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AuX_3-Mediated Selective Head-to-Head Dimerization of Difluoropropargyl Amides

Santos Fustero,*[,†,‡] Paula Bello,[†] Begoña Fernández,[†] Carlos del Pozo,[†] and Gerald B. Hammond[§]

[†]*Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Spain,* [‡]*Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain, and* [§]*Department of Chemistry, University of Louisville, Louisville, Kentucky 40292*

santos.fustero@uv.es; sfustero@cipf.es

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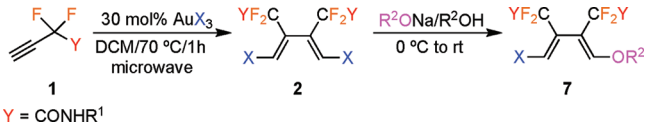

A dimerization of difluoropropargyl amides by reaction with gold(III) halides is described. A reductive elimination of a divinylgold species can be invoked to rationalize its formation. Initial studies of the unusual reactivity of these 1,4-dihalo-1,3-dienes have been performed.

Introduction

The use of gold compounds in homogeneous organic reactions, although undervalued for a long time, has experienced an impressive rebirth during the past decade.[1] Gold's ability to behave as a soft Lewis acid allows it to activate unsaturated functionalities such as alkynes, alkenes, and allenes to create carbon−carbon and carbon−heteroatom bonds under extremely mild conditions.[2] Furthermore, gold complexes efficiently activate sp, sp^2, and sp^3 carbon−hydrogen bonds.[3] Despite the spectacular development of gold chemistry, very few reports concerning the use of fluorinated starting materials have been devised. Most of them are related to diastereoselective aldol condensations between glycine α-anion equivalents and fluorinated aldehydes,[4] ketones,[5] or imines[6] catalyzed by gold(I) complexes. More recently, the use of an (NHC)gold(I) fluoride in a hydrofluorination reaction of alkynes has been reported.[7] A gold(I)-catalyzed alkoxyfluorination converted *β*-hydroxy ynones to 5-halo-3,3′-difluorodihydropyranones, showing the compatibility of gold catalysis with electrophilic fluorinating reagents.[8] Finally, the most recent paper in this series deals with a gold(III)-catalyzed 5-endo-digonal cyclization followed to dehydrofluorination of *gem*-difluorohomopropargylamines to render 2-aryl-3-fluoropyrroles.[9]

In an ongoing project in our laboratory, *gem*-difluoro homopropargylic amides have been used as fluorinated building blocks for the preparation of several nitrogen-containing fluorinated heterocycles.[10] Since alkynes are the most successful and most frequently used reaction partners in gold catalysis, we decided to explore the behavior of these *gem*-difluoropropargylalkynes in the presence of Au(III) salts. To our surprise, the unexpected formation of dihalo dienic systems coming from the head-to-head dimerization of the starting amides was observed. The optimization of the reaction conditions, some mechanistic considerations, and

*To whom correspondence should be addressed. Tel: +34-963544279. Fax: +34-963544938.

(1) (a) Hutchings, G. J.; Brust, M.; Schmidbaur, H. *Chem. Soc. Rev.* **2008**, *37*, 1759. (b) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.

(2) For selected recent reviews, see: (a) Nuñez, E. J.; Echavarren, A. *Chem. Rev.* **2008**, *108*, 3326. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (c) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (d) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847.

(3) For selected recent reviews, see: (a) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (b) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917.

(4) (a) Soloshonok, V. A.; Kacharov, A. D.; Hayashi, T. *Tetrahedron* **1996**, *52*, 245. (b) Soloshonok, V. A.; Hayashi, T. *Tetrahedron Lett.* **1994**, *35*, 1091. (c) Soloshonok, V. A.; Hayashi, T. *Tetrahedron Lett.* **1994**, *35*, 2713.

(5) (a) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, M.; Hayashi, T. *J. Org. Chem.* **1997**, *62*, 3470. (b) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 7845. (c) Soloshonok, V. A.; Hayashi, T.; Ishikawa, K.; Nagashima, N. *Tetrahedron Lett.* **1994**, *35*, 1055.

(6) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969.

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(8) Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2008**, *47*, 7927.

(9) Surmont, R.; Verniest, G.; De Kimpe, N. *Org. Lett.* **2009**, *11*, 2920 and references cited therein.

