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Domino Reactions with Dicyanoalkenes and Fluorinated Conjugated Sulfinyl Imines. A Convenient Strategy for the Generation of Structural Diversity

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Dedicated to Professor Miquel A. Pericás for his scientific contribution and on the occasion of his retirement

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Abstract: Dicyanoalkenes are versatile reagents in organic synthesis and they have been extensively used in a wide variety of organic transformations. However, their reactivity towards fluorinated imines remained almost unnoticed. The divergent reactivity of fluorinated conjugated sulfinyl imines with dicyanoalkenes is described herein. On the one hand, when *tert*-butyl sulfinyl imines were employed, a cycloaromatization cascade process took place preferentially, rendering valuable trifluoromethyl arenes. On the other hand, the reaction with *p*-tolyl sulfinyl imines mainly led to a complex tetracyclic skeleton, involving an azetidinimine rearrangement of a reaction intermediate. Finally, when 1-indanone-derived dicyanoalkenes were employed, the aromatization process was interrupted, rendering a new family of diene derivatives. Theoretical calculations were performed in order to shed light on the mechanistic outcome of this transformation.

Keywords: conjugated fluorinated sulfinyl imines; dicyanoalkenes; trifluoromethylarenes; divergent reactivity; domino reactions

Introduction

Domino reactions, defined by Tiezte and Beifuss as reactions where two or more bonds are formed in one step under the same reaction conditions,[1] allow for increasing molecular complexity from simple starting materials in a single operation, without the need of handling intermediates. In this manner, chemists avoid cost- and time-consuming purification steps, as well as waste generation.[2]

Chemical synthesis of complex molecules is at the forefront of synthetic organic chemistry and it should address significant environmental challenges. In this context, domino reactions fulfil one of the main principles of green chemistry.[3] The fundamental concept behind domino processes is the use of substrates that contain multiple and orthogonal reactive sites, which can sequentially react in a well-organized manner to generate complex skeletons with high levels of chemo-, regio- and stereoselectivity and efficiency.

1,1-Dicyanoalkenes, firstly prepared more than a century ago,[4] are versatile four-carbon synthons, which are easily prepared by condensation of carbonyl compounds with malononitrile and display high chem-

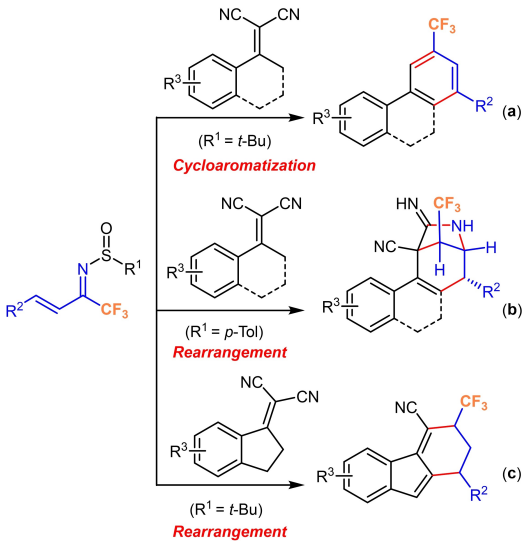
ical reactivity.[5] In spite of their inherent electrophilic nature, dicyanoalkenes bearing enolizable sites possess an ambident character since they can act as nucleophiles through both the α- and γ-positions. For instance, they showed excellent vinylogous donor properties in different addition reactions and the remaining conjugated malononitrile moiety was susceptible for further transformations such as cyclization, reduction or elimination reactions. Therefore, dicyanoalkenes are well suited reagents to be engaged in domino reactions.[6]

It is well known that the incorporation of fluorinated moieties into organic molecules plays a paramount role during lead optimization in drug discovery processes.[7] Thus, approximately 20–25% of drugs and up to 30% of agrochemicals contain at least one fluorine atom.[8] Since fluorine is contained in very few molecules with biological origin,[9] most fluoroorganic compounds are obtained by chemical synthesis. In this context, the use of fluorinated building blocks is one of the most prevalent strategies to introduce fluorine atoms into organic molecules.[10] This approach requires small fluorinated molecules, stable and easily available in large scale. Among them, fluorinated imines are one of the most popular building blocks for the synthesis of fluorinated nitrogen-containing scaffolds by means of the addition of a wide range of nucleophiles.[11] However, the use of conjugated fluorinated imines has remained almost unexplored. The addition of nucleophiles to fluorinated unsaturated ketimines is a challenging task since both regio- and diastereoselectivity issues arise simultaneously. Regarding the use of these imines in nucleophilic addition reactions, there are examples with two main types of fluorinated substrates, namely *N*-unsubstituted imines and *N*-sulfinyl imines. With *N*-unsubstituted imines, both 1,2- and 1,4-additions were described, depending on the type of nucleophile and the reaction conditions.[12] However, the addition of nucleophiles to *N*-sulfinyl imines always took place in a 1,2-fashion.[13]

Since the incorporation of 1,1-dicyanoalkenes as vinylogous nucleophiles in organic synthesis,[14] a great variety of transformations involving these compounds as vinylogous donors with imines, enones, enals or nitroolefins as electrophiles have been reported in the literature. However, as far as we know, only two examples concerning the reaction of 1,1-dicyanoalkenes with fluorinated imines have been reported to date by our research group. In 2018, we developed the asymmetric vinylogous Mannich-type addition of α,α-dicyanoalkenes to α-fluoroalkyl sulfinyl imines, reaction that took place with excellent stereocontrol.[15] More recently, we evaluated the reactivity of 1,1-dicyanoalkenes towards fluorinated conjugated sulfinyl imines and we found that a cycloaromatization cascade process occurred, affording trifluoromethyl arenes,[16] which are substructures present in several top selling pharmaceuticals such as Januvia® (sitagliptin), Celebrex® (celecoxib) or Prozac® (fluoxetine).[17] During the course of this study, a divergent reactivity profile was observed depending on the type of both, the fluorinated sulfinyl imine and the dicyanoalkene employed. Accordingly, when *tert*-butyl sulfinyl imines were employed, a cycloaromatization event took place preferentially, with concomitant loss of the sulfinyl amine and the dicyano moieties (Scheme 1, **a**). However, the reaction of 1,1-dicyanoalkenes with trifluoromethyl *p*-tolyl sulfinyl imines mainly led to complex rearranged tetracylic skeletons bearing the dicyano moieties as major products (Scheme 1, **b**). Finally, when 1-indanone-derived dicyanoalkenes were employed, differently rearranged products were observed (Scheme 1, **c**). The scope and diastereoselectivity of these processes have been studied herein. Moreover, theoretical calculations have been performed in order to gain a fundamental understanding of the reaction mechanism related to the divergent reactivity observed.

