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Acid-mediated decarboxylative C–H coupling between arenes and *O*-allyl carbamates†

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Treatment of *O*-allyl *N*-tosyl carbamates with aromatic compounds in the presence of $Cu(OTf)_2$ or TMSOTf as promoters affords *N*-substituted 1-arylpropan-2-amines, 1,2-diarylpropanes, 1,1-diarylpropanes, or indanes, depending on the nature of the promoter and of the aryl substrates. A full mechanistic rational allowing appreciation of the outcome of these novel C–H based cascades is proposed. An initial acid promoted decarboxylative/deamidative Friedel–Crafts allylation takes place. After protonation of the allylated arene, evolution of the resulting cation may follow different paths depending on the nature of the arene partner and of the allyl moiety in the carbamate.

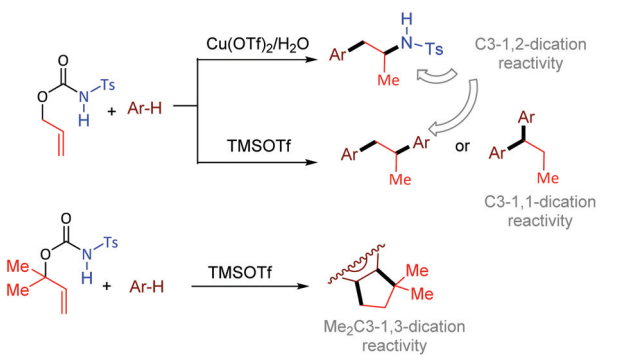
Introduction

In the last century, carbocation-mediated or -catalysed reactions have revolutionised the history of organic chemistry, giving rise to a set of fundamental reactions such as C–C bond formations, eliminations, and rearrangements.[1] In particular, the Friedel–Crafts (FC) alkylation is one of the most powerful organic reactions that allows the selective C–H functionalization of aromatics.[2] Although the FC alkylation has long been studied in many variations, its implementation in cascade reactivities that allow the multiple functionalizations of unsaturated substrates represents an extraordinary way to discover still unexplored reactivity patterns.[3]

In the frame of our long-term study dedicated to carbamates as precursors for metal-catalysed cyclisations,[4] we investigated in particular the behaviour of *O*-allyl *N*-tosyl carbamates. These compounds have been shown to undergo *exo*-[5] or *endo-trig*[6] cyclisations involving further functionalisation of the carbon double bond. Moreover, allyl carbamates can also allow decarboxylative $O \rightarrow N$ allylic rearrangement affording selectively *anti*-Markovnikov hydroamination products.[7] In this work, we show that *O*-allyl carbamates behave as C3 1,2-, 1,1-, and 1,3-dication equivalents, allowing the generation of 1-arylpropan-2-amines, 1,2- and 1,1-diarylpropanes, as well as indane structures, in the presence of $Cu(OTf)_2$ or TMSOTf as acid-promoters (Scheme 1).

Results and discussion

We started our study reacting carbamate **1a** in mesitylene, as aromatic reaction partner and solvent, in the presence of copper(II) triflate as the promoter (Table 1, entry 1). After 6 hours at 100 °C, the reaction provided a mixture of the arylated *N*-tosylamide **2** (36% isolated), together with a big amount of $TsNH_2$ (**4**) arising from the degradation of **1a**. Unchanged starting material was found working at lower temperature, and using a catalytic amount of $Cu(OTf)_2$ (entries 2 and 3). Although using an excess of copper salt at 130 °C led to an increased yield of **2**, the formation of **4** could not be



Scheme 1 Different reactivities in the acid promoted coupling between arenes and *O*-allyl *N*-tosyl carbamates observed in the present study (*bold bonds refer to forming bonds*).