(10) (a) Fustero, S.; Fernández, B.; Bello, P.; del Pozo, C.; Arimitsu, S.; Hammond, G. B. *Org. Lett.* **2007**, *9*, 4251. (b) Arimirtsu, S.; Fernández, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656.

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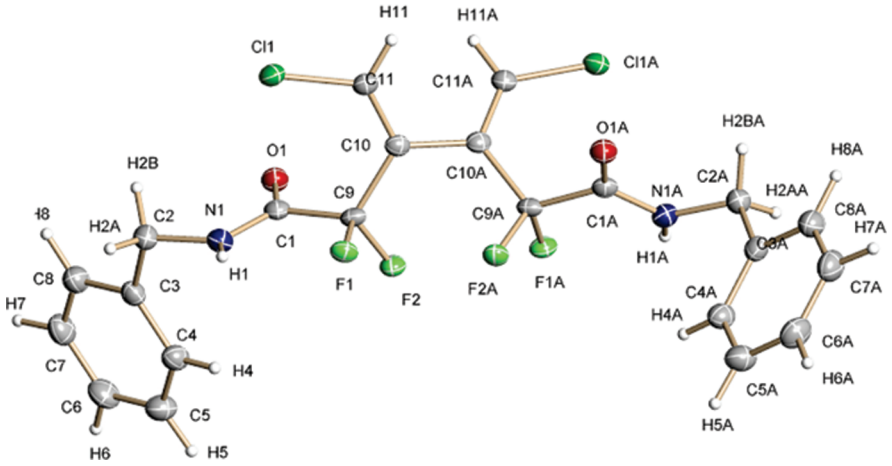


FIGURE 1. Crystal structure of compound **2a**.

preliminary studies of their reactivity are discussed in this paper.

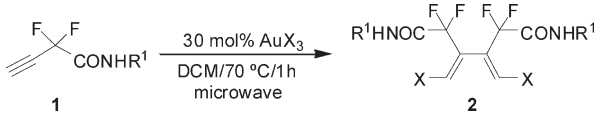
Results and Discussion

When a solution of fluorinated amide **1a** (Y = CONHBn) in CH_2Cl_2 was treated with $AuCl_3$ the dienic system **2a** was isolated as the major product in 33% yield after 20 h at room temperature. The structure of compound **2a** was unambiguously determined by X-ray analysis (Figure 1).[11] The formation of this derivative implied that two chlorine atoms, coming from the gold coordination sphere, were involved in the process. In addition, the structure of the dimer strongly suggested that an oxidative dimerization of the substrate occurred by reductive elimination of a gold(III) species.[12]

Due to the moderate yield of **2a**, we decided to optimize the reaction conditions for its formation since this gold-mediated transformation has no precedents in the literature. Thus, different solvents, temperatures, gold sources, amounts of gold species, and additives were examined in depth. Among the variety of solvents (CH_2Cl_2, THF, CH_3OH, PhMe, $ClCH_2CH_2Cl$, CH_3CN) and temperatures tested, the best results were initially obtained in refluxing CH_2Cl_2 (40% yield). The use of microwave irradiation allowed us to perform the reaction in 1 h at 70 °C, obtaining **2a** in 43% yield (Table 1, entry 1). The use of cationic sources of gold(III), such as $NaAuCl_4$, did not produce a significant change in the final yield, while the use of gold(III) bromide led us to obtain the corresponding diene analogue **2b** with two bromine atoms in 46% yield (Table 1, entry 2).[13] Together with diene **2b**, three more products were detected (as can be seen in detail in Scheme 2) in 24% yield, which indicates that the overall yield of the process is 70%.

With the optimized reaction conditions in hand (microwave heating in CH_2Cl_2 for 1 h in the presence of 30 mol % of the gold source), we extended this methodology to different *gem*-difluoropropargylamides **1**. Thus, a family of dienes **2** was prepared in moderate yields, as depicted in Table 1.[14]

TABLE 1. Dimerization of *gem*-Difluoropropargylamides 1



1 2

entry	1	R^1	X	yield of 2[a,b] (%)
1	**1a**	Bn	Cl	**2a** (43)
2	**1a**	Bn	Br	**2b** (46)
3	**1b**	(*S*)-Ph(CH)Me	Cl	**2c** (50)
4	**1b**	(*S*)-Ph(CH)Me	Br	**2d** (47)
5	**1c**	allyl	Cl	**2e** (48)
6	**1c**	allyl	Br	**2f** (40)
7	**1d**	*n*-propyl	Cl	**2g** (41)
8	**1d**	*n*-propyl	Br	**2h** (40)

[a]Isolated yield after flash column chromatography. [b]Different amounts of other products **3**−**5** (20−25% yield) were also obtained (see Scheme 2).