Results and Discussion

Previous work from our laboratory demonstrated that the reaction of conjugated trifluoromethyl *tert*-butyl sulfinyl imine **1a** with 1,1-dicyanoalkene **3a**, in the presence of DBU, proceeded through an unexpected [3+3] cycloaromatization event, giving rise to tricyclic trifluoromethyl arene **4a**, with loss of the sulfinyl amine moiety and the two cyano groups.[16,18] A detailed study of this transformation led us to recognize that a secondary product, arising from an intramolecular rearrangement, was also formed. This was assigned as tetracycle **5a**, in which the sulfinyl amine



Scheme 1. Divergent reactivity of fluorinated conjugated sulfinyl ketimines with 1,1-dicyanoalkenes.

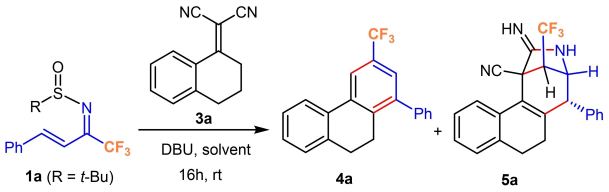
group was lost while both cyano moieties remained at the structure of the product. This reaction was performed in dichloromethane as the solvent and provided nearly equimolecular amounts of products **4a** and **5a** (Table 1, entry 1). Under the same reaction conditions, the use of *p*-tolyl sulfinyl imine **2a** led to a mixture of compounds **4a** and **5a** but, in this case, the rearranged polycycle **5a** was the major product, in 73% isolated yield (Table 1, entry 2). At this point, we decided to evaluate the reaction conditions in order to direct the process to the formation of either **4a** or **5a** selectively. Several organic and inorganic bases were tested, however, DBU was superior in all cases in terms of yield and selectivity.

Interestingly, we found that the solvent had a significant impact in the course of the reaction and the product selectivity. The results of this study of solvents are collected in Table 1.

The reaction of *tert*-butyl sulfinyl imine **1a** with dicyanoalkene **3a** in ethyl acetate as the solvent improved the ratio of products **4a**/**5a** until 2.2:1 in favour of tricycle **4a**, which was isolated in 69% yield (Table 1, entry 3). Conversely, starting from *p*-tolyl sulfinyl imine **2a**, the product selectivity decreased to 1:4 compared to the reaction in dichloromethane (Table 1, entry 4 *vs* entry 2). The use of isopropanol provided the best **4a**/**5a** ratio (3.6: 1), rendering compound **4a** in 76% isolated yield starting from imine **1a** (Table 1, entry 5). However, this solvent did not improve the selectivity with imine **2a** (Table 1, entry 6). Other solvents, such as acetonitrile, 2-methyltetrahydrofurane or toluene were also tested. All of them showed the same tendency concerning the switch in the product selectivity with the type of sulfinyl imine employed (**1a** or **2a**); however, none of them yielded better results than those showed before (Table 1, entries 7–12). In light of this study, we concluded that the optimal conditions for obtaining the cycloaromatization product **4a** involved the use of *tert*-butyl sulfinyl imine **1a** in isopropanol as the solvent (Table 1, entry 5). Alternatively, in order to preferentially achieve the rearranged product **5a**, the solvent of choice was dichloromethane, with *p*-tolyl sulfinyl imine **2a** as starting material (Table 1, entry 2). With these optimized conditions in hand, the scope of the process with respect to conjugated sulfinyl amines **1** and **2** in their reaction with dicyanoalkene **3a** was evaluated and the results are shown in Table 2.

tert-Butyl sulfinyl imines **1a–d** bearing aromatic substituents at the R^2 position were initially tested, employing isopropanol as the solvent. Both electron-donating and electron-withdrawing groups were allowed at the 4 position of the aromatic ring, rendering trifluoromethyl arenes **4a–c** in good yields with **4**/**5** selectivities around 4:1 (Table 2, entries 1–3). The reaction with imine **1d** bearing a 2-bromophenyl group took place with an excellent 15:1 ratio and compound **4d** was isolated in 88% yield (Table 2, entry 4).

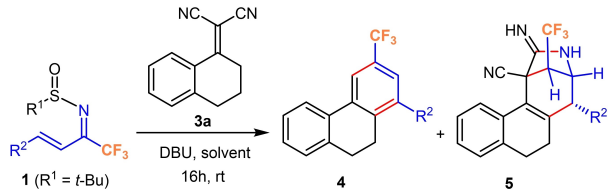
Table 1. Effects of the solvent on the divergent protocol.[a]



Entry	Imine	Solvent	Ratio **4a**/**5a**[b]	Yield **4a**/**5a** (%)[c]
1	**1a**	CH_2Cl_2	1.1:1	53/47
2	**2a**	CH_2Cl_2	1:7.6	10/73
3	**1a**	EtOAc	2.2:1	69/31
4	**2a**	EtOAc	1:4	19/75
5	**1a**	*i*-PrOH	3.6:1	76/21
6	**2a**	*i*-PrOH	1:1.9	34/63
7	**1a**	2-MeTHF	3.4:1	77/23
8	**2a**	2-MeTHF	1:3	24/71
9	**1a**	MeCN	1.7:1	60/36
10	**2a**	MeCN	1:3	23/68
11	**1a**	toluene	2:1	44/25
12	**2a**	toluene	1:4.2	16/67

[a] Reactions were performed with **1a**/**2a** (0.3 mmol), **3a** (2 equiv.) and DBU (2 equiv.) in the corresponding solvent (0.05 M) at rt for 16 h.
[b] Ratio of compounds **4a**/**5a** was determined by means of ^{19}F-NMR integration of the crude reaction mixtures.
[c] Isolated yields after flash column chromatography.

Table 2. Reaction of dicyanoalkene **3a** with conjugated trifluoromethyl sulfinyl imines **1** and **2**.[a]



Entry	Imine	R^2	Ratio **4**/**5**[b]	**4** (yield)[c]/ **5** (yield/dr)[c,d]
1	**1a**	Ph	3.6:1	**4a** (76%)
2	**1b**	4-$MeOC_6H_4$	3:1	**4b** (68%)
3	**1c**	4-ClC_6H_4	3.8:1	**4c** (77%)
4	**1d**	2-BrC_6H_4	15:1	**4d** (88%)
5	**1e**	2-furyl	3.6:1	**4e** (76%)
6	**1f**	propyl	4.3:1	**4f** (46%)
7	**2a**	Ph	1:7.6	**5a** (62%/12:1)
8	**2b**	4-$MeOC_6H_4$	1:6.4	**5b** (71%/12:1)
9	**2c**	4-ClC_6H_4	1:5.8	**5c** (67%/11:1)
10	**2d**	2-BrC_6H_4	–	**5d** (–)[e]
11	**2e**	2-furyl	1:3.5	**5e** (64%/6:1)
12	**2f**	propyl	–	**5f** (–)[e]

[a] Reactions were performed with **1a**/**2a** (0.3 mmol), **3a** (2 equiv.) and DBU (2 equiv.) in isopropanol (0.05 M) for imines **1** or dichloromethane for imines **2** at rt for 16 h.
[b] Ratio of compounds **4a**/**5a** was determined by means of ^{19}F-NMR integration of the crude reaction mixtures.
[c] Isolated yields after flash column chromatography.
[d] Diastereoisomeric ratios of compounds **5** were determined by ^{19}F-NMR integration of the crude reaction mixtures.
[e] Trace amounts of products were observed in these cases.

