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Fluorinated Alcohols As Promoters for the Metal-Free Direct Substitution Reaction of Allylic Alcohols with Nitrogenated, Silylated, and Carbon Nucleophiles

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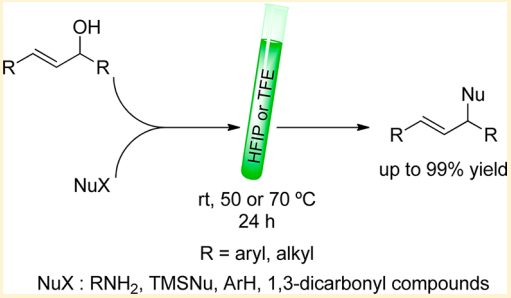
Supporting Information

ABSTRACT: The direct allylic substitution reaction using allylic alcohols in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and 2,2,2-trifluoroethanol (TFE) as reaction media is described. The developed procedure is simple, works under mild conditions (rt, 50 and 70 °C), and proves to be very general, since different nitrogenated nucleophiles and carbon nucleophiles can be used achieving high yields, especially when HFIP is employed as solvent and aromatic allylic alcohols are the substrates. Thus, sulfonamides, carbamates, carboxamides, and amines can be successfully employed as nitrogen-based nucleophiles. Likewise, silylated nucleophiles such as trimethylsilylazide, allyltrimethylsilane, trimethylsilane, and trimethylsilylphenylacetylene give the corresponding allylic substitution products in high yields. Good results for the Friedel−Crafts adducts are also achieved with aromatic compounds (phenol, anisole, indole, and anilines) as nucleophiles. Particularly interesting are the results obtained with electron-rich anilines, which can behave as nitrogenated or carbon nucleophiles depending on their electronic properties and the solvent employed. In addition, 1,3-dicarbonyl compounds (acetylacetone and Meldrum's acid) are also successfully employed as soft carbon nucleophiles. Studies for mechanism elucidation are also reported, pointing toward the existence of carbocationic intermediates and two working reaction pathways for the obtention of the allylic substitution product.



INTRODUCTION

The unique chemical and physical properties of fluoroalkyl alcohols, which possess a high hydrogen bond donor ability along with a low nucleophilicity and high polarity and ionizing power values, have drawn attention about the use of these particular molecules in organic chemistry transformations mainly as additives in catalyzed reactions or as solvents.[1,2] In this latter sense and as a result of the mentioned properties, they have been traditionally used to solubilize those molecules that are not soluble in the most common organic solvents, especially in biochemistry when working with peptides and nucleic acids and in the polymer industry for polyamides and polyacrylonitriles. In addition, fluoroalkyl alcohols turned out to be more effective than traditionally employed solvents, including their nonfluorinated analogues, in some organic synthesis processes. Thus, results were considerably enhanced by using these solvents in some oxidation (especially in epoxidation reactions and oxidation of sulfur compounds) and in reduction, hydrogenation, and cycloaddition-type reactions.[1] Furthermore, acting as solvents, these molecules can also promote some reactions by themselves. Thus, the group of Bégué and Bonnet-Delpon have reported a Povarov-type [4 + 2] cycloaddition,[3] a ring opening of oxiranes with aromatic amines,[4] and aza-Michael reactions,[5] mediated by 2,2,2-trifluoroethanol (TFE) and by 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvents.

In the past years, the intermolecular allylic substitution reaction (and particularly the direct amination reaction) of allylic alcohols has emerged as a straightforward and environmentally friendly way to get access to allylic amines.[6] Our group, in the search for new and efficient strategies for this purpose, has recently reported the use of Lewis and Brønsted acids, such as $[(PhO)_3P]AuOTf$,[7a] AgOTf,[7a] $FeCl_3·6H_2O$,[7b] and TfOH,[7b] as catalysts able to successfully accomplish this transformation. In this sense, in the search for a metal-free strategy to carry out this process, we envisage the possibility of the use of fluorinated alcohols as effective reaction media able to activate the hydroxy functionality of allylic alcohols through hydrogen-bonding, hence promoting the direct allylic nucleophilic substitution.[8]

RESULTS AND DISCUSSION

The direct amination between (*E*)-1,3-diphenylprop-2-en-1-ol (**1a**) and *p*-toluensulfonamide (**2a**) was chosen as a model for the optimization of the reaction conditions (Table 1) using 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as readily available and inexpensive fluorinated alcohols acting as solvents and reaction promoters (Table 1).[9]

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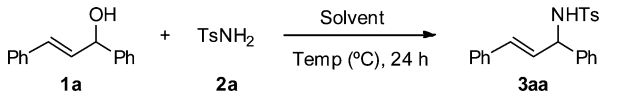
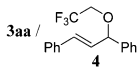
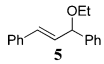
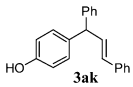
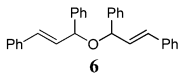
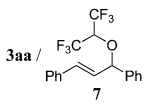
Table 1. Optimization of Reaction Parameters[a]



Entry	Solvent	Temp. (°C)	Product (%)	Yield[b]
1	HFIP	50	**3aa**	>95
2	TFE	50	**3aa** /  **4**	84/16
3	TFE	70	**3aa**	>95
4	EtOH	70	 **5**	>95
5	PhOH	70	 **3ak**	>95
6	H_2O	70	 **6**	90
7	HFIP[c]	50	**6**	87
8	HFIP[d]	50	**3aa** /  **7**	60/40
9	TFE[d]	70	—	—
10	HFIP[e]	50	**3aa/7**	50/50
11	TFE[e]	70	**3aa/4**	81/19

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 equiv), and 500 μL of the solvent (1 M solution of **1a**). [b]Determined from ^{1}H NMR analysis of the crude mixture. [c]1 equiv (53 μL) was used. [d]250 μL of the solvent was used (2 M solution of **1a**). [e]Reaction performed under MW irradiation (40 W, 36 psi).

In the case of HFIP the reaction was carried out at 50 °C, giving product **3aa** in almost quantitative yields after 24 h (Table 1, entry 1). At this temperature and using TFE, 84% yield was obtained for the amination product, obtaining a 16% of byproduct **4** resulting from the attack of the solvent (Table 1, entry 2). However, raising the temperature to 70 °C provided quantitative yields for **3aa** (Table 1, entry 3). When the reaction was carried out at this temperature but using ethanol as solvent[7] (Table 1, entry 4), the corresponding ether **5** was obtained as sole product due to the higher nucleophilicity of this alcohol (N_{EtOH} = 0, N_{TFE} = −2.78, and N_{HFIP} = −4.23).[1] For the sake of comparison in terms of Brønsted acidity we decided to perform the amination reaction in PhOH as reaction media[9] [pK_a(PhOH) = 9.95, pK_a(TFE) = 12.37, and pK_a(HFIP) = 9.30][1] obtaining the Friedel−Crafts adduct **3ak** as major product (Table 1, entry 5). Finally, when water, which also possesses a high polarity and hydrogen bond ability, was used as solvent, dimerization product **6** was the main product observed (Table 1, entry 6).[9,10] Next, reduction of the fluoroalkyl alcohol quantity was attempted, but unfortunately the use of a stoichiometric amount of HFIP gave rise to the formation of dimer **6** (Table 1, entry 7). Using half of the amount of solvent led to an incomplete reaction in the case of HFIP, along with the formation of ether **7** as byproduct, and a complex mixture of products when TFE was employed (Table 1, entries 8 and 9, respectively). Both solvents were also tested in a reaction carried out under microwave irradiation for 30 min, but a mixture of **3aa** and products resulting from the competitive reaction of the solvent were observed (Table 1, entries 10 and 11).