A plausible explanation for the reaction mechanism should start with the metal coordination toward the triple bond to form complex **A**, which would undergo a halogen−ligand exchange to render cationic intermediate **B**. Since it can be assumed that the *gem*-difluoro propargylic unit is like an α,β-unsaturated functionality,[15] it is reasonable to think that a halogen addition to the terminal alkyne might take place, affording the vinylgold intermediate **C**. An analogous sequence (alkyne−metal coordination, halogen−ligand exchange, and nucleophilic attack) would generate divinyl intermediate **D**, which would finally render dihalo dienes **2** by means of reductive elimination (Scheme 1).

The formation of these highly functionalized head-to-head dimers **2** is rather unusual, since gold species are not prone to undergo reductive elimination.[16] In addition, the incorporation of the halogen atoms to the final dienic

(11) For the X-ray structure of **2a**, see the Supporting Information.

(12) The formation of a dimer in the reaction of allenyl carbinols with $AuCl_3$ has been recently reported, although as a side reaction product. A reductive elimination of gold(III) species was invoked to explain its formation: Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387.

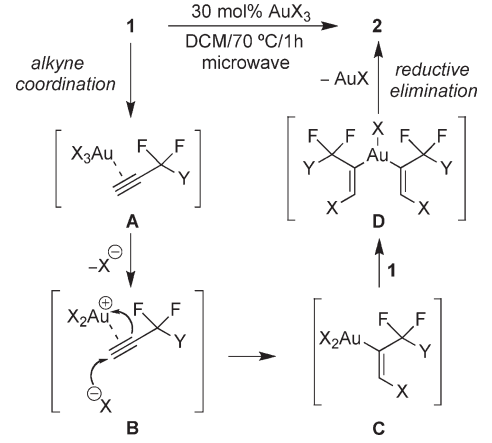
(13) With other catalysts such as $PtBr_2$ or $PdCl_2$ no formation of dimeric derivatives was detected.

(14) When internal alkynes in the starting amides **1** were used, the recovery of the starting material was observed in all cases studied.

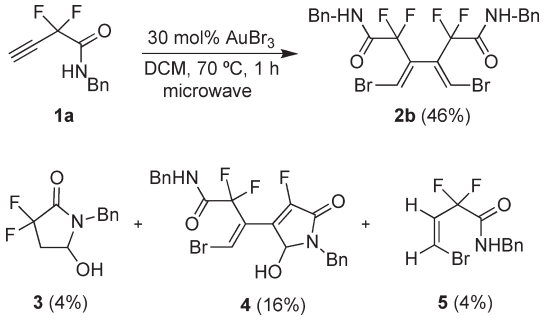
(15) We had previously observed this behavior in the intramolecular hydroamination reaction of fluorinated amide **1a** mediated by TBAF. See ref 10a.

(16) Gold is not usually involved in redox catalytic cycles: Gorin, D. G.; Toste, D. N. *Nature* **2007**, *446*, 395.

SCHEME 1. Mechanistic Proposal



SCHEME 2. Identification of the Minor Products 3−5



structure is quite surprising.[17] Despite the presence of the amidic nitrogen, which is likely to act as an intramolecular nucleophile once complex **A** has been formed, the incorporation of the halogen atoms is the preferred reaction pathway (the hydroamination compound derived from the intramolecular attack of the amidic nitrogen was also observed, although as a minor product; see Scheme 3). Most likely, the *gem*-difluoro moiety plays an important role in the overall process, decreasing the nucleophilicity of the nitrogen and, at the same time, activating the alkyne for the intermolecular nucleophilic addition of the halogen.