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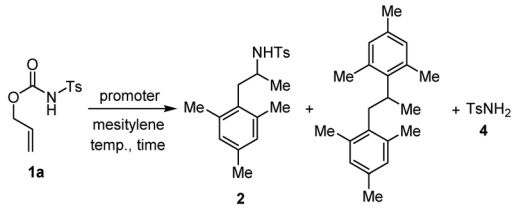
Table 1 Optimization of reaction conditions[a]



Entry	Promoter (equiv.)	Temp. (°C)	Time (h)	Product(s) (% yield)[b]
1	$Cu(OTf)_2$ (1.0)	100	6.0	**2** (36) + **4** (43)
2	$Cu(OTf)_2$ (1.0)	50	24	S.M.
3	$Cu(OTf)_2$ (0.1)	100	24	S.M.
4	$Cu(OTf)_2$ (4.0)	130	3.0	**2** (85) + **4** (11)
5	$Cu(OTf)_2$ (4.0)[c]	130	4.0	**2** (77) + **4** (22)
6	PTSA (4.0)	130 [d]	1.5	**2** (59) + **4** (18)
7	H_2SO_4 (1.0)	130	4.0	**2** (25) + **4** (14)
8	AgOTf (4.0)	130	1.5	**2** (25) + **4** (31)
9	TfOH (0.05)	130	4.0	**2** (69) + **4** (26)
10	TfOH (0.05)[e]	130	4.0	**2** (58) + **4** (41)
11	TfOH (0.05)[f]	130	4.0	degr. products
12	$BF_3{\cdot}Et_2O$ (1.0)	100 [d]	0.5	**2** (21) + **3** (63)
13	$BF_3{\cdot}Et_2O$ (4.0)	130[d]	1.5	**2** (15) + **3** (72)
14	TMSOTf (0.05)	130	3.0	**2** (23) + **4** (41)
15	TMSOTf (4.0)	130	3.0	**3** (89)
16	TMSOTf (4.0)[g]	80	4.0	**3** (79)

[a] Reaction conditions: **1a** (1.0 equiv.), mesitylene (0.25 M), oil bath as heat source. [b] Isolated yields. [c] Chlorobenzene/H_2O as solvent (96/4 v/v) (0.4 M) with mesitylene (5.0 equiv.). [d] MW irradiation at 300 W. [e] Chlorobenzene as the solvent (0.25 M) with mesitylene (5.0 equiv.). [f] DMF as the solvent (0.25 M) with mesitylene (5.0 equiv.). [g] DCE (0.25 M) with mesitylene (5.0 equiv.).

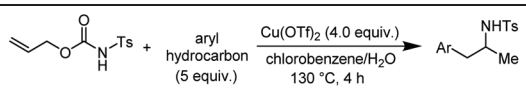
avoided (entry 4). Carrying out the reaction in chlorobenzene in the presence of mesitylene (5.0 equiv.) and H_2O (96/4 v/v) allowed to obtain **2** and **4** in 77% and 22% yields, respectively (entry 5). Although this protocol does not represent an improvement in terms of yields, it shows that it is possible to work in the presence of a solvent other than the aromatic reaction partner itself.

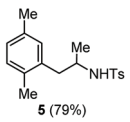
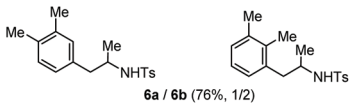
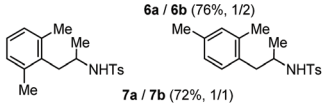
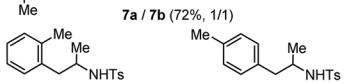
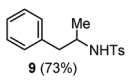
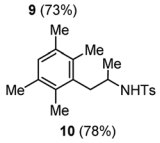
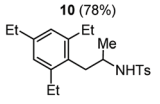
Different promoters were then tested, using either conventional heating or microwave irradiation. However, *p*-toluenesulfonic acid, H_2SO_4 and silver(I) triflate behaved analogously to $Cu(OTf)_2$ (Table 1, entries 6–8). Assuming that the above described reaction conditions involved the *in situ* generation of TfOH, we also tested a catalytic amount of this acid in different solvents (entries 9–11). Working in mesitylene or in chlorobenzene with 5.0 equivalents of mesitylene, the recovery of $TsNH_2$ was still high, whereas the use of DMF gave only intractable degradation products. The use of $F_3B{\cdot}OEt_2$ disclosed a new reactivity involving the double arylation to the allyl moiety. Indeed, treatment of **1a** with a stoichiometric or an excess amount of $F_3B{\cdot}OEt_2$ under microwave irradiation furnished a mixture of **2** and the 1,2-diarylpropane **3** (entries 12 and 13). Switch to TMSOTf as the acid promoter was then considered. While the use of a catalytic amount of this promoter afforded a mixture of **2** and **4** (entry 14), an excess amount of it (4.0 equiv.) gladly brought about the selective formation of **3** in 89% yield (entry 15). A similar result was also obtained using DCE as solvent (entry 16).