Once the optimal conditions were established (Table 1, entries 1 and 3), different nitrogenated nucleophiles were evaluated for the direct allylic amination reaction onto alcohol **1a** mediated by HFIP and TFE (Scheme 2 and Table 2). As mentioned above *p*-toluenesulfonamide (**2a**) gave rise to the amination product **3aa** in almost quantitative yields in both solvents after purification (Table 2, entries 1 and 2). Under these optimal conditions benzylcarbamate (**2b**) led to the formation of **3ab** in excellent yields (Table 2, entries 3 and 4). However, *tert*-butylcarbamate (**2c**) afforded **3ac** in modest 45% and 32% yields, respectively (Table 2, entries 5 and 6). Benzamide gave only moderate yield when HFIP was used as solvent (Table 2, entry 7). Surprisingly, a higher 80% yield was obtained for **3ad** by using TFE as solvent (Table 2, entry 8). Electron-poor aniline such as *p*-nitroaniline (**2e**) afforded the amination product **3ae** in low yield in HFIP, but excellent yield was achieved when the reaction was carried out in TFE (Table 2, entries 9 and 10). Other anilines were also tested, but to our surprise Friedel−Crafts alkylation products were obtained (see Table 4). Encouraged by these results, more basic amines, which have remained elusive in most of the direct allylic amination reaction reported to date,[11] were next tested. When benzylamine (**2f**) was used as nucleophile, high yield was obtained only using HFIP as solvent probably due to the more acidic nature but lower nucleophilicity and higher hydrogen bond ability of this fluoroalkyl alcohol compared to TFE (Table 2, entries 11 and 12). The same behavior was observed when (*R*)-α-methyl benzylamine (**2g**) was evaluated, giving product **3ag** in a 60% as a 1.2:1 diastereomeric mixture (Table 2, entries 13 and 14). Similar results were also achieved with the more basic aliphatic *n*-butylamine (**2h**) as nucleophile (Table 2, entries 15 and 16). As mentioned above, TFE did not promote the amination reaction of any of these more basic amines. Finally when trimethylsilyl azide (**2i**), which to the best of our knowledge has never been successfully employed for the direct amination of allylic alcohols in a metal-free process,[12] was used as nucleophile, excellent yield was reached for compound **3ai** with HFIP as solvent (Table 2, entry 17). However, the use of TFE yielded the corresponding product in a lower 51% yield (Table 2, entry 18). Other nitrogen-based nucleophiles such as aqueous ammonia, phthalimide, and its corresponding potassium salt were also tested under the same reaction conditions, giving low yields at the best (ca. 10%) for the corresponding amination products. It can be summarized that HFIP shows in general significantly better performance than TFE for the direct amination of the allylic alcohol **1a**, and in addition, lower temperatures and equivalents of solvent were required.

Next, other allylic alcohols were submitted to the HFIP- and TFE-mediated allylic substitution reaction under the standard conditions and using $TsNH_2$ **2a** as nucleophile (Table 3). Thus, alcohol **1b** gave rise to the corresponding amination product **3ba** in good yields with both solvents (Table 3, entries 1 and 2). Similar results in terms of yields were observed when (*Z*)-**1b** was the used as substrate, obtaining the (*E*)-isomer as reaction product (Table 3, entries 3 and 4). However, with the allylic alcohol **1c**, moderate yields in product **3ba** were obtained even when 2 equiv of sulfonamide were employed (Table 3,

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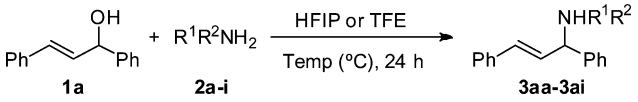
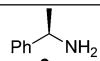
Table 2. Direct Allylic Amination of 1a Mediated by Either HFIP or TFE[a]



Entry	Solvent (°C)	$R^1R^2NH_2$	Product	Yield (%)[b]
1	HFIP (50)	$TsNH_2$ **2a**	**3aa**	96
2	TFE (70)		**3aa**	93
3	HFIP (50)	$CbzNH_2$ **2b**	**3ab**	89
4	TFE (70)		**3ab**	87
5	HFIP (50)	$BocNH_2$ **2c**	**3ac**	45
6	TFE (70)		**3ac**	32
7	HFIP (50)	$PhC(O)NH_2$ **2d**	**3ad**	52
8	TFE (70)		**3ad**	80
9	HFIP (50)	pNO_2-$C_6H_4NH_2$ **2e**	**3ae**	<15
10	TFE (70)		**3ae**	97
11	HFIP (50)	$BnNH_2$ **2f**	**3af**	73
12	TFE (70)		**3af**	—
13	HFIP (50)	 **2g**	**3ag**	60 (1.2:1)[c]
14	TFE (70)		**3ag**	—
15	HFIP (50)	$C_4H_9NH_2$ **2h**	**3ah**	57 (64)[d]
16	TFE (70)		**3ah**	—
17	HFIP (50)	$TMSN_3$ **2i**	**3ai**	96
18	TFE (70)		**3ai**	51

[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.5 equiv), and 500 μL of the solvent (1 M solution of **1a**). [b]Isolated yields after flash chromatography. [c]Determined by GC and ^{1}H NMR. [d]In brackets, yield using 2 equiv of butylamine.

entries 5 and 6). According to these results, alcohol **1b** is the substrate of choice to prepare sulfonamide **3ba**. Compound **3da** was obtained in 79% yield when cyclohex-2-enol (**1d**) was employed as substrate in HFIP as solvent, failing the reaction in TFE (Table 3, entries 7 and 8). Moderate yields were achieved in both solvents when the reaction was performed with alcohol **1e** (Table 3, entries 9 and 10). In both cases approximately the same regioisomeric mixture of compounds **3ae** and **3ae′** (the latter arising from the γ-addition)[13] were isolated. Next, alcohols **1f** and **1g** were evaluated. When the allylic alcohol bearing a terminal olefin **1f** was used, a mixture of compounds **3fa** and **3fa′** in 30% and 27% yield was obtained in HFIP and TFE, respectively. In both cases, compound **3fa′** having the most substituted olefin was the major regioisomer in a 3:1 ratio (Table 3, entries 11 and 12). However, when **1g** was employed, **3ga** was the sole regioisomer observed. Surprisingly, when the reaction was carried out in HFIP, a low 15% for the amination product was obtained, whereas **3ga** was isolated in a 43% yield when TFE was the solvent (Table 3, entries 13 and 14). It is worth noting that the corresponding fluoroalkyl ethers were obtained as byproduct, the amount of unreacted allylic alcohol being in all cases negligible (<5%). Other allylic alcohols such as cinnamyl alcohol, 1-phenyl-2-propen-1-ol, crotyl alcohol, sorbic alcohol, and penta-1,4-dien-3-ol were tested without success.

Next, to broaden the scope of this methodology, we turned our attention onto carbon nucleophiles (Table 4). First, Friedel−Crafts-type reaction onto allylic alcohol **1a** was examined. Thus, anisole (**2j**) and phenol (**2k**), both reacting only at the *para* position, gave rise to the corresponding alkylation adducts **3aj** and **3ak**, respectively, with higher yields when using HFIP compared with TFE as solvent (Table 4, entries 1−4). When indole (**2l**) was employed as nucleophile, **3al** was regioselectively isolated in excellent yields regardless of the fluoroalkyl alcohol used (Table 4, entries 5 and 6). Electron-rich anilines, which in principle were expected to proceed through a direct amination reaction, were next evaluated as carbon nucleophiles. Thus, *p*-anisidine afforded in high yields exclusively the Friedel−Crafts type alkylation product **3am** regardless of the solvent employed (Table 4, entries 7 and 8). However, *p*-chloroaniline gave rise to the formation of alkylation or amination products **3an** or **3an′**, respectively, depending on the solvent employed (Table 4, entries 9 and 10). The formation of the Friedel−Crafts adduct **3an** could also be sought as result of a direct amination and subsequent Hofmann−Martius rearrangement, as described by other groups.[14]

Next, trimethylsilylated nucleophiles were evaluated. The use of allyltrimethylsilane (**2o**) afforded the corresponding diene **3ao** in almost quantitative yields in both solvents (Table 4, entries 11 and 12). To our delight, the more challenging

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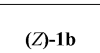
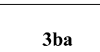
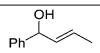
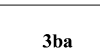
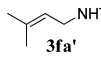
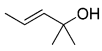
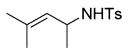
Table 3. Direct Allylic Amination of 1b−g Mediated by Either HFIP or TFE[a]

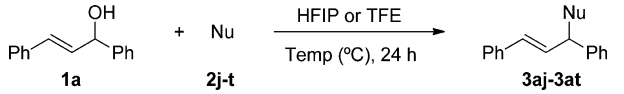
Entry	1	Solvent (°C)	Product	Yield (%)[b]
1		HFIP (50)		68
2	**1b**	TFE (70)	**3ba**	54
3		HFIP (50)		52
4	**(*Z*)-1b**	TFE (70)	**3ba**	43
5		HFIP (50)		36 (52)[c]
6	**1c**	TFE (70)	**3ba**	30 (35)[c]
7		HFIP (50)		79
8	**1d**	TFE (70)	**3da**	—
9		HFIP (50)		57 (75/25)[c,d]
10	**1e**	TFE (70)	 **3ea'**	52 (83/17)[c,d]
11		HFIP (50)		30 (25/75)[c,d]
12	**1f**	TFE (70)	 **3fa'**	27 (25/75)[c,d]
13		HFIP (50)		15[c]
14	**1g**	TFE (70)	**3ga**	43[c]

[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.5 equiv), and 500 μL of the solvent (1 M solution of **1**). [b]Isolated yield after flash chromatography. [c]2 equiv of nucleophile was used. [d]Product ratio determined by ^{1}H NMR analysis of the crude mixture.

