sequential and tandem polycyclisations in one step. This In^{III} or Bi^{III} one-pot catalytic reaction represents an attractive alternative for the construction of polycyclic compounds and constitutes a 100% atom-economic process. Mechanistic insights suggest a hydrated Lewis acid catalysis. On the basis of the experimental results and theoretical calculations, five-membered lactonisation is favoured over five-membered carbocyclisation, whereas six-membered carbocyclisation is observed in competition with six-membered lactonisation.

Experimental Section

General Cyclisation Procedure: The aromatic compound **1a**–**1u** (1 mmol) and $Bi(OTf)_3$ or $In(OTf)_3$ (0.01 to 0.1 mmol) were heated to reflux for 2–6 h in anhydrous solvent [$(CH_2)_2Cl_2$ or CH_3NO_2, 5 mL] under an inert atmosphere. The reaction was quenched with ice water and extracted with Et_2O (3×10 mL) and brine (3×10 mL). The organic layer was concentrated under reduced pressure, and the product was purified by flash chromatography (pentane/Et_2O 95:5). Compounds **2a**–**2i**, **2m**–**2u**, **3k** and **3m** are known compounds; see Supporting Information.

Supporting Information (see footnote on the first page of this article): Analytical data for **3j** and **3l** (^1H and ^{13}C NMR spectroscopy and MS), DFT structures of transition states for the lactonisation and carbocyclisation reactions.

Acknowledgments

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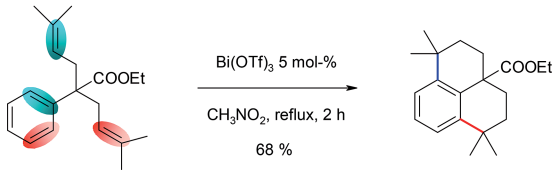
Lewis Acid Catalysis

Graphical Abstract



Nonactivated aromatic compounds bearing side-chain olefin substituents were cyclised into polycyclic compounds in good-to-excellent yields under $In(OTf)_3$ (OTf = trifluoromethanesulfonate) and $Bi(OTf)_3$ catalysis. This intramolecular cycloisomerisation leads to the synthesis of indane, tetralin or benzosuberan derivatives and allows sequential and tandem polycyclisations in one step.

Keywords: Indium / Bismuth / Lewis acids / Cyclization / Polycycles