Moreover, imines **1e** and **1f**, containing heteroaromatic and aliphatic substituents, respectively, at the R^2 position, provided the corresponding trifluoromethyl arenes **4e**,**f** in useful synthetic yields (Table 2, entries 5, 6). On the other hand, reactions of *p*-tolyl sulfinyl imines **2** with dicyanoalkene **3a** were carried out in dichloromethane and they were highly selective towards the formation of polycycles **5**. It is important to notice that four stereogenic centers were generated in the formation of these compounds in a highly diastereoselective fashion (up to 12:1).[19] Imines **2a–c** bearing aromatic substituents at the R^2 position gave products **5** in good yields with high **5**/**4** selectivity and excellent diastereoselectivities (Table 2, entries 7–9). However, imine **2d**, with the 2-bromophenyl moiety, provided trace amounts of the desired product **5d**, probably due to steric reasons, and decomposition of the starting imine was observed instead (Table 2, entry 10). 2-Furyl-substituted imine **2e** also gave the corresponding tetracyclic product **5e** in good yield, although a slight decrease in chemo- and diastereoselectivity was detected in this case (Table 3, entry 11). Finally, the reaction with β-propyl-substituted imine **2f** did not proceed but only trace amounts of product **5f** were isolated (Table 3, entry 12).

The next step of our study was the evaluation of the domino protocol with several dicyanoalkenes **3**, which include bicyclic derivatives from 1-tetralone and 4-chromanone, as well as monocyclic compounds arising from acetophenone and aliphatic dicyanoalkenes. The scope of the reaction of 1,1-dicyanoalkenes **3** with fluorinated conjugated sulfinyl amines **1a** and **2a** is shown in Table 3.

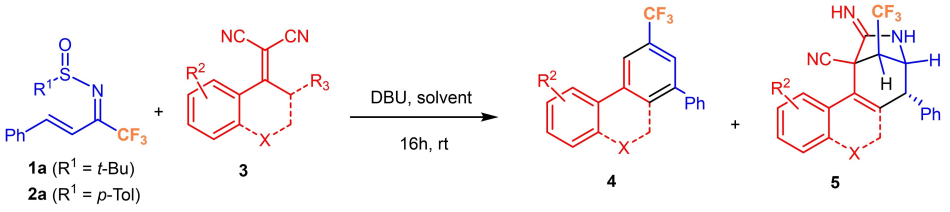
Reaction of conjugated sulfinyl imine **1a** with bicyclic dicyanoalkene **3b**, derived from 4-chromanone, proceeded with excellent product selectivity and gave the trifluoromethylated tricyclic product **4g** in 83% yield (Table 3, entry 1). Similarly, substrates **3c–f**, derived from 1-tetralone, reacted with imine **1a** in isopropanol as the solvent to render trifluoromethyl arenes **4h–k** in good yields with **4**/**5** selectivities up to 5.7:1, regardless the electronic properties and position of the substituents at the aromatic ring (Table 3, entries 2–5). As previously observed with dicyanoalkene **3a** (see Table 2), when bicyclic dicyanoalkenes **3c–f** reacted with *p*-tolyl sulfinyl imine **2a** in dichloromethane, the selectivity of the process changed and polycyclic products **5h–k** were isolated in good yields (Table 3, entries 7–10). In the case of the 4-chromanone-derived dicyanoalkene **3b**, compound **5g** was obtained in low yield (28%) (Table 3, entry 6), showing the high preference of substrate **3b** for the formation of the corresponding trifluorometyhl arene **4g**, even with imine **2a**. Noteworthy, reactions leading to products **5** took place with excellent diastereocontrol in all cases (up to 20:1).

Dicyanoalkene **3g**, containing a thiophene moiety, behaved as expected and gave rise to tricycle **4l** in 58% yield and tetracycle **5l** in 57% yield, from conjugated trifluoromehyl imines **1a** (in isopropanol) and **2a** (in dichloromethane), respectively, with moderate product selectivity in both cases (Table 3, entries 11, 12).

Monocyclic dicyanoalkenes **3h–l**, derived from acetophenone, bearing either electron-donating or electron-withdrawing substituents, afforded the desired biphenyl trifluoromethyl arenes **4m–q**, in their reaction with imine **1a**, with complete selectivity (**4**/**5** > 20:1) and good yields (Table 3, entries 13–17). In order to achieve the results indicated, these reactions required the slow addition of the dicyanoalkene to a solution of imine **1a** and DBU in dichloromethane; otherwise, dimerization of the dicyanoalkene occurred instead of the cycloaromatization process.[16] Due to the low solubility of dicyanoalkenes **3h–l** in isopropanol, their reactions with with *tert*-butyl sulfinyl imine **1a** were performed in dichloromethane in order to facilitate the slow addition procedure.

In the same way, monocyclic dicyanoalkenes **3m**, **n** containing heteroaromatic substituents required their

Table 3. Reaction of conjugated trifluoromethyl sulfinyl imines **1 a** and **2 a** with 1,1-dicyanoalkenes **3**.[a,b,c]

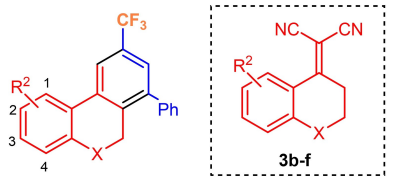


1a (R^1 = *t*-Bu)
2a (R^1 = *p*-Tol)

3

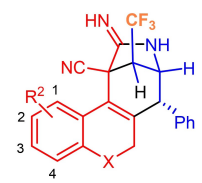
4

5

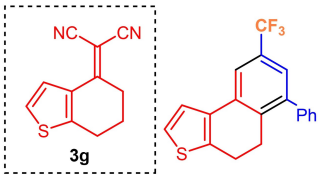


3b-f

1. **4g** (**4**/**5** >20:1, X= O, R^2= H, 83%), from **1a** and **3b**
2. **4h** (**4**/**5**= 5.7:1, X= CH_2, R^2= 2-Br, 74%), from **1a** and **3c**
3. **4i** (**4**/**5**= 3.9:1, X= CH_2, R^2= 2-MeO, 74%), from **1a** and **3d**
4. **4j** (**4**/**5**= 3.9:1, X= CH_2, R^2= 4-MeO, 77%), from **1a** and **3e**
5. **4k** (**4**/**5**= 4.6:1, X= CH_2, R^2= 2,3-$(MeO)_2$, 75%), from **1a** and **3f**