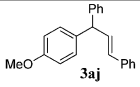
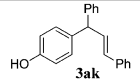
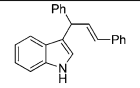
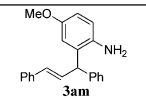
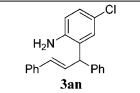
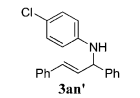
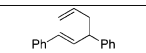
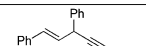
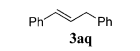
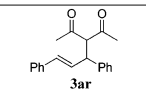
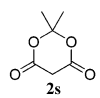
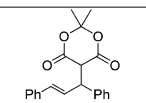
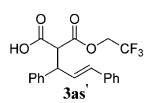
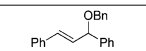
phenylacetylene derivative **2p** led to the formation of the 1,4-enyne **3ap** in good yields (Table 4, entries 13 and 14). Encouraged by these results, other silylated carbon nucleophiles such as trimethylsilyl cyanide and (trimethylsilyl)-trifluoromethane were also tested, giving unfortunately very poor results at the best. In contrast, triethylsilane (**2q**) turned out be an excellent nucleophile, especially when HFIP was used as solvent, giving rise to the formation of the deoxygenation product **3aq** in 87% and 62% yield, respectively (Table 4, entries 15 and 16).

1,3-Dicarbonyl compounds were next evaluated as nucleophiles. When the reaction between alcohol **1a** and dimethyl malonate was carried out in both fluorinated alcohols the expected product was not produced. In contrast, the less basic acetylacetone (**2r**) gave the corresponding substitution product **3ar** in excellent yields when the less Brønsted acidic solvent TFE was employed (Table 3, entry 18).[15] Meldrum's acid was next employed as nucleophile, leading to the desired substitution product **3as** even when more acidic HFIP was the solvent (Table 4, entry 19). However, the reaction carried out in TFE gave rise in high yield to the formation of the malonic acid monoester **3as′** as a result of the cleavage of cyclic ketal and subsequent transesterification of the product **3as** (Table 4, entry 20). Finally, benzylic alcohol **2t** was also tested, giving mainly ethers **4** and **7**, respectively, as main products.

Table 4. Allylic Substitution of 1a with Carbon Nucleophiles Mediated by Either HFIP or TFE[a]



1a **2j-t** **3aj-3at**

Entry	Nu	Solvent (°C)	3	Yield (%)[b]
1	Anisole **2j**	HFIP (50)	 **3aj**	88
2		TFE (70)		58
3	Phenol **2k**	HFIP (50)	 **3ak**	75
4		TFE (70)		56
5	Indole **2l**	HFIP (50)	 **3al**	96
6		TFE (70)		94
7	*p*MeO-$C_6H_4NH_2$ **2m**	HFIP (50)	 **3am**	93
8		TFE (70)		93
9	*p*Cl-$C_6H_4NH_2$ **2n**	HFIP (50)	 **3an**	90
10		TFE (70)	 **3an'**	92
11	 **2o**	HFIP (50)	 **3ao**	98
12		TFE (70)		98
13	PhC≡CTMS **2p**	HFIP (50)	 **3ap**	61
14		TFE (70)		58
15	Et_3SiH **2q**	HFIP (50)	 **3aq**	87
16		TFE (70)		62
17	 **2r**	HFIP (50)	 **3ar**	64
18		TFE (70)		95
19	 **2s**	HFIP (50)	 **3as**	60
20		TFE (70)	 **3as'**	85[c]
21	BnOH **2t**	HFIP (50)	 **3at**	13
22		TFE (70)		—

[a]Reaction conditions: **1a** (0.5 mmol), **2** (1.5 equiv), and 500 μL of the solvent (1 M solution of **1a**). [b]Isolated yield after flash chromatography. [c]Obtained as a 1:1 diastereomeric mixture.

Only a 13% yield of compound **3at** was obtained in HFIP (Table 3, entries 21 and 22).

Finally, in a parallel manner, other allylic free alcohols were also tested in the reaction with different carbon nucleophiles. Thus, **1b**, **1c**, and **1d** were submitted to the allylic substitution reaction with anisole (**2j**), indole (**2l**), allyltrimethylsilane (**2o**),

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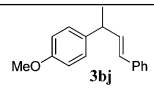
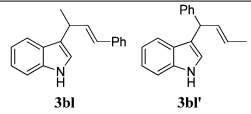
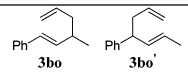
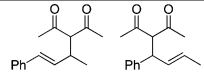
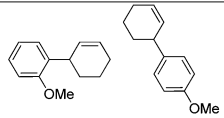
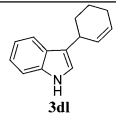
Table 5. Allylic Substitution of Alcohols 1b−d with Carbon Nucleophiles Mediated by Either HFIP or TFE[a]

Entry	1	Nu	Solvent (°C)	Product	Yield (%)[b]
1		Anisole **2j**	HFIP (50)	 **3bj**	48
2			TFE (70)		21
3	 **1b**	Indole **2l**	HFIP (50)	 **3bl** **3bl'**	53 (50/50)[c]
4			TFE (70)		50 (>99/0)[c]
5		 **2o**	HFIP (50)	 **3bo** **3bo'**	71 (60/40)[c]
6			TFE (70)		88[d] (60/40)[c]
7		 **2r**	HFIP (50)	 **3br** **3br'**	76 (50/50)[c]
8			TFE (70)		75 (60/40)[c]
9		Anisole **2j**	HFIP (50)	**3bj**	66
10			TFE (70)		51
11		Indole **2l**	HFIP (50)	**3bl/3bl'**	99 (50/50)[c]
12	 **1c**		TFE (70)		95 (60/40)[c]
13		 **2o**	HFIP (50)	**3bo/3bo'**	90[d] (55/45)[c]
14			TFE (70)		47 (50/50)[c]
15		 **2r**	HFIP (50)	**3br/3br'**	50 (60/40)[c]
16			TFE (70)		<15 (50/50)[c]
17		Anisole **2j**	HFIP (50)	 **3dj** **3dj'**	69[d] (45/24)[c,e]
18			TFE (70)		58[d] (36/26)[c,e]
19	 **1d**	Indole **2l**	HFIP (50)	 **3dl**	<10
20			TFE (70)		—
21		 **2o**	HFIP (50)	 **3do**	57[d]
22			TFE (70)		—
23		 **2r**	HFIP (50)	 **3dr**	<15
24			TFE (70)		—

[a]Reaction conditions: **1** (0.5 mmol), **2** (2 equiv), and 500 μL of the solvent (1 M solution of **1a**). [b]Isolated yields after flash chromatography. [c]Product ratio determined by ^{1}H NMR and/or GC analysis of the crude mixture. [d]Because of the impossible separation of the substitution product from the corresponding fluoroalkyl ether and/or the starting material, the yield was determined by ^{1}H NMR and/or GC analysis of the crude mixture. [e]The 31% and 38% missing from the product distribution corresponds to the disubstitution product 2,4-bis(cyclohex-2-enyl)anisole **3dj″**.

and acetylacetone (**2r**) as representative carbonucleophiles under the typical reaction conditions (Table 5). When anisole (**2k**) was the nucleophile of choice, regioisomeric alcohols **1b** and **1c** produced the same Friedel−Crafts adduct **3bj** as a single isomer, obtaining better yields in both solvents when alcohol **1c** was the substrate employed (Table 5, compare entries 1 and 2 with 9 and 10). Alcohol **1b** reacting with indole (**2l**) as nucleophile gave rise to the corresponding substitution products, regioisomers **3bl** and **3bl′**, in 53% and 50% yield, respectively, when HFIP and TFE were used as solvents (Table 5, entries 3 and 4). It is worth mentioning that whereas a 1:1 regioisomeric mixture of α- and γ-substitution products **3bl** and **3bl′** was obtained in HFIP, the reaction performed in TFE afforded **3bl** as single product. On the other hand, regioisomeric mixtures of the α- and γ-substitution products **3bl** and **3bl′** were obtained in excellent yields in both solvents when indole (**2l**) reacted with alcohol **1c** (Table 5, entries 11 and 12). Next, allylTMS **2o** was tested as nucleophile. Thus, in the case of alcohol **1b**, 71% and 88% yield for the corresponding diene, which was obtained as a 60/40 regioisomeric mixture **3bo**/**3bo′**, was achieved in HFIP and TFE, respectively (Table 5, entries 5 and 6). A similar situation