Considering the mechanistic proposal shown in Scheme 1, it became apparent that this process was stoichiometric in gold.[18] Since the halogen atoms of the final products come from the metal salt, it would be necessary to use 50 mol % of the gold source to enable the formation of 100% of the final product. However, when increasing the amount of the catalyst to 50 mol % lower yields of the desired products as well as more complex reaction mixtures were obtained. Attempts to perform the process in a catalytic fashion would involve the reoxidation of gold(I) (formed after the reductive elimination) to gold(III), and the addition of an external halogen source. In spite of a recent report on the reoxidation og gold using $PhI(OAc)_2$[19] and *tert*-butyl hydroperoxide,[20] in our case it was not possible to perform a catalytic dimerization reaction with the use of these additives in the presence of a halogen source (KBr or LiCl).[21] The use of other additives, such as $CuCl_2$[22] or 1,4-benzoquinone,[23] commonly applied in palladium chemistry, was also unsuccessful.[24]

A more detailed study of the reaction between **1a** and $AuBr_3$ under the optimized conditions led us to identify other compounds formed during the process. Together with dimer **2b**, formed in 46% yield, we also detected minor amounts of compounds **3** (4%), **4** (16%), and **5** (4%) (Scheme 2).

The formation of compounds **3** and **4** could be explained through an alternative reaction pathway. After the activation of the triple bond by gold coordination (intermediate **A**, Scheme 3), an intramolecular hydroamination of the amidic nitrogen could take place (instead of a halogen intermolecular attack) to render intermediate lactam **E**. Protodemetalation followed by double-bond hydration during the workup process would explain the formation of product **3** (Scheme 3). The second major product **4** could also be rationalized from intermediate **E**. This vinylgold intermediate could coordinate another alkyne molecule to the metal (intermediate **G**) followed by halogen exchange and nucleophilic attack to afford intermediate **I**. Reductive elimination of the divinylgold species would generate the new dienic structure (intermediate **J**) that after hydration and subsequent loss of HF during the workup would render asymmetric diene **4** in 16% yield (Scheme 3).[25]

Bromoalkene **5** could be explained by proto-demetalation of the vinylgold species **C** (Scheme 1) before the coordination with another alkyne molecule.

In order to evaluate the influence of the fluorine atoms in the formation of dimers **2**, the *gem*-difluoro moiety was substituted by two methyl groups in compound **6**.[26] When **6** was subjected to the optimized conditions in the presence of $AuCl_3$, a complex mixture was observed (Scheme 4). Although steric requirements of two methyl groups are higher than those of two fluorine atoms, this result indicates the important role played by fluorine in the overall process.

From a synthetic point of view, dimers **2** are fluorinated 1,4-dihalo-1,3-dienes. These systems contain a 1,3-butadiene skeleton and two halogen atoms for further functionalization,

(17) A similar incorporation of a chlorine atom was previously reported in the reaction of ethyl propiolate with gold(I) complexes when the reaction was performed in the presence of $BF_3 \cdot OEt_2$. Its formation was assumed considering that when no other nucleophile is present, the corresponding gold−alkyne π complex reacts with a chloride ion: Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485.

(18) The use of gold complexes in stoichiometric reactions is rare. For a recent example, see: (a) Sahoo, A. K.; Nakamura, Y.; Aratani, N.; Kim, K. S.; Noh, S. B.; Shinokubo, H.; Kim, D.; Osuka, A. *Org. Lett.* **2006**, *8*, 4141. See also: (b) Fuchita, Y.; Utsinomiya, Y.; Yasutake, M. *J. Chem. Soc., Dalton Trans. 1* **2001**, 2330. (c) Zamora, F.; Amo-Ochoa, P.; Fischer, B.; Schimanski, A.; Lippert, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 2274.

(19) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, 386.

(20) Wegner, H. A.; Ahles, S.; Neuburger, M. *Chem.—Eur. J.* **2008**, *14*, 11310.

(21) LiCl was very recently used as halogen source in chloropalladation reactions of a triple bond: Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442.

(22) $CuCl_2$ was used both as oxidant additive and halogen source in palladium-catalyzed reactions: (a) Tang, S.; Yu, Q.-F.; Peng, P.; Li, J.-H.; Zhong, P.; Tang, R.-Y. *Org. Lett.* **2007**, *9*, 3413. (b) Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* **2003**, *5*, 4429.