Among the range of branched amines, *N*-substituted phenethylamine derivatives have been widely studied in recent years for their value in organic, bioorganic, and medicinal chemistry.[8] We thus set out to test the decarboxylative arylation/hydroamination described above with other aromatic hydrocarbons (Table 2).

Accordingly, reacting allyl carbamate **1a** in *p*-xylene under the conditions of Table 1, entry 5 [$Cu(OTf)_2$ (4 equiv.), chlorobenzene[9]/H_2O (96/4 v/v), 130 °C, 4.0 h] afforded the corresponding arylated 2-tosylaminopropane **5** as the sole product in good yield (Table 2, entry 1). The reaction carried out in *o*-xylene, *m*-xylene, or toluene gave the corresponding arylation/hydroamination products as mixtures of two regioisomers **6a**/**6b**, **7a**/**7b**, and **8a**/**8b** (entries 2–4). The less electron-rich benzene also provided the expected arylation/hydroamination product **9**[10] in acceptable yield (entry 5). Finally, the heavily alkylated arenes durene and 1,3,5-triethylbenzene gave the

Table 2 Synthesis of the *N*-substituted phenethylamines[a]



Entry	Aryl hydrocarbon	Product(s) (% yield)[b]
1[c]	*p*-Xylene	 **5** (79%)
2	*o*-Xylene	 **6a / 6b** (76%, 1/2)
3	*m*-Xylene	 **7a / 7b** (72%, 1/1)
4	Toluene	 **8a / 8b** (29%, 1/2)
5	Benzene	 **9** (73%)
6	1,2,4,5-Tetramethylbenzene	 **10** (78%)
7	1,3,5-Triethylbenzene	 **11** (74%)

[a] Reaction conditions: **1a** (1.0 equiv.), $Cu(OTf)_2$ (4.0 equiv.), aryl hydrocarbon (5.0 equiv.), chlorobenzene/H_2O as solvent (96/4 v/v) (0.4 M), 130 °C, 4 h. [b] Isolated yields. Isomeric ratios calculated from the ^{1}H-NMR of the crude reaction mixture. [c] Scale up: performing the reaction with 5 mmol of **1a** at 130 °C, after 6 h **5** was obtained in 71% yield.

corresponding cascade products **10** and **11** in good yields (entries 6 and 7).