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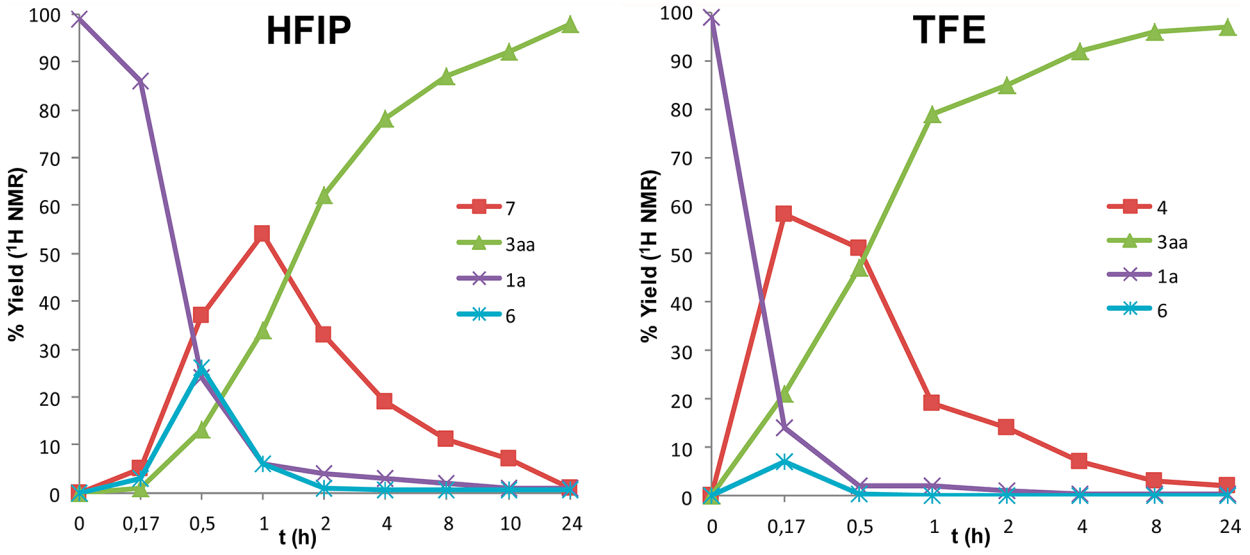
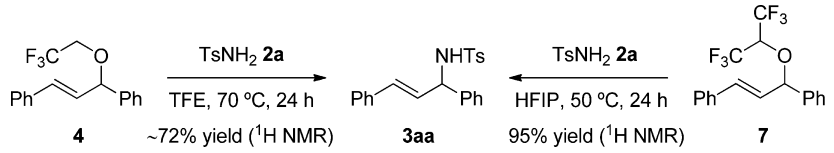


Figure 1. Reaction kinetics.

Scheme 1. Allylic Amination Reaction onto Ethers 4 and 7



was found when alcohol **1c** was allowed to react with the same nucleophile, giving approximately a 1:1 ratio for **3bo** and **3bo′**. In this case, substantially higher yield was obtained when HFIP was the solvent employed (Table 5, entries 13 and 14). Finally, diketone **2r** was tested in the reaction with regioisomeric substrates **1b** and **1c**. In the first case similar yields in both solvents were achieved for the mixture **3br**/**3br′** (Table 5, entries 7 and 8). However, when **1c** was the substrate employed, a drop in the yield, especially in the case of TFE, for the mixture **3br**/**3br′** was observed (Table 5, entries 15 and 16).

Contrary to the previous examples, cyclohex-2-enol (**1d**) proved to be in general less reactive with the carbon nucleophiles. Thus, anisole afforded 69% and 58% yield in HFIP and TFE, respectively, for the Friedel−Crafts adduct, although a rather complicated inseparable mixture of the *para*- and *ortho*-substituted anisole, **3dj** and **3dj′**, and dicyclohexenylanisole **3dj″** products together with traces of corresponding fluoroalkyl ether was obtained after flash chromatography (Table 5, entries 17 and 18). However, indole only produced a very poor yield at best for the product **3dl** when HFIP was the solvent (Table 5, entries 19 and 20). Next, allyltrimethylsilane (**2o**) was evaluated, giving rise to product **3do** in 57% yield only in the HFIP-promoted allylic substitution (Table 5, entries 21 and 22). Unfortunately, when diketone **2r** was the nucleophile, very poor results were achieved (Table 5, entries 23 and 24). In those reactions in which full conversion toward the substitution product was not achieved, the corresponding fluoroalkyl ether was obtained. In the cases of alcohols **1b** and **1c** the same ether (**8** or **9**, see below in Scheme 3) was obtained as the consequence of a double bond isomerization.

Mechanistic Considerations. The fact that ethers **4** and **7** were obtained as main byproduct when allylic alcohol **1a** was employed regardless the nucleophile employed (see, for example, Table 1, entries 2 and 8) drew our attention with regard to the reaction mechanism. This observation led us to suppose that an equilibrium between the formation of the expected substitution product and the ether formation might be taking place during the process. To corroborate this point a kinetic study of the reaction of **1a** with sulfonamide **2a** under optimal reaction conditions (Table 2, entries 1 and 2) was carried out in both solvents (Figure 1). From this study different conclusions can be drawn: first, according to Figure 1, these ethers (and dimer **6** in the case of HFIP-mediated reaction) are formed more quickly than the corresponding amination product, and apparently the allylic amination mediated by fluoroalkyl alcohols also takes place onto these ethers, although at a slower rate. Consequently, **3aa** can be considered a result of two operating processes, direct amination onto alcohol **1a** and the indirect allylic substitution onto ethers **4** and **7**. Another interesting point is that the reaction carried out in TFE is faster than in HFIP despite the higher hydrogen bond ability and acidity of the latter, although this can be rationalize from the use of higher temperatures and number of equivalents.[9] Finally, as observed in the kinetic study the reaction was finished in less than 24 h in both cases.

Another experiment that confirms that ethers **4** and **7** can suffer allylic amination mediated by these fluoroalkyl alcohols was designed (Scheme 1). Thus, these compounds were synthesized and submitted to the direct amination reaction under the standard reaction conditions mentioned above (see Table 1). The amination product **3aa** was cleanly obtained in high yields when HFIP was used. Similar results were obtained with TFE although in lower yields (decomposition products were also observed). Then, the opposite reaction was also tested. Thus, when allylic sulfonamide **3aa** was allowed to react for 24 h in HFIP or TFE as solvents at the corresponding temperature, unaltered **3aa** together with decomposition

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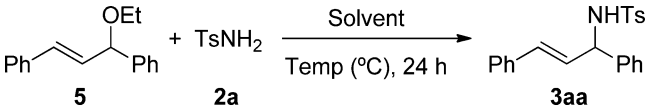
products (which were more abundant in the case of TFE) were recovered, suggesting the nonreversibility of the reaction.

Taking advantage of this last experiment we envisioned the use of fluoroalkyl alcohols as promoters of allylic amination onto allylic ethers. Thus, ethyl ether **5** reacted with *p*-toluensulfonamide **2a**, giving rise after 24 h to the amination product **3aa** in high yields when HFIP was employed as reaction media. The TFE-mediated reaction gave the corresponding product **3aa** in a 70% yield, although several unidentified byproducts were observed (Scheme 2). The

Scheme 2. TFE and HFIP Allylic Amination Reaction onto Ether 5

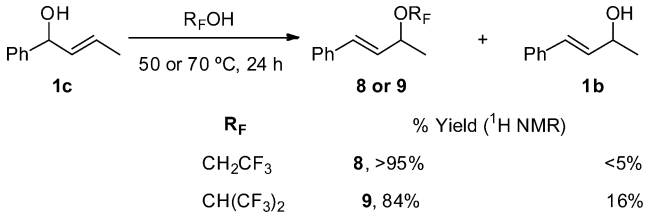


reactivity of the ethers toward allylic substitution reaction can also explain the low yields obtained when benzylic alcohol **2t** was used as nucleophile (Table 4, entries 21 and 22), since the presumably formed benzyl ether **3at** can suffer another substitution reaction with the more abundant fluoroalkyl alcohol forming ethers **4** and **7** (indeed, these ethers were detected as main products when BnOH was used as nucleophile).