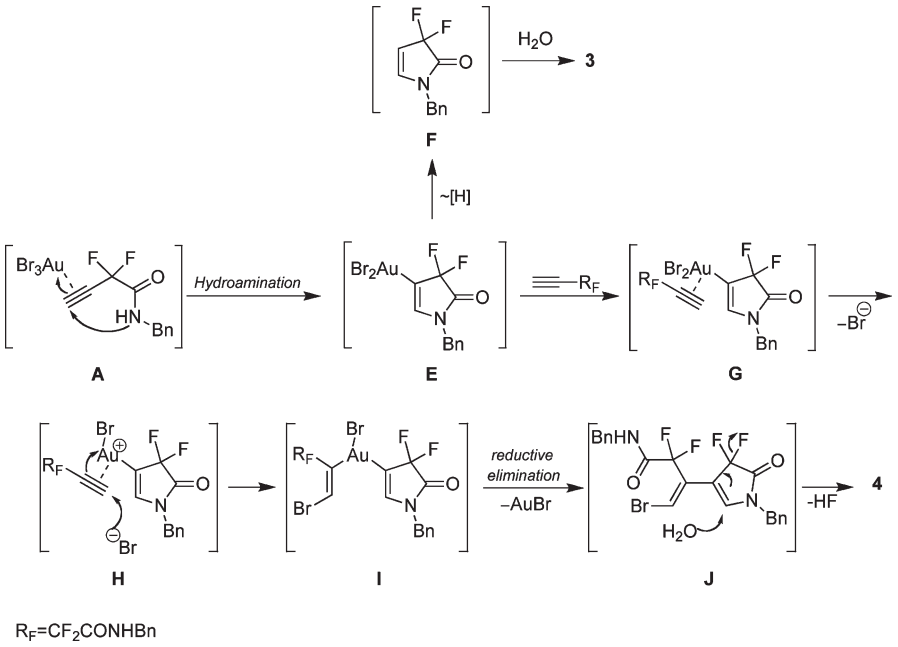
(23) 1,4-Benzoquinone was used for the reoxidation of Pd(0) to Pd(II): (a) Piera, J.; Persson, A.; Caldentey, X.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2007**, *129*, 14120. (b) Piera, J.; Närhi, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2006**, *45*, 6914.

(24) When $AgSbF_5$ was used as additive, only the product derived from the hydroamination of the amidic-nitrogen over the triple bond was observed.

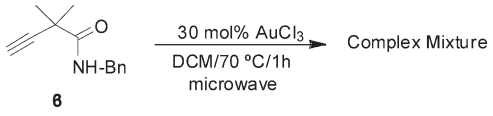
(25) Probably the driving force of this process would be the generation of more conjugation along the backbone of product **4**.

(26) For the preparation of compound **6**, see the Supporting Information.

SCHEME 3. Possible Explanation for the Formation of 3 and 4



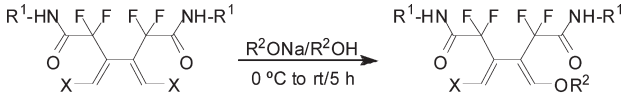
SCHEME 4. Dimerization Attempt with Nonfluorinated Alkyne 6



which makes them useful building blocks in the preparation of conjugated systems. The reaction described here represents a new protocol for the preparation of 1,4-disubstituted 1,3-butadienes that cannot easily be prepared through other methods.[27] Therefore, we decided to perform preliminary studies of the reactivity of systems **2**. We found that they were unreactive in the Diels–Alder reaction, even in the presence of a Lewis acid. However, when **2a** was treated with sodium methoxide in methanol, a desymmetrization reaction of the dienic system occurred yielding compound **7a**, in which only one of the halogen atoms had been replaced by the oxygen nucleophile (Table 2, entry 1). Probably, once the first halogen atom is replaced by the methoxy group, the electronic requirements of the new dienic system are different, and the addition of a second equivalent is not favored. The results obtained in the extension of this protocol to other starting dienes **2** and alcohols are summarized in Table 2.