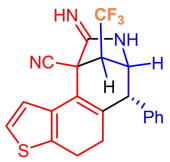


6. **5g** (**5**/**4**= 1:1.8, 20:1 dr, X= O, R^2= H, 28%), from **2a** and **3b**
7. **5h** (**5**/**4**= 2.6:1, 10:1 dr, X= CH_2, R^2= 2-Br, 58%), from **2a** and **3c**
8. **5i** (**5**/**4**= 7.9:1, 12:1 dr, X= CH_2, R^2= 2-MeO, 62%), from **2a** and **3d**
9. **5j** (**5**/**4**= 7.5:1, 13:1 dr, X= CH_2, R^2= 4-MeO, 79%), from **2a** and **3e**
10. **5k** (**5**/**4**= 5.3:1, 14:1 dr, X= CH_2, R^2= 2,3-$(MeO)_2$, 60%), from **2a** and **3f**

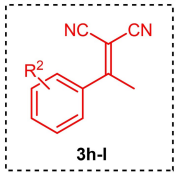


3g

11. **4l** (**4**/**5**= 3.8:1, 58%), from **1a** and **3g**

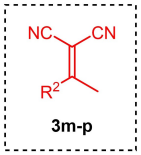


12. **5l** (**5**/**4**= 2.2:1, 57%, 16:1 dr), from **2a** and **3g**



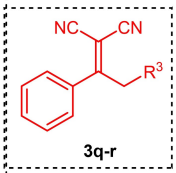
3h-l

13.[e] **4m** (**4**/**5** >20:1, R^2= 4-MeO, 61%), from **1a** and **3h**
14.[e] **4n** (**4**/**5** >20:1, R^2= 4-Me, 81%), from **1a** and **3i**
15.[e] **4o** (**4**/**5** >20:1, R^2= H, 78%), from **1a** and **3j**
16.[e] **4p** (**4**/**5** >20:1, R^2= 2-Br, 71%), from **1a** and **3k**
17.[e] **4q** (**4**/**5** >20:1, R^2= 4-Br, 59%), from **1a** and **3l**



3m-p

18.[e] **4r** (**4**/**5** >20:1, R^2= 2-furyl, 52%), from **1a** and **3m**
19.[e] **4s** (**4**/**5** >20:1, R^2= 2-thienyl, 57%), from **1a** and **3n**
20.[f] **4t** (**4**/**5** >20:1, R^2= *t*-Bu, 40%), from **1a** and **3o**
21.[g] **4u** (**4**/**5** >20:1, R^2= $(MeO)_2CH$, 30%), from **1a** and **3p**



3q-r

22. **5m** (**5**/**4** >20:1, 3.3:1 dr, R^3= Me, 61%), from **2a** and **3q**
23. **5n** (**5**/**4** >20:1, 2.8:1 dr, R^3= Ph, 73%), from **2a** and **3r**

[a] In general, reactions were performed with **1 a**/**2 a** (0.3 mmol), **3** (2 equiv.) and DBU (2 equiv.) at rt for 16 h in dichloromethane, except for reactions leading to compounds **4 g–l** that were carried out in isopropanol.
[b] Ratio of compounds **4**/**5** was determined by means of ^{19}F-NMR integration of the crude reaction mixtures.
[c] Isolated yields after flash column chromatography.
[d] Diastereoisomeric ratios (dr) of compounds **5** were determined by ^{19}F-NMR integration of the crude reaction mixtures.
[e] Slow addition of the dicyanoalkene (**3 h–n**) to a solution of imine **1 a** and DBU was necessary in order to attain the indicated results.
[f] When this reaction was carried out in isopropanol, compound **4 t** was obtained in 53% yield.
[g] When this reaction was carried out in isopropanol, compound **4 u** was obtained in 35% yield.

slow addition to a solution of imine **1 a** and DBU in dichloromethane to provide the corresponding trifluoromethyl arenes **4 r**, **s** in moderate yields and complete selectivity, as no formation of polycycles **5** was observed (Table 3, entries 18, 19).

We also evaluated the use of dicyanoalkenes bearing aliphatic substituents (**3 o**, **p**). Their reactions with imine **1 a** took place with complete selectivity in the formation of products **4 t**, **u**, which were isolated in moderate yields (Table 3, entries 20, 21). Since those dicyanoalkenes did not undergo dimerization under the reaction conditions, the use of isopropanol as the solvent slightly improve the chemical yields.

At this point, it is worth mentioning that all monocyclic and aliphatic dicyanoalkenes tested (**3 h–p**), unsubstituted at the γ-position, were not reactive with *p*-tolyl sulfinyl imine **2 a** under the optimized reaction conditions. On the contrary, we found that dicyanoalkenes arising from acetophenones substituted at the α-position (**3 q**, **r**), were unreactive against *tert*-

butyl sulfinyl imine **1a** while their reaction with *p*-tolyl sulfinyl imine **2a** provided exclusively the corresponding tetracyclic products **5m**, **n** in good yields with moderate diastereoselectivity (Table 3, entries 22, 23).

During the evaluation of the reaction scope regarding the dicyanoalkene counterpart, we did an interesting finding. When imine **1a** was subjected to 1,1-dicyanoalkene **6a** derived from 1-indanone under the optimized reaction conditions, a new tricyclic product bearing two stereocenters (**7a**) was isolated in 62% yield as a nearly 3:1 mixture of diastereoisomers (Table 4, entry 1).[20] This product showed a conjugated diene moiety, with loss of the sulfinyl amine group and one of the cyano groups remaining in the structure. With this result in hand, we decided to evaluate the scope of this new divergent reactivity profile employing different conjugated trifluoromethyl imines **1**, **2** and 1-indanone-derived dicyanoalkenes **6** (Table 4).

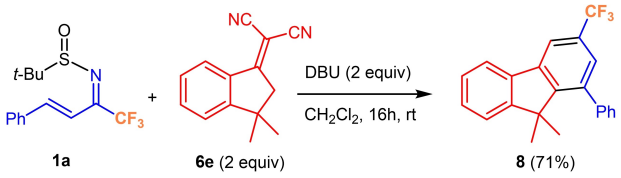
Firstly, the reaction of dicyanoalkene **6a** with *p*-tolyl sulfinyl imine **2a** was tested in order to examine the influence of the type of sulfinyl moiety. This reaction also led to compound **7a**. Although the process was more diastereoselective than those with *tert*-butyl sulfinyl imine **1a**, a clear drop in yield was observed (Table 4, entry 2), so the rest of examples were studied with *tert*-butyl sulfinyl imines **1**.

1,1-Dicyanoalkenes **6b–d**, differently substituted at the 6-position of the indene moiety, reacted with imine **1a** to render the corresponding diene derivatives **7b–d** in moderate to good yields with moderate diastereoselectivity (Table 4, entries 3–5). The reaction with substrates bearing electron-donating groups (**6b**, **c**) proceeded in higher yields than that of compound **6d** containing an electron-withdrawing group.