The fact that the same product **3ba** was obtained when alcohols **1b**, (*Z*)-**1b**′, and **1c** were used (Table 3, entries 1−6) seems to imply a double bond isomerization and points out a possible carbocationic intermediate involved in this reaction. To corroborate these assumptions we decided to submit the enantioenriched alcohol (*S*)-**1b** (65% ee) to the allylic amination reaction under the standard conditions (Table 3, entries 1 and 2). After 24 h racemic **3ba** was obtained as main product in both solvents.[16] The isomerization of the double bond was confirmed by submitting allylic alcohol **1c** under the optimized reaction conditions (1 M solution at 50 or 70 °C for HFIP and TFE, respectively) in the absence of any nucleophile using both solvents. As expected and according to the regioselectivity observed for this alcohol (Table 3, entries 5 and 6), the corresponding isomerized ether together with some alcohol **1b** were the main reaction products, suggesting an isomerization of the double bond toward the thermodinamically most stable olefin prior the amination occurs (Scheme 3).[7b,17]

However, this isomerization mechanism seems not to be applicable when alcohols **1b** and **1c** were allowed to react with carbon nucleophiles since a mixture of α- and γ-substitution

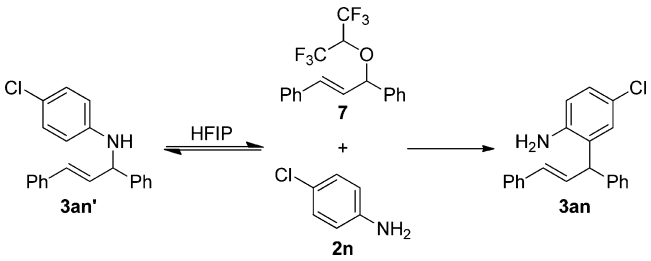
Scheme 3. TFE- and HFIP-Mediated Isomerization of Alcohol 1c



products was obtained. These results can be rationalized from a kinetic point of view. In this sense, the reaction between **1b** and acetylacetone (**2s**) in both solvents was monitored by GC, demonstrating high conversion toward both regioisomers in the same ratio as the above-mentioned (Table 5, entries 7 and 8) in less than 1 h. These results remained practically constant after 24 h and could mean that the reaction is faster than a possible isomerization reaction toward the most stable olefin, the attack onto the α- and γ-position of the common π-allyl cationic intermediate generated from both allylic alcohols (or ethers **8** and **9**) being equiprobable. The fact that **3br** was the major regioisomer in front of **3br**′ when the reaction was run in TFE can be explained by the higher temperatures employed with this solvent, favoring the formation of the thermodynamically controlled product **3br**. As a consequence of this hypothesis, which in addition would support it, higher yields are obtained when carbon nucleophiles react with alcohols **1b** and **1c** in comparison with the amination reaction with the same substrates.

In addition, we decided to corroborate whether a Hofmann−Martius-type rearrangement[14] was responsible for the allylic substitution products, **3am** and **3an**, obtained when electron-rich anilines were used as nucleophiles. For this purpose, a 1 M solution of compound **3an**′ in HFIP was stirred at 50 °C for 24 h. After this time, fluoroalkyl ether **7** and Friedel−Crafts adduct **3an** (in an 80:20 ratio) and *p*-chloroaniline (**2n**) were the only products observed in the mixture, pointing toward a reversible process between the formation of the amination product **3an**′ and ether **7** through an activation of the amine moiety by the fluorinated alcohol. This equilibrium is displaced by the irreversible formation of the product **3an** (Scheme 4). This

Scheme 4. Possible Mechanism for the Formation of Products 3an and 3an′



hypothesis would also explain the different behavior observed in both anilines since the more basic allylic amine **3am** can be easily activated by TFE and HFIP through hydrogen bond and/or protonation, whereas the less basic product **3an** is activated only by the more acidic HFIP with higher hydrogen bond ability.

Finally, it is worth mentioning that when we were trying to understand the mechanism to explain the excellent performance of silylated nucleophiles, we realized that the reaction of allyltrimethylsilane (**2o**) with allylic alcohol **1a** took place in less than 30 min even at room temperature in both solvents. The same trend was observed when the reaction was performed with $TMSN_3$ **2i** and Et_3SiH **2q** in HFIP as solvent, with the reaction, at room temperature, taking less than 1 h to complete. At this point, we decided to monitor by GC−MS the reaction between the alcohol **1a** and trimethylsilylazide (**2i**), and at the early stages of the reaction the formation of the corresponding trimethylsilylether **10** was observed. This fact would transform

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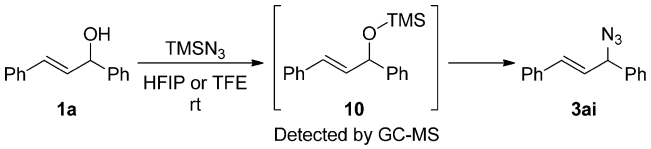
the hydroxyl function into a better leaving group, and consequently the reaction becomes faster (Scheme 5).

Scheme 5. Possible Mechanism for Allylic Substitution with Silylated Nucleophiles



CONCLUSIONS

In this work, a new strategy for allylic substitution reaction onto allylic free alcohols using fluoroalkyl alcohols, 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), as reaction promoters has been developed. This simple procedure allows the introduction of a wide range of nucleophiles under mild reaction conditions, giving rise to the allylic substitution products in high yields, especially when HFIP was the solvent of choice. This new methodology can be considered not only as an alternative to metal or Brønsted acid catalyzed allylic substitution reactions but also as complementary since some nucleophiles that fail in most of the existing procedures (i.e., basic aliphatic amines) can be used. In addition, the mechanistic studies of the direct allylic amination reaction suggested that the formation of the products can be sought as a result of two operating pathways: a direct substitution reaction and an indirect process that implies a double substitution. In both solvents, a carbocationic intermediate is postulated due to the racemization observed when enantioenriched allylic alcohols were employed. Finally, the regioselectivity of this amination process is seemingly the result of the isomerization of the double bond, mediated by these fluorinated alcohols, toward the most energetically stable olefin prior to the substitution reaction taking place. However, this isomerization does not apparently occur in the case of carbon nucleophiles where a mixture of kinetic and thermodynamic products was obtained.

EXPERIMENTAL SECTION

General Procedure for Allylic Subsitution Reaction. Onto an open air tube containing a 1 M solution of the allylic alcohol (0.5 mmol) in HFIP or TFE (500 μL) was added the corresponding nucleophile (0.75−1 mmol). The reaction mixture was then stirred for 24 h at the indicated temperature for each solvent (see tables). After the reaction time the volatiles were evaporated, and the crude compounds were purified by flash chromatography when necessary.

Physical and spectroscopic data are given below. For known compounds, only ^{1}H and ^{13}C NMR data are listed.

(*E*)-*N*-(1,3-Diphenylallyl)-4-methylbenzenesulfonamide (3aa).[7,33] White solid (174 mg, 96%); mp 140−141 °C (lit.[30] 136−137 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.97 (d, J = 7.1 Hz, 1H), 5.11 (t, J = 6.9 Hz, 1H), 6.10 (dd, J = 15.8, 6.7 Hz, 1H), 6.35 (d, J = 15.9 Hz, 1H,) 7.10−7.30 (m, 12H), 7.65 (d, J = 8.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 59.7, 126.5, 127.0, 127.3, 127.9, 128.1, 128.4, 128.7, 128.9, 129.4, 132.1, 136.0, 137.7 139.6, 143.3 ppm.

(*E*)-Benzyl 1,3-Diphenylallylcarbamate (3ab).[7] White solid (153 mg, 89%); mp 109 °C (lit.[7a] 110 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15 (m, 3H), 5.54 (br s, 1H), 6.33 (dd, J = 15.9, 6.0 Hz, 1H), 6.56 (d, J = 16 Hz, 1H), 7.10−7.49 (m, 15H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.7, 66.9, 126.5, 127.0, 127.7, 128.1, 128.2, 128.5, 128.8, 129.0, 129.4, 131.2, 135.2, 136.5, 140.9, 142.1, 156.7 ppm.

(*E*)-*tert*-Butyl 1,3-Diphenylallylcarbamate (3ac).[7b,34] White solid (70 mg, 45%); mp 117 °C (lit.[31] 115−116 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 4.96 (s, 1H), 5.46 (s, 1H), 6.32 (dd, J = 15.9, 6.0 Hz, 1H), 6.54 (dd, J = 15.9, 1.2 Hz, 1H), 7.20−7.38 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 56.3, 79.7, 126.5, 126.9, 127.5, 127.6, 128.5, 128.7, 129.5, 130.8, 136.5, 141.3, 154.9 ppm.