The Ullmann coupling between *N*-centered nucleophiles and aryl halides has been successfully extended to vinylic C–N bond formation.[28] The intramolecular version of this reaction is particularly interesting since it allows the creation of nitrogen heterocycles. This strategy has been successfully used in natural product synthesis.[29] The application of Ullmann-type conditions to substrates **2** would lead to the corresponding fluorinated bis-2-pyrrolidones. Vinyl bromides were found to be good partners in the vinylic coupling. Thus, when substrate **2b** was treated with CuI and Cs_2CO_3 in refluxing toluene, the formation of bicyclic system **8b** took place in moderate yield (Scheme 5), while chlorine derivative **2a** was unreactive under the same reaction conditions. Dienes **2d** and **2h** cyclized under the same conditions to afford the corresponding bicyclic derivatives **8c**,**d** in 40% and 70% yield, respectively.

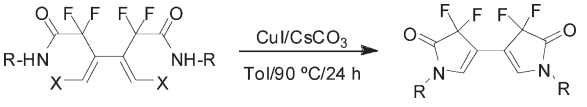
TABLE 2. Desymmetrization of Dienes 2



entry	2	X	R^1	R^2	7 (% yield)[a]
1	**2a**	Cl	Bn	Me	**7a** (94)
2	**2b**	Br	Bn	Me	**7b** (85)
3	**2d**	Br	(*S*)-Ph(CH)Me	Me	**7c** (88)
4	**2g**	Cl	*n*-propyl	Me	**7d** (60)
5	**2h**	Br	*n*-propyl	Me	**7e** (65)
6	**2a**	Cl	Bn	Et	**7f** (55)
7	**2b**	Br	Bn	Et	**7g** (50)

[a]Isolated yield after flash column chromatography.

SCHEME 5. Reaction of Dienes 2 with CuI



2a (R = Bn, X = Cl)
2b (R = Bn, X = Br)
2d (R = (*S*)-Ph(CH)Me, X = Br)
2h (R = Pr, X = Br)

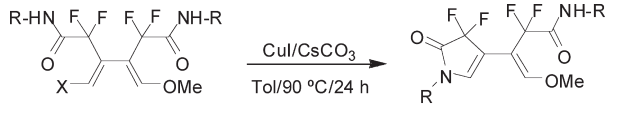
8a (0%)
8b (47%)
8c (40%)
8d (70%)

(27) For a recent review of the preparation of multiply substituted butadiene containing building blocks, see: Xi, Z.; Zhang, W.-X. *Synlett* **2008**, 2557.

(28) Zhao, Q.; Li, C. *Org. Lett.* **2008**, *10*, 4037 and references cited therein.

(29) For recent examples, see: (a) Jiang, B.; Tian, H.; Huang, Z.-G.; Xu, M. *Org. Lett.* **2008**, *10*, 2737. (b) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572.

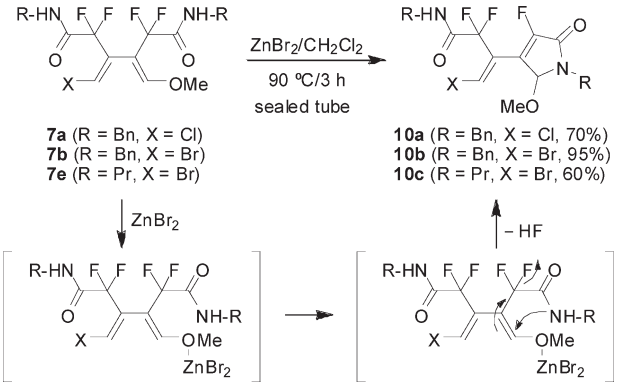
SCHEME 6. Reaction of Dienes 7 with CuI



7a (R = Bn, X = Cl)
7b (R = Bn, X = Br)
7c (R = (*S*)-Ph(CH)Me, X = Br)
7e (R = Pr, X = Br)

9a (0%)
9b (65%)
9c (41%)
9d (62%)

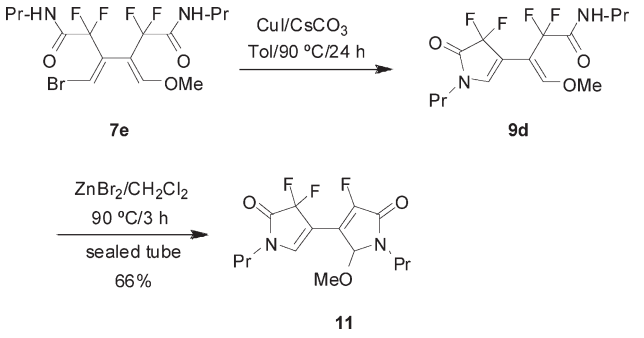
SCHEME 7. Reaction of Dienes 7 with $ZnBr_2$