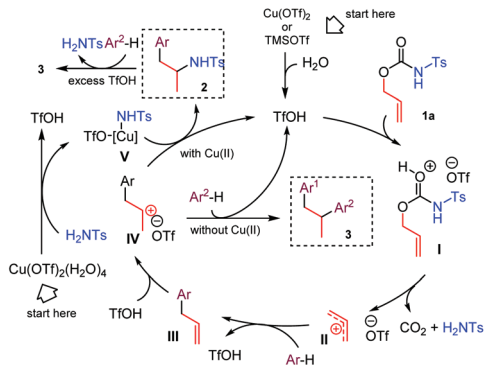
We propose for the above double coupling reactions the following mechanism, shown in the case of carbamate **1a** (Scheme 2). First, we assume that triflic acid is formed *in situ* from $Cu(OTf)_2$ (or TMSOTf) and water.[11] Following protonation at the carbonyl oxygen atom of the carbamate function generates the activated *O*-allyl carbamate **I**, which undergoes a decarboxylative/deamidative FC alkylation by attack of arene to give intermediate **III** passing through an allyl carbenium ion **II**. Subsequent Markovnikov protonation of **III** generates the allyl carbenium ion **IV**. At this point, the nature of the additive directs the reaction path. In the presence of copper triflate, the extruded *N*-tosylamide can coordinate the metal, generating the amido copper-complex **V**, which selectively attacks the carbenium ion **IV**, affording the hydroamination product **2**.[12] Alternatively, when TMSOTf is used, intermediate **IV** undergoes a second FC allylation, providing the 1,2-diarylpropane **3**. Finally, in the presence of excess triflic acid product **2** suffers a deamidative substitution by mesitylene *via* an incipient or discrete carbenium ion, to afford the diarylated product **3**.

Corollary experiments using the *O*-allyl *N*-4-chlorophenyl carbamate **1b** in place of **1a** were carried out next (Scheme 3). Running the reaction in mesitylene/H_2O (98/2 v/v) in the presence of $Cu(OTf)_2$ as the promoter gave the diarylated product **3**, and not the corresponding aniline derivative. However, carrying out the same reaction in the presence of exogenous H_2NTs (2.0 equiv.) afforded a mixture of the arylated/hydroaminated derivative **2** and the diarylated derivative **3**. These results corroborate the above proposed mechanism and show that tosylamine is a competent nitrogen nucleophile to trap the carbenium ion **IV** when $Cu(OTf)_2$ is used as the promoter.

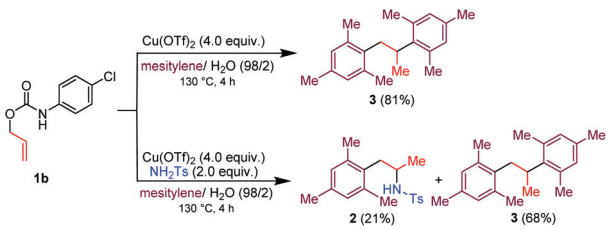
The scope of the reaction was evaluated next, keeping the promoting system $Cu(OTf)_2/H_2O$ in chlorobenzene (Table 3). On the one hand, reacting *O*-allyl *N*-2-nosylcarbamate **1c** with 5 equiv. of mesitylene (entry 1), and carbamate **1a** with mesityl bromide (entry 2), 4-methylanisole (entry 3), 4-bromoanisole (entry 4) gave the corresponding hydroaminated products **12–15** in fair to good yields. On the other hand, strongly activated arenes such as 1,3,5-trimethoxybenzene gave the diarylated product **16** as the only product (entry 5).

To have a better knowledge of the behaviour of this C–H cascade as a function of the adopted reaction protocol and the nature of the engaged reaction partners, other tests were undertaken. Accordingly, the C–H coupling between variously substituted *N*-tosyl carbamates in the presence of the Cu $(OTf)_2/H_2O$ system and 5.0 equivalents of arene was next tested (Scheme 4). In the event, each isomeric carbamate **1d–f** converged toward the same corresponding arylation/hydroamination product, namely **17** when reacted with mesitylene and **18** when reacted with *p*-xylene.

Such a reactivity suggests the convergence of **1d**, **1e** and **1f** toward the common allylic carbenium ion **VI**, which, after the

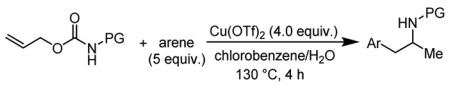


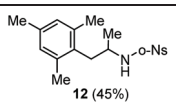
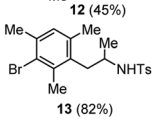
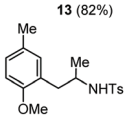
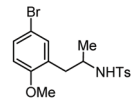
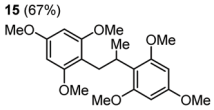
Scheme 2 Proposed mechanisms for the acid-mediated decarboxylative C–H coupling between arenes and *O*-allyl carbamates.