(*E*)-*N*-(1,3-Diphenylallyl)benzamide (3ad).[7b,21] White solid (125 mg, 80%); mp 163−164 °C (lit.[20] 157−159 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (t, J = 7.0 Hz, 1H), 6.44 (dd, J = 15.9, 6.0 Hz, 1H), 6.55 (s broad, 1H), 6.62 (d, J = 15.9 Hz, 1H), 7.30−7.43 (m, 13H), 7.83 (d, J = 7.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 126.5, 127.0, 127.1, 127.2, 127.8 128.5, 128.6, 128.7, 128.9, 131.6, 131.7, 134.3, 136.3, 140.7, 166.4 ppm.

(*E*)-4-Nitro-*N*-(1,3-diphenylallyl)aniline (3ae).[7b,34] Yellow solid (160 mg, 97%); mp 146−147 °C (lit.[31] 140−141 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (d, J = 4.5 Hz, 1H), 5.20 (t, J = 5.4 Hz, 1H), 6.37 (dd, J = 15.9, 6.0 Hz, 1H), 6.56−6.63 (m, 3H), 7.25−7.41 (m, 10H), 8.05 (d, J = 9.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.0, 112.1, 126.2, 126.6, 127.1, 128.1, 128.2, 128.5, 128.7, 129.1, 132.2, 136.0, 138.5, 140.2, 152.1 ppm.

(*E*)-*N*-Benzyl-1,3-diphenylprop-2-en-1-amine (3af).[18] Colorless oil (109 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (s, 1H), 3.77 (d, J = 4.36 Hz, 2H), 4.39 (d, J = 7.5 Hz, 1H), 6.31 (dd, J = 15.8, 7.5 Hz, 1H), 6.57 (d, J = 15.8 Hz, 1H), 7.17−7.43 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.3, 64.5, 126.4, 126.9, 127.3, 127.3, 127.4, 128.1, 128.4, 128.5, 128.6, 130.3, 132.5, 136.8, 140.3, 142.8 ppm.

(*E*)-1,3-Diphenyl-*N*-(1-phenylethyl)prop-2-en-1-amine (3ag).[19] Obtained as 1.2:1 inseparable mixture of diatereoisomers. Yellow oil (94 mg, 60%). Major diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, J = 6.7 Hz, 3H), 1.73 (s, 1H), 3.65 (q, J = 6.7 Hz, 1H), 4.18 (d, J = 6.5 Hz, 1H), 6.28 (dd, J = 15.9, 6.6 Hz, 1H), 6.45 (d, J = 15.9 Hz, 1H), 7.24−7.30 (m, 15H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 54.8, 62.2, 126.3, 126.7, 127.1, 127.3, 127.5, 128.4, 128.5, 128.6, 128.6, 129.1, 129.5, 133.1, 136.9 ppm. Minor diastereoisomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, J = 6.7 Hz, 3H), 1.73 (s, 1H), 3.95 (q, J = 6.7 Hz, 1H), 4.17 (d, J = 7.9 Hz, 1H), 6.25 (dd, J = 15.8, 7.9 Hz, 1H), 6.42 (d, J = 15.8 Hz, 1H), 7.21−7.39 (m, 15H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 55.0, 61.9, 126.4, 126.7, 126.9, 127.1, 127.4, 127.9, 128.5, 129.1, 129.4, 131.0, 131.9, 136.9, 143.2, 145.5 ppm.

(*E*)-*N*-(1,3-Diphenyl-2-propenyl)butylamine (3ah).[20] Colorless oil (85 mg, 64%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.32−1.47 (m, 2H), 1.48−1.63 (m, 2H), 2.59 (ddt, J = 33.2, 11.4, 7.1 Hz, 2H), 4.34 (d, J = 7.4 Hz, 1H), 6.30 (dd, J = 15.8, 7.4 Hz, 1H), 7.24−7.38 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.5, 32.3, 47.5, 65.7, 126.3, 127.1, 127.2, 127.3, 128.4, 128.5, 130.0, 132.9, 136.9, 143.1 ppm.

(*E*)-3-Azido-1,3-diphenyl-1-propene (3ai).[12] Colorless oil (113 mg, 96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (d, J = 7.3 Hz, 1H), 6.28 (dd, J = 7.3, 15.6 Hz, 1H), 6.71 (d, J = 15.6 Hz, 1H), 7.23−7.41 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.2, 126.8, 126.9, 127.1, 128.2, 128.4, 128.6, 128.7, 132.9, 138.5, 139.5 ppm.

(*E*)-3-(4-Methoxyphenyl)-1,3-diphenylprop-1-ene (3aj).[7b] Yellow oil (132 mg, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.84 (d, J = 5.6 Hz, 1H), 6.32 (d, J = 15.8 Hz, 1H), 6.65 (dd, J = 15.8, 5.6 Hz, 1H), 6.84 (d, J = 8.5 Hz, 2H), 7.13−7.37 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.3, 55.2, 113.8, 126.2, 126.3, 127.2, 128.4, 128.5, 128.6, 129.6, 131.1, 132.9, 135.6, 137.3, 143.8, 158.1 ppm.

(*E*)-4-(1,3-Diphenylallyl)phenol (3ak).[21] Yellow oil (107 mg, 75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, J = 7.4 Hz, 1H), 5.21 (s, 1H), 6.31 (d, J = 15.8, 1H), 6.63 (dd, J = 15.8, 7.5 Hz, 1H), 6.76 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.3 Hz, 2H), 7.14−7.42 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.3, 115.3, 126.2, 126.3, 127.2, 128.4, 128.4, 128.5, 129.7, 131.1, 132.8, 135.6, 137.2, 143.7, 154.1 ppm.

(*E*)-3-(1,3-Diphenylallyl)indole (3al).[7b] Brownish oil (148 mg, 96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (d, J = 7.3 Hz, 1H), 6.43

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(d, J = 15.8 Hz, 1H), 6.72 (dd, J = 15.8, 7.3 Hz, 1H), 6.90 (s, 1H), 7.02 (t, J = 7.1 Hz, 1H), 7.24−7.35 (m, 13H), 7.99 (br s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.1, 111.1, 119.4, 119.9, 122.1, 122.6, 126.3, 126.4, 126.6, 126.7, 127.1, 127.7, 128.4, 128.5, 130.5, 132.5, 136.6, 137.5, 143.3 ppm.

(*E*)-4-Methoxy-2-(1,3-diphenylallyl)aniline (3am). Yellow sticky oil (147 mg, 93%); R_f 0.41(hexane/ethyl acetate 4:1); IR (ATR) ν 3025, 2926, 1599, 1497, 1257, 1041 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (br s, 2H), 3.74 (s, 3H), 4.93 (d, J = 6.9 Hz, 1H), 6.31 (d, J = 16.0 Hz, 1H), 6.65−6.76 (m, 4H), 7.24−7.41 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.6, 55.6, 112.2, 115.8, 117.5, 126.4, 126.9, 127.4, 128.5, 128.7, 128.9, 130.1, 131.2, 131.7, 137.1, 137.9, 141.6, 153.0 ppm. MS (EI): m/z 315 [M$^+$, 63%], 313 (22), 311 (43), 224 (100), 223 (80), 209 (20), 193 (17),191 (19), 181 (24), 180 (36), 165 (18), 115 (18), 106 (21), 105 (20), 91 (27); HRMS calcd for $C_{22}H_{21}NO$ 315.1623, found 315.1646.

(*E*)-4-Chloro-2-(1,3-diphenylallyl)aniline (3an). Colorless oil (144 mg, 90%); R_f 0.44 (hexane/ethyl acetate 4:1); IR (ATR) ν 2917, 2849, 1487, 1260, 1091, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (br s, 2H), 4.88 (d, J = 6.9 Hz, 1H), 6.33 (d, J = 15.9 Hz, 1H), 6.66 (m, 2H), 7.11 (m, 2H), 7.28−7.43 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.5, 117.6, 123.6, 126.4, 127.1, 127.4, 127.6, 128.5, 128.7, 128.8, 128.9, 129.8, 130.4, 132.1, 136.9, 140.9, 142.8 ppm. MS (EI): m/z 319 [M$^+$, 29%], 284 (20), 230 (34), 229 (43), 228 (100), 227 (69), 206 (21), 193 (67), 191 (24), 165 (18), 91 (21); HRMS calcd for $C_{21}H_{18}ClN$ 319.1128, found 319.1121.

(*E*)-4-Chloro-*N*-(1,3-Diphenylallyl)aniline (3an′).[7b] Yellow oil (147 mg, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (d, J = 6.1 Hz, 1H), 5.03 (d, J = 6.1 Hz, 1H), 6.36 (dd, J = 15.8, 6.1 Hz, 1H), 6.53−6.58 (m, 3H), 7.07 (d, J = 8.7 Hz, 2H), 7.25−7.39 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.7, 114.7, 122.3, 126.5, 127.1, 127.7, 127.8, 128.6, 128.9, 129.0, 130.1, 131.3, 136.4, 141.6, 145.7 ppm.