7a (R = Bn, X = Cl)
7b (R = Bn, X = Br)
7e (R = Pr, X = Br)

10a (R = Bn, X = Cl, 70%)
10b (R = Bn, X = Br, 95%)
10c (R = Pr, X = Br, 60%)

SCHEME 8. Preparation of Asymmetric Bicyclic Derivatives 11



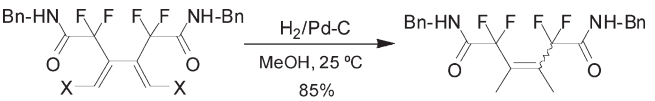
7e **9d** **11**

Likewise, bromine-containing dienes **7b**,**d**,**h** cyclized under the copper-catalyzed conditions to give monocyclic 2-pyrrolidones **9b**−**d**, respectively, in moderate to good chemical yields (Scheme 6). Again, no reaction was observed in the chlorine analogue **7a**.

As previously mentioned, dienes **2** were unreactive in the Diels−Alder reaction under usual conditions. However, when those conditions were applied to compounds **7** in the presence of a Lewis acid, the clean formation of a new product was observed. Thus, when **7a**,**b**,**e** were heated in a sealed tube in the presence of zinc bromide, cyclized products **10a**,**b**,**e** were obtained in excellent yields (Scheme 7). Presumably, the chelation of the Lewis acid with the methoxy group activates the α-position for a nucleophilic attack of the amidic nitrogen. In addition, the cyclization is favored by the loss of HF, giving rise to the highly conjugated pyrrolidones **10** in good chemical yields.

Combining the reactions mentioned before, it was possible to create asymmetric bicyclic derivatives **11**. Thus, as a representative example, when substrate **7e** was treated with CuI, the bromine-containing side of the dienic system

SCHEME 9. Hydrogenation of Dienic Systems 2a,b



2a (X = Cl)
2b (X = Br)

12

cyclized to afford compound **9d**, which was subjected without further purification to the Lewis acid-mediated cyclization. The methoxy side of the diene cyclized under this conditions to afford bicycle **11** in 66% overall yield (Scheme 8).

Finally, hydrogenation reactions were tested on dienes **2a**,**b**. To our surprise, when these substrates were treated with atmospheric pressure of nitrogen under palladium catalysis, the unexpected formation of fluorinated olefins **12** was observed, indicating once again the unusual reactivity shown by these substrates (Scheme 9).[30]

Conclusions

In conclusion, the microwave irradiation of a solution of fluorinated amides **1** in the presence of AuX_3 (X = Cl, Br) led to the unexpected formation of head-to-head dimers **2** with the incorporation of two halogen atoms to the final dienic backbone. The role of the *gem*-difluoro moiety in the process seems to be essential for the unusual behavior of these alkynes not observed to date in a gold-mediated process. Preliminary studies on the reactivity of compounds **2** allowed us to perform the desymmetrization of the dienic structure, giving rise to derivatives **4**. The amidic nitrogen of compounds **2** and **4** was coupled whith the vinylic moiety of the dienic backbone when bromine was the halogen partner. Compounds **4** cyclized under acidic conditions involving the vinyl ether moiety. Efforts directed to the understanding of the reactivity of **2** and **4** will be reported in due course.

Experimental Section

All microwave experiments were carried out at 0.1 M solution in a typically 0.5−2 mL vial with an Initiator 2.0, by Biotage. The solutions were prestirred before irradiation was started. The absorbance of the solvent was set as "normal", and 3−4 bar at 70 °C was reached. The reaction time was initiated as soon the system reached the input temperature, although approximately 2 min was needed to reach it.

General Procedure for the Preparation of Dimers 2. AuX_3 (30 mol %) was added to a solution of the corresponding amide **3** (0.5 mmol) in anhydrous CH_2Cl_2 (0.2 M) in a microwave vial. The vial was sealed and the solution heated with an air-flow at 70 °C during 1 h under microwave irradiation, and the pressure was liberated with a needle before removal of the vial cap. The solution was then filtered, concentrated, and purified by means of flash chromatography on silica gel with *n*-hexane−diethyl ether 7/3 as eluent.