Conjugated sulfinyl imines **1c** and **1b** bearing aromatic substituents at the R^2 position with an electron-withdrawing and electron-donating group, respectively, also reacted with dicyanoalkene **6a** satisfactorily (Table 4, entries 6, 7).

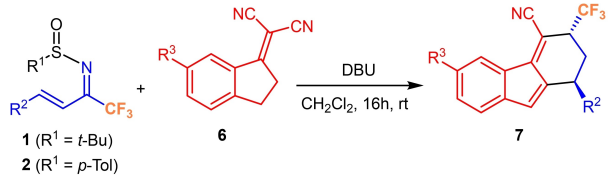
Additionally, we tested the relevance of the substitution at the C3-position of the starting dicyanoalkene. Compound **6e**, in which two methyl groups are present at that position, gave rise to the cycloaromatization product **8** in 71% yield upon reaction with imine **1a** (Scheme 2).

The last step of our study was the evaluation of the domino protocol with other conjugated sulfinyl imines (**9** and **10**) different than trifluoromethyl imines **1** and **2**. The results of this study are summarized in Table 5. First attempt was performed with *tert*-butyl sulfinyl imine **9a** bearing a CF_2H moiety. Its reaction with 1,1-



Scheme 2. Reaction of trifluoromethyl *tert*-butyl sulfinyl imine **1a** with 1,1-dicyanoalkene **6e**.

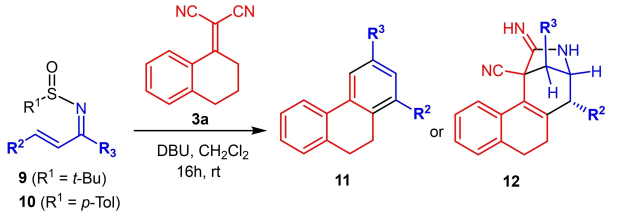
Table 4. Reaction of 1-indanonde-derived dicyanoalkenes **6** with conjugated trifluoromethyl sulfinyl imines **1** and **2**.[a]



Entry	Imine	R^2	**6** (R^3)	**7** (yield/dr)[b,c]
1	**1a**	Ph	**6a** (H)	**7a** (62%/2.9:1)
2	**2a**	Ph	**6a** (H)	**7a** (23%/4:1)
3	**1a**	Ph	**6b** (Me)	**7b** (63%/3.1:1)
4	**1a**	Ph	**6c** (OMe)	**7c** (68%/3:1)
5	**1a**	Ph	**6d** (Br)	**7d** (39%/3:1)
6	**1c**	4-ClC_6H_4	**6a** (H)	**7e** (62%/2.8:1)
7	**1b**	4-$MeOC_6H_4$	**6a** (H)	**7f** (52%/2.5:1)

[a] Reactions were performed with **1**/**2** (0.3 mmol), **6** (2 equiv.) and DBU (2 equiv.) in dichloromethane (0.05 M) at rt for 16 h.
[b] Isolated yields after flash column chromatography.
[c] Diastereoisomeric ratios of compounds **7** were determined by ^{19}F-NMR integration of the crude reaction mixtures.

Table 5. Reaction of dicyanoalkenes **3a** with fluorinated and non-fluorinated conjugated sulfinyl imines **9** and **10**.[a]



Entry	Imine	R^2	R^3	Product **11** (yield) or **12** (yield/dr)[b,c]
1	**9a**	Ph	CF_2H	**11a** (12%)
2	**10a**	Ph	CF_2H	**11a** (20%)
3	**9b**	Ph	Ph	**11b** (41%)
4	**10b**	Ph	Ph	**11b** (71%)
5	**9c**	CF_3	Ph	**11c** (35%)
6	**10c**	CF_3	Ph	**11c** (86%)
7	**9d**	Ph	CO_2Et	**12** (79%/13:1)
8	**10d**	Ph	CO_2Et	**12** (33%/5:1)

[a] Reactions were performed with **9**/**10** (0.3 mmol), **3a** (2 equiv.) and DBU (2 equiv.) in dichloromethane (0.05 M) at rt for 16 h.
[b] Isolated yields after flash column chromatography.
[c] Diastereoisomeric ratio of compound **12a** was determined by ^{19}F-NMR integration of the crude reaction mixtures.

dicyanoalkene **3a** afforded the cycloaromatization product **11a** in low yield (12%) (Table 5, entry 1). When the analogous *p*-tolyl sulfinyl imine **10a** was employed, the expected rearrangement did not take place, but the same cycloaromatization product **11a** was obtained in 20% yield (Table 5, entry 2). Similarly, starting from non-fluorinated aromatic imines **9b** and **10b**, only the cycloaromatization product **11b** was detected in both cases. This tricyclic derivative was isolated in 41% and 71% yield from *tert*-butyl- and *p*-tolyl sulfinyl imines **9b** and **10b**, respectively (Table 5, entries 3, 4).

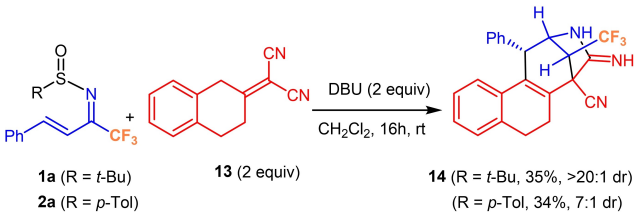
Aromatic imines **9c** and **10c**, bearing a β-trifluoromethyl group (R^2 position) also provided exclusively the tricyclic derivative **11c** in 35% and 86% yield, respectively (Table 5, entries 5, 6).

With these data in hand, it seems that the electron-withdrawing capacity of the substituent at the R^3 position plays an important role in the process. Therefore, we synthesized sulfinyl imines **9d** and **10d** bearing an ester group at the R^3 position instead the trifluoromethyl group present in imines **1** and **2**. Both substrates reacted with dicyanoalkene **3a** and rendered the rearranged polycycle **12**, in 79% and 33% yield with 13:1 and 5:1 dr, starting from *tert*-butyl- and *p*-tolyl sulfinyl imines **9d** and **10d**, respectively (Table 5, entries 7, 8).