(*E*)-1,3-Diphenyl-1,5-hexadiene (3ao).[7b] Yellow oil (115 mg, 98%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (t, J = 7.5 Hz, 2H), 3.52 (m, 1H), 4.97−5.08 (m, 2H), 5.72−5.81 (m, 1H), 6.37 (d, J = 5.4 Hz, 2H), 7.25−7.33 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.1, 48.9, 116.3, 126.1, 126.3, 127.1, 127.7, 128.4, 128.5, 129.7, 133.4, 136.5, 137.4, 143.8 ppm.

(*E*)-1,3,5-Triphenylpent-1-en-4-yne (3ap).[22] Yellow oil (90 mg, 61%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (d, J = 6.5 Hz, 1H), 6.34 (dd, J = 15.7, 6.5 Hz, 1H), 6.78 (dd, J = 15.7, 1.1 Hz, 1H), 7.25−7.39 (m, 13H), 7.48−7.51 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.2, 85.4, 88.8, 123.4, 126.5, 127.1, 127.5, 127.7, 128.0, 128.2, 128.5, 128.7, 129.6, 130.4, 131.7, 136.8, 140.3 ppm.

(*E*)-1,3-Diphenylpropene (3aq).[23] Yellow oil (94 mg, 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (d, J = 6 Hz, 2H), 6.32−6.48 (m, 2H), 7.19−7.37 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.3, 126.1, 126.2, 127.1, 128.4, 128.6, 129.2, 131.0, 137.4, 140.1 ppm.

(*E*)-3-(1,3-Diphenylallyl)pentane-2,4-dione (3ar).[24] White solid (139 mg, 95%); mp 85−86 °C (lit.[23] 85−87 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.25 (s, 3H), 4.32−4.36 (m, 2H), 6.19 (ddd, J = 15.8, 5.1, 2.9 Hz, 1H), 6.43 (d, J = 15.8 Hz, 1H), 7.17−7.36 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 30.0, 49.1, 74.4, 126.3, 127.2, 127.7, 127.8, 128.5, 129.0, 129.2, 131.6, 136.5, 140.0, 202.6, 202.8 ppm.

(*E*)-5-(1,3-Diphenylallyl)-2,2-dimethyl-1,3-dioxane-4−6-dione (3as).[25] White powder (101 mg, 60%); mp 142 °C (lit.[24] 141−142 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 3H), 1.71 (s, 3H), 3.96 (d, J = 2.8 Hz, 1H), 4.73 (dd, J = 9.2, 2.8 Hz, 1H), 6.65 (d, J = 15.8 Hz, 1H), 6.92 (dd, J = 15.8 9.2 Hz, 1H), 7.15−7.52 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.6, 28.2, 47.4, 52.5, 105.3, 126.5, 127.4, 127.7, 127.9, 128.4, 128.5, 128.7, 133.4, 136.6, 139.7, 164.4 ppm.

(*E*)-3,5-Diphenyl-2-[(2,2,2-trifluoroethoxy)carbonyl]pent-4-enoic acid (3as′). Obtained as 1:1 diastereomeric mixture. White solid (161 mg, 85%); mp 105−106 °C; R_f 0.28 (hexane/ethyl acetate 4:1); IR (ATR) ν 3026, 2161, 1978, 1761, 1600,1412, 1286, 1258, 1179, 1140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (d, J = 4.0 Hz, 1H), 4.11 (d, J = 3.6 Hz, 1H), 4.28 (m, 4H), 4.50 (m, 2H), 6.37 (dd, J = 15.7, 8.6 Hz, 2H), 6.53 (d, J = 15.7 Hz, 1H), 7.29 (m, 10H), 8.72 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.06, 57.00, 57.07, 60.60−61.35 (m), 124.19, 124.36, 126.31, 126.42, 126.47, 127.47, 127.52, 127.75, 127.80, 128.23, 128.52, 128.75, 128.89, 132.47, 132.58, 136.43, 136.56, 139.23, 139.40, 165.73, 166.05, 171.53, 171.82 ppm. MS (EI): m/z 334 [M$^+$ − CO_2), 18%], 206 (15), 194 (16), 193 (100), 192 (47), 191 (15), 178 (25), 128 (13), 115 (80), 91 (27); HRMS-CO_2 calcd for $C_{19}H_{17}F_3O_2$ 334.1181, found 334.1183.

(*E*)-Benzyl 1,3-Diphenylallyl Ether (3at).[26] Colorless oil (20 mg, 13%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (s, 2H), 5.01 (d, J = 7 Hz, 1H), 6.34 (dd, J = 15.9, 7 Hz, 1H), 6.63 (d, J = 15.9 Hz, 1H), 7.22−7.44 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.1, 81.6, 126.6, 126.8, 126.9, 127.5, 127.7, 128.1, 128.3, 128.5, 128.7, 130.2, 131.5, 136.5, 138.4, 141.1 ppm.

(*E*)-4-Methyl-*N*-(4-phenylbut-3-en-2-yl)benzenesulfonamide (3ba).[7b,35] White solid (102 mg, 68%); mp 88−89 °C (lit.[32] 96−98 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.6 Hz, 3H), 2.34 (s, 3H), 4.05−4.15 (m, 1H), 5.08 (br s, 1H), 5.83 (dd, J = 16.0, 6.8 Hz, 1H), 6.28 (d, J = 16.0 Hz, 1H), 7.14−7.20 (m, 7H, ArH), 7.75 (d, J = 8.4, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.9, 51.6, 126.3,127.2, 127.6, 128.4, 129.5, 130.1, 130.5, 136.1, 138.1, 143.3 ppm. HPLC: Daicel Chiralcel OD-H column, hexane/2-propanol 95:5, flow rate 1 mL/min, λ = 254 nm, t_R = 27.8 and 31.1 min.

***N*-(Cyclohex-2-enyl)-4-methylbenzenesulfonamide (3da).**[7b,36] White solid (99 mg, 79%); mp 102−103 °C (lit.[33] 97−98 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44−1.61 (m, 2H), 1.70−1.84 (m, 2H), 1.87−2.03 (m, 2H), 2.43 (s, 3H), 3.81 (br s, 1H), 4.54 (d, J = 8.0 Hz, 1H), 5.32−5.37 (m, 1H), 5.74−5.78 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 21.5, 24.5, 30.3, 48.9, 126.9, 127.0, 129.6, 131.5, 138.3, 143.2 ppm.

***N*-[1-(Cyclohex-1-en-1-yl)ethyl]-4-methylbenzenesulfonamide (3ea).**[27] Obtained as inseparable mixture with the regioisomer **3ea′**. The following data corresponds to **3ea**. White solid (80 mg, 57%); mp 65 °C (**3ea**/**3ea′** 83:17); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, J = 8.0 Hz, 2H), 1.26 (m, 1H), 1.37 (m, 2H), 1.47 (m, 1H), 1.67 (m, 1H), 1.75−1.87 (br m, 3H), 2.43 (s, 3H), 3.84 (p, J = 7.0 Hz, 1H), 4.65 (br s, 1H), 5.46 (br s, 1H), 7,28 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.5, 22.0, 22.1, 23.5, 24.8, 55.5, 123.9, 127.3, 129.3, 136.9, 138.2, 142.9 ppm.

4-Methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide (3fa′).[28] Obtained as diastereomeric mixture **3fa**/**3fa′** in a 3:1 ratio. The following data corresponds to the inseparable mixture. Colorless oil (36 mg, 30%); R_f 0.52 (hexane/ethyl acetate 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 6H, **3fa**), 1.54 (s, 3H, **3fa′**), 1.64 (s, 3H, **3fa′**), 2.41 (s, 3H, **3fa**), 2.43 (s, 3H, **3fa′**), 3.54 (t, J = 6.4 Hz, 2H, **3fa′**), 4.25 (br s, 1H, **3fa′**) 4.60 (br s, 1H, **3fa**), 4.94−5.12 (m, 2H, **3fa** + 1H, **3fa′**), 5.79 (dd, J = 10.4, 17.2 Hz, 1H, **3fa**), 7.30 (d, J = 8.4 Hz, 2H **3fa′** + 2H **3fa′**), 7.75 (d, J = 8.4 Hz, 2H **3fa′** + 2H **3fa′**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 21.5, 25.5, 27.7, 41.0, 112.8, 118.7, 127.2, 129.3, 129.6, 135.0, 137.6, 143.3 ppm.