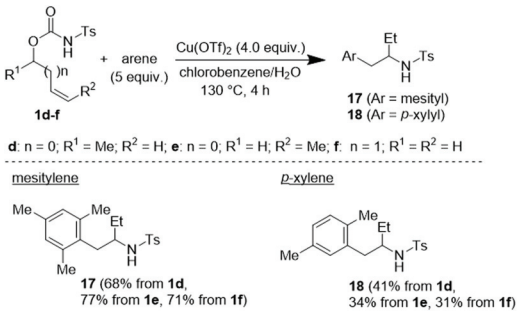
Scheme 3 $Cu(OTf)_2/H_2O$ mediated decarboxylative C–H couplings between mesitylene and *O*-allyl *N*-4-chlorophenyl carbamate. Reaction condition involves the use of 100 μL of H_2O for 1 mmol of **1b**.

Table 3 Other C–H couplings with heterosubstituted arenes[a]

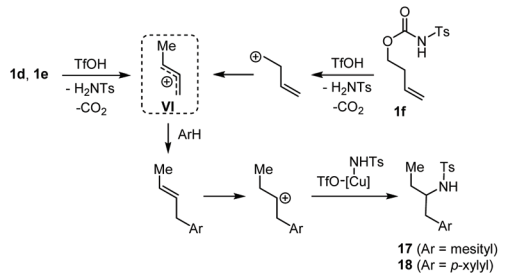


Entry	Arene	PG	Product(s) (% yield)[b]
1[c]	Mesitylene	*o*-Ns	 **12** (45%)
2	Mesitylbromide	Ts	 **13** (82%)
3	4-Methylanisole	Ts	 **14** (77%)
4	4-Bromoanisole	Ts	 **15** (67%)
5	1,3,5-Trimethoxybenzene	Ts	 **16** (61%)

[a] Reaction conditions: *N*-protected *O*-allyl carbamate (1.0 equiv.), Cu $(OTf)_2$ (4.0 equiv.), arene (5.0 equiv.), chlorobenzene/H_2O as solvent (96/4 v/v) (0.4 M), 130 °C, 4 h. [b] Isolated yields. [c] The reaction was carried out in mesitylene as solvent (0.25 M).



Scheme 4 Reaction with $Cu(OTf)_2$ with substituents on the allylic chain of the *N*-tosyl carbamates.



Scheme 5 Proposed mechanism for the $Cu(OTf)_2$ promoted transformation of **1d–f** into **17** and **18**.

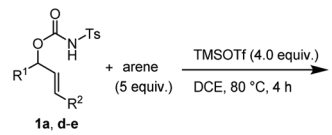
FC reaction, undergoes a regioselective Cu-promoted hydroamination (Scheme 5).

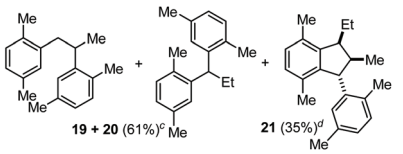
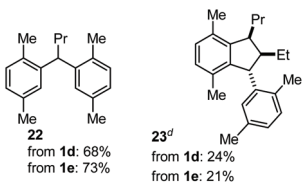
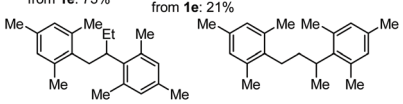
The coupling of *N*-tosyl carbamates **1a**, and **1d–e** was also tested using TMSOTf as acid promoter in DCE at 80 °C (Table 4). In this case, reaction of **1a** with *p*-xylene gave an inseparable mixture made of the 1,2-diarylated product **19**, the 1,1-diarylated product **20**, and indane **21** (entry 1). Carbamates **1d** and **1e** converged again toward a mixture of the 1,1-diarylated product **22** and the indane **23** when reacted with *p*-xylene (entry 2), and toward a mixture of the 1,2-diarylated product **24** and 1,3-diarylated product **25** when reacted with mesitylene (entry 3).