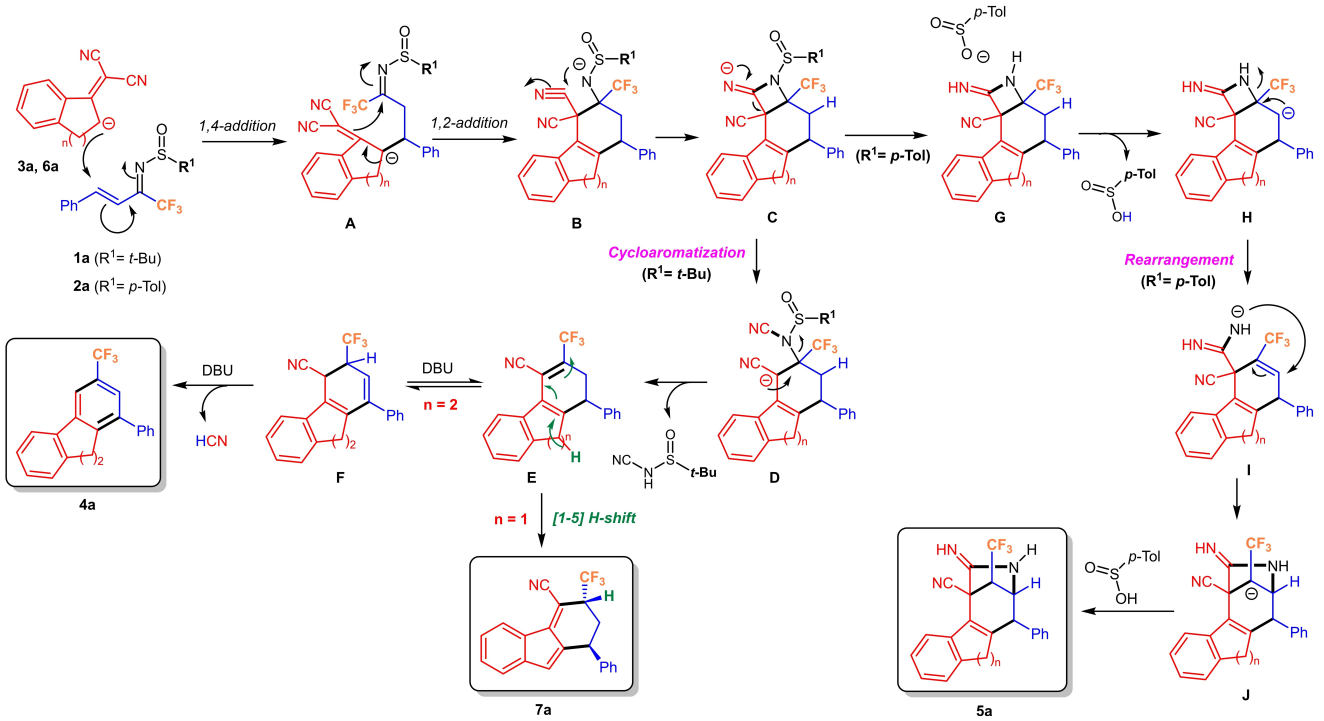
Finally, 1,1-dicyanoalkene **13**, derived from 2-tetralone, was also tested in the process. Both trifluoromethyl imines **1a** and **2a** provided the rearranged product **14** in moderated yield (35% and 34%, respectively), although with excellent diastereoselectivity starting from **1a** (Scheme 3).

The synthesis of compounds **4a** and **5a** was tested on a multigram scale. Thus, starting from 1.51 g of sulfinyl imine **1a** and 0.98 g of dicyanoalkene **3a**, 1.15 g of compound **4a** were obtained in 71% yield in *i*-PrOH as solvent. On the other hand, when 0.98 g of **3a** were treated with 1.68 g of sulfinyl imine **2a** in DCM, 1.54 g of **5a** were obtained in 78% yield, indicating that no significant erosion of the final yield was observed.

Once confirmed the unexpected molecular skeletons of products **4**, **5** and **7**, a mechanistic proposal to explain their formation, based on computational calculations (see Supporting Information for details), has been outlined below in Scheme 4. Initially, the starting 1,1-dicyanoalkenes **3a** or **6a** would undergo conjugated addition to sulfinyl imines **1a** or **2a** through the



Scheme 3. Reaction of trifluoromethyl imines **1a** and **2a** with 1,1-dicyanoalkene **13**.



Scheme 4. Mechanistic proposal for the formation of products **4**, **5** and **7**.

γ-position to render anionic intermediate **A**. This would evolve into species **B** by means of intramolecular 1,2-addition to the sulfinyl imine moiety through the α-position of the dicyanoalkene. Then, intermediate **B** would undergo intramolecular nucleophilic addition of the nitrogen amide to one of the cyano groups, affording the key intermediate **C**, which contains an azetidine imine unit. The divergent reactivity observed, according to the type of sulfinyl imine employed in the process, would rely on this intermediate. Therefore, starting from *tert*-butyl sulfinyl imine **1a** (R = *t*-Bu), the azetidine moiety in **C** would preferentially open, probably due to steric issues related to the *tert*-butyl group, and species **D** would be formed. This would eliminate the sulfinyl imine group and deliver diene **E**, which would isomerize to diene **F**, finally rendering the cycloaromatization product **4a** by loss of HCN.

When dicyanoalkene **6a**, derived from 1-indanone, was employed an alternative pathway would be preferred and intermediate **E** would undergo 1,5-hydrogen shift leading to final product **7a**. Most likely, the presence of a five-membered ring in this case would hinder the planarity required to achieve the aromatization event and diene **7** would be favoured.

On the other hand, starting from *p*-tolyl sulfinyl imine **2a** (R = *p*-Tol), the key intermediate **C** would preferentially undergo migration of the sulfinyl group to the iminic nitrogen followed by hydrolysis to give the tetracyclic intermediate **G**, where the rearrangement would take place. Thus, an acid-base reaction to abstract the α-proton to the CF_3 group followed by azetidine ring opening and intramolecular aza-Michael-type addition would deliver carbanion **J**, which would be diastereoselectively protonated by *p*-tosylic acid to yield the final tetracycle **5a**.

It is important to point out that the formation of compound **5a** would involve a rearrangement of intermediate **G**, that contains an azetidinimine unit,[21] to the corresponding final pyrrolidine core.[22] There are several precedents in the literature of this type of rearrangement with analogous *N*-sulfonyl β-lactams, that usually proceed either spontaneously or by simple heating.[23] As far as we know, only one example of this type of base catalyzed-rearrangement has been reported to date.[24]

Furthermore, the experimental results showed that the presence of an electron-withdrawing group attached to the iminic carbon at the starting imines (R^3 position, Table 5) was crucial for the formation of rearranged polycyclic products **5** and **12**. In this context, we could relate this finding to the acidity of the α-protons in intermediate **G**, which would be crucial for triggering the subsequent rearrangement. That intermediate from difluoromethyl and phenyl imines **9a–c** and **10a–c** (see Table 5, entries 1–6) would not be acidic enough for undergoing the rearrangement process, while it would efficiently occur starting form trifluoromethyl imines **2** (see Tables 2, 3) and ethoxycarbonyl imine **9d** (see Table 5, entries 7, 8).

Two years ago, we reported a theoretical study about the reaction of *tert*-butyl sulfinyl imine **1a** with 1,1-dicyanoalkene **3a**.[16] Now, in light of the divergent behaviour showed by *p*-tolyl sulfinyl imines, we decided to apply previous calculations to imine **2a** in order to understand the reactivity observed. The energy profiles corresponding to the reactions of imines **1a** and **2a** with 1,1-dicyanoalkene **3a** are showed in Scheme 5.