4-Methyl-*N*-(4-methylpent-3-en-2-yl)benzenesulfonamide (3ga). Yellow sticky oil (54 mg, 43%); R_f 0.46 (hexane/ethyl acetate 4:1); IR (ATR) ν 3268, 2953, 1715, 1598, 1453, 1376, 1323, 1157, 1085, 1072, 980 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J = 6.6 Hz, 3H), 1.44 (s, 3H), 1.51 (s, 3H), 2.41 (s, 3H), 4.10 (dq, J = 9.0, 6.6 Hz, 1H), 4.52 (br s, 1H), 4.79 (dd, J = 9.0, 2.6 Hz, 1H), 7.26 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 21.5, 22.5, 25.3, 48.1, 126.1, 127.2, 129.3, 134.2, 138.2, 142.9 ppm. MS (EI): m/z 253 [M$^+$, 1%], 239 (14), 238 (100), 154 (44), 98 (39), 91 (77), 83 (28), 82 (31); HRMS calcd for $C_{13}H_{19}NO_2S$ 253.1136, found 253.1117.

(*E*)-4-(4-Phenylbut-3-en-2-yl)anisole (3bj).[29] Colorless oil (79 mg, 66%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, J = 7.0 Hz, 3H), 3.60 (p, J = 6.9 Hz, 1H), 3.78 (s, 3H), 6.35−6.37 (m, 2H), 6.86 (d, J = 8.7 Hz, 2H), 7.16−7.35 (m, 7H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 41.7, 55.2, 113.8, 126.1, 127.0, 128.2, 128.4, 135.5, 137.6, 137.7, 158.0 ppm.

(*E*)-3-(4-Phenylbut-3-en-2-yl)-1*H*-indole (3bl).[30] Brown oil (62 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, J = 7.0 Hz, 3H), 3.93 (p, J = 6.9 Hz, 1H), 6.46−6.48 (m, 2H), 6.98−7.33 (m, 9H), 7.67

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(d, J = 7.9 Hz, 1H), 7.90 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 34.2, 111.1, 119.2, 120.4, 122.0, 126.1, 126.5, 126.8, 128.4, 128.7, 135.4, 136.5, 137.8 ppm.

(*E*)-3-(1-Phenylbut-2-en-1-yl)-1*H*-indole (3bl′).[30] Obtained as inseparable mixture with the regioisomer **3bl**. The following data corresponds to **3bl′**. Brown oil (122 mg, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ1.71 (d, J = 6.5 Hz, 3H), 4.89 (d, J = 7.5 Hz, 1H), 5.49−5.54 (m, 1H), 5.90−5.94 (m, 1H), 6.85 (d, J = 2.3 Hz, 1H), 6.98−7.33 (m, 8H), 7.67 (d, J = 7.9 Hz, 1H), 7.90 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 46.0, 111.1, 119.6, 120.4, 121.9, 126.1, 126.2, 126.8, 128.1, 128.2, 128.4, 135.4, 137.7 ppm.

3-Methyl-1-phenylhexa-1,5-diene (3bo) and 4-Phenylhepta-1,5-diene (3bo′).[31] The mixture of the two regioisomers could not be separated. Colorless oil (61 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 6.7 Hz, 3H, **3bo**), 1.71 (dd, J = 6.3, 0.8 Hz, 3H, **3bo′**), 2.15−2.27 (m, 2H, **3bo**), 2.41−2.52 (m, 1H **3bo**+ 2H **3bo′**), 3.34 (q, J = 7.5 Hz, 1H **3bo′**), 4.98−5.12 (m, 2H **3bo** + 2H **3bo′**), 5.46−5.91 (m, 1H **3bo** + 3H **3bo′**), 6.20 (dd, J = 15.9, 7.5 Hz, 1H **3bo**), 6.41 (d, J = 15.9 Hz, 1H **3bo**), 7.18−7.40 (m, 5H **3bo** + 5 H **3bo′**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 19.9, 36.9, 40.4, 41.4, 48.8, 115.8, 116.0, 125.1, 126.0, 127.6, 128.3, 128.4, 134.4, 136.0, 136.9, 137.8, 144.8 ppm.

(*E*)-3-(4-Phenylbut-3-en-2-yl)pentane-2,4-dione (3br) and (*E*)-3-(1-Phenylbut-2-en-1-yl)pentane-2,4-dione (3br′).[32] Obtained as inseparable mixture of regioisomers. Colorless oil (88 mg, 76%). **3br**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, J = 6.7 Hz, 3H), 2.13 (s, 3H), 2.22 (s, 3H), 3.14−3.28 (m, 1H), 3.69 (d, J = 10.4 Hz, 1H), 5.99 (dd, J = 15.9, 8.6 Hz, 1H), 6.44 (d, J = 15.9 Hz, 1H), 7.12−7.30 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 30.0, 30.1, 37.8, 75.6, 126.9, 127.7, 128.8, 130.7, 130.9, 136.7, 203.0, 203.1, ppm. **3br′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (d, J = 6.3 Hz, 3H), 1.87 (s, 3H), 2.23 (s, 3H), 4.10 (dd, J = 11.6, 7.3 Hz, 1H), 4.21 (d, J = 11.7 Hz, 1H), 5.46−5.51 (m, 2H), 7.12−7.30 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 29.5, 29.7, 49.1, 74.7, 126.2, 127.5, 128.5, 130.8, 130.9, 140.7, 203.4, 203.5 ppm.

3-(4′-Methoxyphenyl)cyclohex-1-ene (3dj′).[30] Only a small amount of this product was isolated. The yield of the mixture (**3dj′** + **3dj** + **3dj″**) was determined by ^{1}H NMR (see Table 5). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46−2.10 (m, 6H), 3.33−3.38 (m, 1H), 3.79 (s, 3H), 5.66−5.71 (m, 1H), 5.83−5.89 (m, 1H), 6.84 (d, J = 8.5 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 25.0, 32.7, 40.9, 55.3, 113.6, 128.1, 128.6, 130.5, 138.5, 157.8 ppm.

3-(2′-Methoxyphenyl)cyclohex-1-ene (3dj).[30] This product could not be separated from the disubstituted product (2,4-dicyclohex-2-enyl)anisole **3dj″** and small amounts of anisole. The experimental data is given for the mixture and only the peaks for ^{1}H and ^{13}C NMR are listed since the integration was not accurate. Yield of the mixture (**3dj′** + **3dj** + **3dj″**) was determined by ^{1}H NMR (see Table 5). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46−2.11 (m, 18H, 6H **3dj** + 12H **3dj″**), 3.32−3.37 (m, 1H, **3dj″**), 3.80 (s, 3H, **3dj″**), 3.83 (s, 3H, **3dl**), 3.84 (m, 2H, 1H **3dl** + 1H **3dj″**), 5.63−5.72 (m, 3H, 1H **3dl** + 2H **3dj″**), 5.82−5.93 (m, 3H, 1H **3dl** + 2H **3dj″**), 6.79 (d, J = 8.9 Hz, 1H, **3dj″**), 6.84−6.93 (m, 2H, **3dl**), 7.01 (m, 2H, **3dj″**), 7.15−7.20 (m, 2H, **3dl**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.1, 21.3, 25.0, 25.2, 30.1, 30.2, 32.7, 34.2, 34.4, 41.1, 41.2, 55.3, 55.4, 109.9, 110.2, 120.3, 125.6, 126.8, 127.9, 128.2, 128.2, 128.3, 128.4, 130.2, 130.4, 130.6, 130.7, 134.2, 155.2, 156.8 ppm. MS(IE): **3dl** m/z 188 [M$^+$, 100%], 173 (31), 160 (25), 159 (48), 145 (27), 115 (26), 91 (32); disubst. m/z 268 [M$^+$, 100%], 187 (54), 159 (20), 121 (17), 81 (17).

3-Allylcyclohex-1-ene (3do).[31] Colorless oil. Due to the impossible separation of the substitution product from the corresponding fluoroalkyl ether and the starting material, the yield was determined by GC analysis of the crude mixture (see Table 5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, 2H), 1.49 (m, 2H), 1.73 (m, 2H), 1.93−2.03 (m, 4H), 2.14 (m, 1H), 5.00 (m, 2H), 5.59 (m, 1H), 5.67 (m, 1H), 5.83 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 25.3, 28.9, 35.0, 40.4, 115.9, 127.2, 131.2, 137.5 ppm.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General remarks, ^{1}H and ^{13}C NMR spectra copies of all new compounds and ^{1}H NMR copies of known compounds (GC−MS copy in the case of **3do**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Rosa Claramunt on the occasion of her 65th birthday

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