The reactivity observed with the above experiments deserves further remarks. First, the formation of **19**, **20**, and **21** (Table 4, entry 1) can be rationalized as follows (Scheme 6, top part). After the first FC allylation of *p*-xylene, Markovnikov protonation and interception of the resulting carbenium ion **VII** by a second molecule of *p*-xylene generates **19**. However, *p*-xylene – less nucleophilic than mesitylene – allows a competitive **VII**-to-**VIII** 1,2-hydride shift that takes place before the second FC reaction, generating **20**. At this point, the benzylic carbocation **VIII** and the styrene **IX** could react together through a formal [3 + 2] cycloaddition giving the Wheland intermediate **X** which can evolve into **21**.[13]

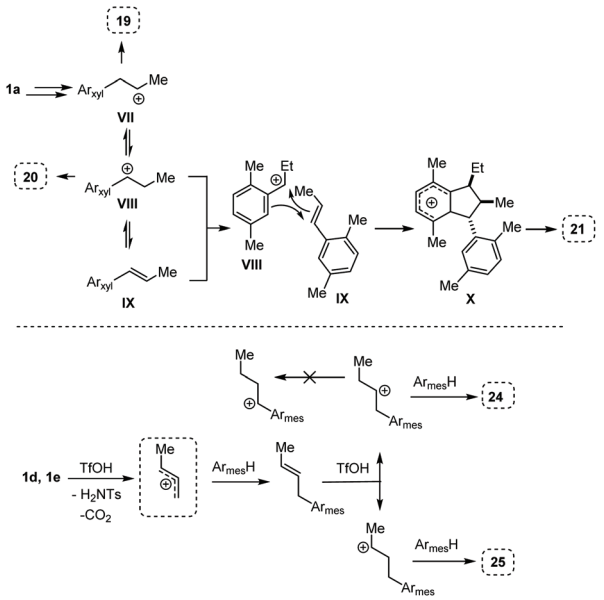
The outcome of entry 3 in Table 4 needs further observations, too. Indeed, in this case, the protonation after the first

Table 4 TMSOTf mediated C–H couplings involving differently substituted unsaturated carbamate derivatives[a]



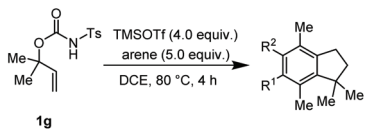
Entry[d]	1	Arene	Product(s) (% yield)[b]
1[c]	**1a**	*p*-Xylene	 **19** + **20** (61%)[c] **21** (35%)[d]
2	**1d**, **1e**	*p*-Xylene	 **22** from **1d**: 68% from **1e**: 73%; **23**[d] from **1d**: 24% from **1e**: 21%
3	**1d**, **1e**	Mesitylene	 **24** from **1d**: 27% from **1e**: 32%; **25** from **1d**: 69% from **1e**: 65%

[a] Reaction conditions: **1a** (1.0 equiv.), TMSOTf (4.0 equiv.), arene (5.0 equiv.), DCE (0.4 M), 80 °C, 4 h. [b] Isolated yields. Isomeric ratios calculated from the ^{1}H-NMR of the crude reaction mixture. [c] **19** + **20** isomeric ratio: 1/1. [d] The relative configuration of indane structures **21** and **23** was determined by NOESY experiment.

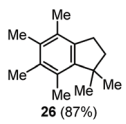
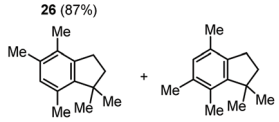
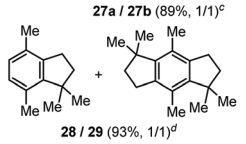


Scheme 6 Proposed mechanisms associated to the reactions of Table 5. Top part: entry 1, from **1a** to **19**, **20**, and **21**. Bottom part: entry 3, from **1d** or **1e** to **24** and **25**.