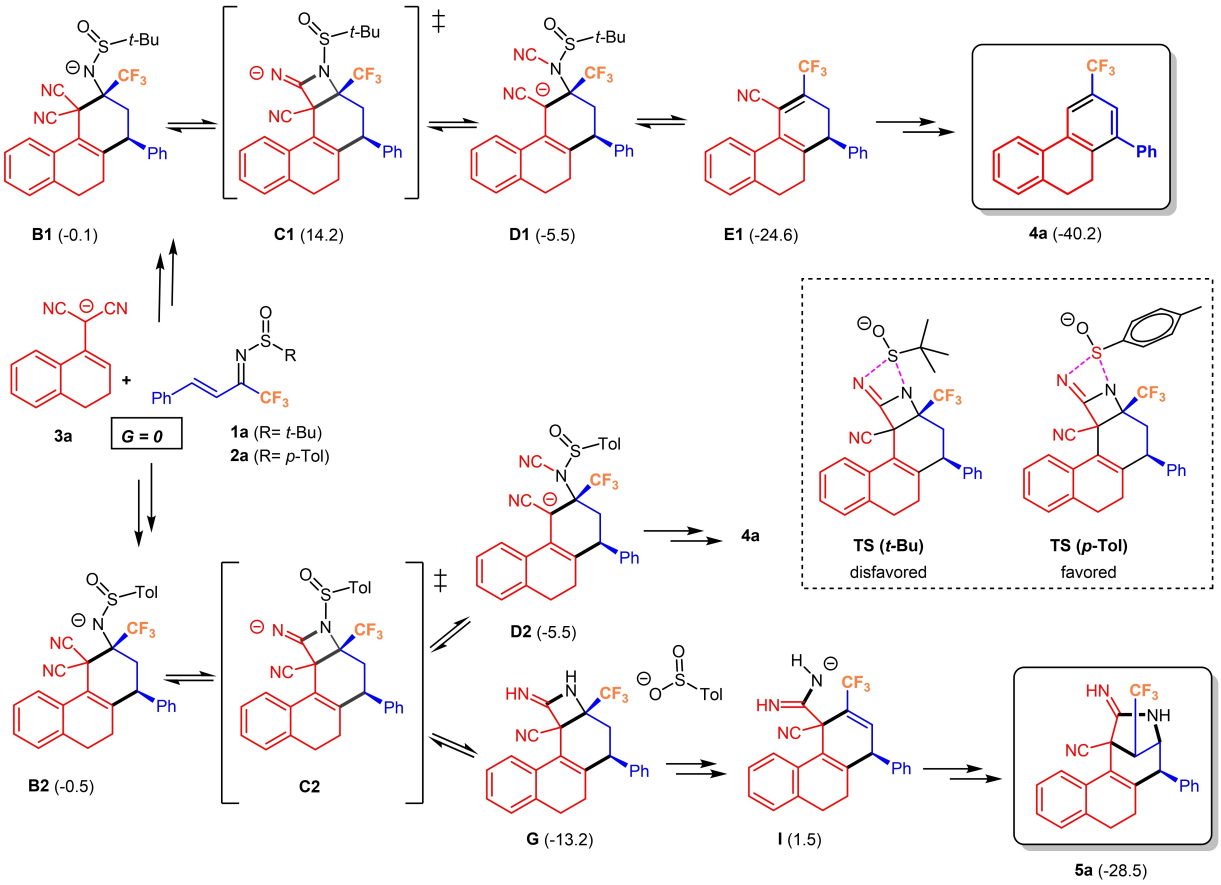
The calculations were performed at the M06-2X/6-31g** level with the Gaussian 16 suite of programs.[25] The mixture of deprotonated **3a** and imines **1a** and **2a** were taken as starting points (G = 0) of the energy profile. The reason for using the anion and not **3a** is to make all the following structures comparable in terms of total charge (−1) and number of atoms.

Unlike the calculations with imine **1a**, where all points of the energy profile were identified including transition states and the energy minima, with imine **2a** transition states were not found; however, points identified shed some light into the studied transformation.

For *p*-tolyl sulfinyl imine **2a**, two alternative energy profile pathways would coexist, to render products **4** and **5**.

The formation of intermediates **B1** and **B2** after 1,4-nucleophilic addition followed by intramolecular 1,2-addition would be identical for both imines, **1a** and **2a**. Then, the attack of the sulfinyl nitrogen atom to the cyano group would give the azetidinimine rings **C1** and **C2**. At this point, the energy profile for the reaction with *p*-tolyl sulfinyl imine **2a** bifurcates in two branches. On the one hand, intermediate **D2**, analogous to **D1**, would evolve into the cycloaromatization product **4a**. On the other hand, intermediate **G** (Δ = −13.2 kcal/mol), resulting from migration and hydrolysis of the sulfinyl moiety, would be much more stable than **D2** (Δ = −5.5 kcal/mol). Although the corresponding transition states were not found, it can be hypothesized that the presence of the bulky *t*-Bu substituent would work against this highly strained transition structure ([TS (*t*-Bu) and TS (*p*-Tol), Scheme 5), whereas the aromatic *p*-tolyl group might electronically favor it, in accordance with the experimental results.

Finally, intermediate **G** would rearrange to the final tetracyclic skeleton through ring opening of the four membered imidamide to anion **I**, followed by ring closure to the much more stable five membered cycle **5a** (Δ = −28.5 kcal/mol).



Scheme 5. Computed alternative pathways for the reaction of *tert*-butyl sulfinyl imine **1a** and *p*-tolyl sulfinyl imine **2a** with dicyanoalkene **3a**. Values of Δ in brackets are given in kcal/mol^{-1}.

Conclusion

In this work, the reaction of 1,1-dicyanoalkenes **3** with fluorinated conjugated imines **1** and **2** has been evaluated. Imines **1** containing the *tert*-butyl sulfinyl group reacted with dicyanoalkenes **3** in the presence of DBU as a base to render trifluoromethyl arenes **4** in yields ranging from 35% to 84% by means of a cycloaromatization domino process preferentially, when the reaction was performed in isopropanol as the solvent. However, the reaction with *p*-tolyl sulfinyl imines **2** in dichloromethane mainly rendered polycycles **5** through an azetidinimine rearrangement in yields ranging from 28% to 79% and diastereoselectivities up to 20:1. Moreover, when 1-indanone derived dicyanoalkenes **6** were employed, the cycloaromatization event was interrupted, giving rise to dienes **7** in yields ranging from 39% to 68% and diastereoselectivies up to 4:1.

It is worth mentioning that this divergent reactivity observed allows for achieving great structural diversity by means of a proper choice of the type of sulfinyl amine, the solvent and the nature of the dicyanoalkene. This methodology fulfils some of the important principles of green chemistry since it is a tandem protocol, which takes place under mild conditions: at room temperature, air-tolerant process from readily available starting materials (conjugated fluorinated sulfinyl imines and dicyanoalkenes).

Experimental Section

General Procedure for the Synthesis of Trifluoroarenes 4, Polycycles 5 and Dienes 7

In a 50 mL round bottom flask fitted with a magnetic stirring bar, the corresponding sulfinylimine **1** or **2** (0.3 mmol), solvent (6 mL) and DBU (0.6 mmol) were loaded. After stirring the reaction mixture for 5 min at room temperature, a solution of the corresponding dicyanoalkene **3** (0.6 mmol) in DCM (3 mL) was added. After stirring for 16 additional hours at rt, the solvents were removed and the crude product purified by means of flash column chromatography.

With acetophenone-derived dicyanoalkenes **3h–n**, a solution of the corresponding dicyanoalkene **3** (0.6 mmol) in DCM (3 mL) was slowly added with a syringe pump over 3 h (1 mL/h), and the resulting mixture stirred for 13 h at rt.

1-Phenyl-3-(trifluoromethyl)-9,10-dihydrophenanthrene (4 a)

Starting from dicyanoalkene **3 a** (116.5 mg), *t*-butyl-sulfinamide 1a (91.0 mg) and DBU (90 μL), following the general procedure mentioned above in *i*-PrOH as solvent, the titled compound **3 a** was obtained as a white solid (73.6 mg, 76%) after purification by column chromatography with Hex:EtOAc (10:1) as eluent. M. p. = 89–91 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (dqd, J = 1.9, 0.6 and 0.5 Hz, 1H), 7.82 (ddt, J = 7.5, 1.4 and 0.5 Hz, 1H), 7.5 (m, 1H), 7.46 (m, 2H), 7.43 (m, 1H), 7.37 (m, 1H), 7.36 (m, 2H), 7.31 (td, J = 7.2 and 1.4, Hz, 2H), 7.26 (m, 1H), 2.85 (m, 2H), 2.77 (m, 2H), ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 141.96, 140.3, 138.95 (q, J = 1.4 Hz), 137.53, 136.12, 133.91, 129.37, 128.5, 128.42, 128.13 (q, J = 272.3 Hz), 128.11, 127.74, 127.38, 124.44, 125.59 (q, J = 3.8 Hz), 120.02 (q, J = 3.8 Hz), 26.6, 28.75 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −62.4 ppm. HRMS (ESI) calcd. for ($M-H_2+H^+$) $C_{21}H_{14}F_3$: 323.1048; found 323.1058.

Polycycle 5 a

Starting from dicyanoalkene **3 a** (116.5 mg), *p*-tolyl-sulfinamide **2 a** (106.0 mg) and DBU (90 μL), following the general procedure mentioned above in CH_2Cl_2 as solvent, the titled compound **5 a** was obtained as a light yellow oil (73 mg, 62%) after purification by column chromatography with Hex:EtOAc (10:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (bd, J = 7.7 Hz, 1H), 7.36 (m, 2H), 7.33 (m, 1H), 7.30 (m, 1H), 7.26 (m, 2H), 7.17 (m, 2H), 4.38 (dq, 1H, J = 7.3 and 4.1 Hz), 3.98 (m, 1H), 3.55 (dd, J = 4.2 and 2.9 Hz), 2.89 (m, 1H), 2.81 (m, 1H), 2.19 (m, 1H), 2.16 (m, 1H) ppm. ^{13}C NMR (75.48 MHz, $CDCl_3$) δ 163.85, 147.66, 139.71, 136.68, 130.04, 129.53, 129.49, 129.08, 128.53, 128.04, 127.44, 127.21, 125.32 (q, J = 280.5 Hz), 121.93, 118.43 (q, J = 25.4 Hz), 75.63 (q, J = 4.1 Hz), 61.0, 59.84 (q, J = 1.6 Hz), 58.77, 28.25, 23.71 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ −76.0 ppm. HRMS (ESI) calcd. for $C_{23}H_{19}F_3N_3$: 394.1519; found 394.1526.

Diene 7 a

Starting from dicyanoalkene **6 a** (72.0 mg), *t*-butyl sulfinamide **1 a** (61.0 mg) and DBU (90 μL), following the general procedure mentioned above in CH_2Cl_2 as solvent, the titled compound **7 a** was obtained as a separable mixture of diastereoisomers (42 mg, 62%, 2.1 dr) as orange solids after purification by column chromatography with Hex:EtOAc (100:1). **Major isomer**: M. p. = 96.3–98.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.5, 1.0 Hz, 1H), 7.40–7.36 (m, 2H), 7.34–7.30 (m, 1H), 7.29–7.25 (m, 3H), 7.21 (td, J = 7.6, 1.2 Hz, 1H), 7.05 (d, J = 7.2 Hz, 1H), 6.26 (d, J = 2.4 Hz, 1H), 4.10–4.02 (m, 1H), 3.47 (qdd, J = 8.8, 5.6, 2.7 Hz, 1H), 2.44 (ddd, J = 14.2, 4.9, 2.7 Hz, 1H), 2.26 (dddd, J = 14.2, 12.9, 5.6, 1.4 Hz, 1H). ^{19}F NMR (471 MHz, $CDCl_3$) δ −66.85 (d, J = 8.9 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.67, 143.50, 141.85, 139.85, 134.02, 132.14, 131.56, 129.09, 128.22, 127.65, 127.06, 126.07 (d, J = 282.2 Hz), 124.31, 121.68, 117.17, 100.10 (q, J = 2.3 Hz), 42.48 (q, J = 28.0 Hz), 38.16, 32.08. HRMS (ESI/Q-TOF) calculated m/z $C_{21}H_{15}F_3N$ $[M+H]^+$: 338.1151 found 338.1144.

Minor Isomer

M. p. = 165.2–166.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 7.5 Hz, 1H), 7.43–7.37 (m, 2H), 7.36–7.32 (m, 1H), 7.32–7.28 (m, 2H), 7.28–7.25 (m, 1H), 7.22 (td, J = 7.6, 1.2 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.20 (d, J = 2.6 Hz, 1H), 3.76 (dt, J = 13.5, 3.6 Hz, 1H), 3.59 (dqd, J = 12.5, 8.5, 4.2 Hz, 1H), 2.44 (dt, J = 12.9, 4.2 Hz, 1H), 2.12 (q, J = 12.9 Hz, 1H). ^{19}F NMR (471 MHz, $CDCl_3$) δ −68.39 (d, J = 8.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.45, 143.65, 141.26, 140.27, 132.55, 132.11, 131.41, 129.13, 128.14, 127.80, 126.98, 125.50 (q, J = 280.7 Hz), 124.51, 121.63, 115.91, 101.41 (q, J = 2.2 Hz), 44.49 (q, J = 27.8 Hz), 41.00, 32.60 (q, J = 2.5 Hz). HRMS (ESI/Q-TOF) calculated m/z $C_{21}H_{15}F_3N$ $[M+H]^+$: 338.1151 found 338.1140.

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