Table 5 Reaction with TMSOTf with α,α-dimethyl substituted *O*-allyl *N*-tosyl carbamates[a]

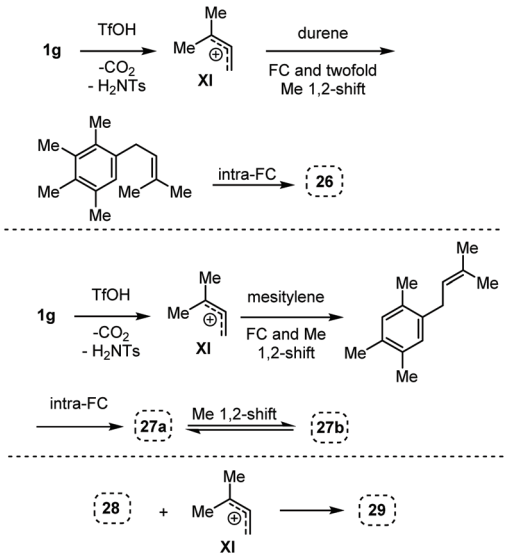


1g

Entry	Arene	Product(s) (% yield)[b]
1	Durene	 **26** (87%)
2[c]	Mesitylene	 **27a / 27b** (89%, 1/1)[c]
3[d]	*p*-Xylene	 **28 / 29** (93%, 1/1)[d]

[a] Reaction conditions: **1a** (1.0 equiv.), TMSOTf (4.0 equiv.), arene (5.0 equiv.), DCE (0.4 M), 80 °C, 4 h. [b] Isolated yields. Isomeric ratios calculated from the ^{1}H-NMR of the crude reaction mixture. [c] 1 : 1 isomeric ratio. [d] **28** + **29** in 1 : 1 ratio.

FC reaction is non-regioselective, and the very nucleophilic mesitylene intercepts the two resulting carbenium ions to give a mixture of **24** and **25**. In this case, the very reactive arene does not let the time for a homobenzylic-to-benzylic cation 1,2-hydride shift (Scheme 6, bottom part).



Scheme 7 Proposed mechanisms for the generation of the indane structures **26**, **27a** and **27b** and of hydrindacene **29** from carbamate **1g**.

The α,α-dimethyl substituted *O*-allyl *N*-tosyl carbamate **1g** was investigated next (Table 5). Thus, treatment of this carbamate with durene under the usual TMSOTf conditions gave indane **26** in 87% yield (entry 1). Analogous treatment with mesitylene afforded an inseparable mixture of the two isomeric indanes **27a** and **27b** in 89% yield (entry 2), while reaction with *p*-xylene gave an inseparable 1 : 1 mixture of the indane **28** and the hydrindacene **29** in 93% yield (entry 3).

Here, in contrast to the previous cases, a one-to-one coupling between the carbamate and the arene takes place, generating indane structures. This is likely due to the fact that after the first FC allylation on the less substituted allyl terminus **XI**,[14] the aromatic ring is favourably biased to undergo a second, intramolecular, FC reaction. It should be noted that in the cases of mesitylene and durene, 1,2-methyl migrations on the aryl moiety[15] take place – before or after the first FC reaction – opening the way to the final intramolecular FC reaction (Scheme 7). However, a second carbocation species could attack the highly reactive indane **28** providing the hydrindacene **29**.[16]

Conclusions

In summary, this work shows for the first time that *O*-allyl carbamates are ideal C3 dication equivalents. Acidic conditions expected to generate *in situ* TfOH enable decarboxylative FC/hydromidation sequences or twofold FC alkylations, most of which proceed in synthetically useful yields. According to the nature of the arene partner and of the allyl moiety in the carbamate, the mechanisms can take different paths, all of them mechanistically justified. These results offer the chemist a rich palette of synthetic opportunities, further enriching the

domains of cascade reactions in general, and FC, and hydroaminations in particular.

Conflicts of interest

There are no conflicts to declare.

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