(3*Z*,4*Z*)-N^1,N^6-Dibenzyl-3,4-bis(chloromethylene)-2,2,5,5-tetrafluorohexanediamide (2a). Following the general procedure described above, 50 mg of **2a** (43%) was obtained as a white solid starting from 100 mg of **1a**. Mp = 108−110 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.52 (d, *J* = 5.7 Hz, 4H), 6.78 (s, 2H), 6.89 (br s, 2H), 7.28−7.39 (m, 10H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ

(30) The configuration of the double bond in compound **12** was not determined.

43.7, 112.0 (t, $^1J_{CF}$ = 256.0 Hz), 127.9, 128.0, 129.7 (t, $^3J_{CF}$ = 3.5 Hz), 131.4 (t, $^2J_{CF}$ = 29.3 Hz), 136.4, 162.4 (t, $^2J_{CF}$ = 29.9 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −101.3 (s, 2 × 2F). HRMS: calcd for (M^+) $C_{22}H_{18}Cl_2F_4N_2O_2$ 488.0681, found 488.0687.

Preparation of Compounds 3,[10a] 4, and 5. Following the general procedure described above for the synthesis of dimers **2**, the reaction of difluoropropargyl amide **1b** with $AuBr_3$ led to the formation of compounds **2b**, **3**, **4**, and **5**. Thus, starting from 300 mg of **1b**, together with 192 mg of diene **2b** (46%), 14 mg of **3** (4%), 112 mg of **4** (16%), and 17 mg of **5** (4%) were obtained.

(*Z*)-*N*-Benzyl-3-(1-benzyl-4-fluoro-2-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-4-bromo-2,2-difluoro-3-butynamide (4). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.33 (d, J = 15.0 Hz, 1H), 4.48 (dd, J_1 = 14.5 Hz, J_2 = 15.8 Hz, 1H), 4.58 (dd, J_1 = 14.5 Hz, J_2 = 5.8 Hz, 1H) 4.98 (d, J = 15.0 Hz, 1H), 5.06 (d, J = 3.8 Hz, 1H), 5.49 (ddd, J_{1HF} = 6.8 Hz, J_2 = 3.8 Hz, J_{3HF} = 2.0 Hz, 1H), 7.06 (br s, 1H), 7.08 (dd, J_{1HF} = 3.4 Hz, J_{2HF} = 1.9 Hz, 1H), 7.27−7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 43.4, 44.1, 78.0 (dd, $^3J_{CF}$ = 8.4 Hz, $^4J_{CF}$ = 5.2 Hz), 112.8 (dd, $^1J_{CF}$ = 252.3 Hz, $^1J_{CF}$ = 262.0 Hz), 119.4 (m), 125.2, 127.8, 128.0, 128.4, 128.8, 129.0, 135.5, 136.1, 150.3 8 (d, $^1J_{CF}$ = 291.3 Hz), 160.6 (d, $^2J_{CF}$ = 31 Hz), 163.1 (t, $^2J_{CF}$ = 29.3 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −98.9 (dd, $^1J_{FF}$ = 272.1 Hz, $^5J_{FF}$ = 2 Hz, 1F), −101.9 (dddd, $^1J_{FF}$ = 272.1 Hz, $^5J_{FF}$ = 4.6 Hz, J_{FH} = 3.4 Hz, J_{FH} = 2 Hz, 1F), −137.4 (dddd, $^5J_{FF}$ = 4.6 Hz, $^5J_{FF}$ = 2 Hz, J_{FH} = 6.8 Hz, J_{FH} = 1.8 Hz, 1F). HRMS: calcd for (M^+) $C_{22}H_{18}BrF_3N_2O_3$ 494.0453, found 494.0462.

(*Z*)-*N*-Benzyl-4-bromo-2,2-difluoro-3-butynamide (5). White solid. Mp: 65−67 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.54 (d, J = 5.7 Hz, 2H), 6.66 (dt, J_{1HF} = 11.6 Hz, J_2 = 8.4 Hz, 1H), 6.74 (br s, 1H), 6.78 (dt, J_1 = 8.4 Hz, J_2 = 1.5 Hz), 7.30−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 43.7, 113.1 (t, $^1J_{CF}$ = 248.6 Hz), 115.5 (t, $^3J_{CF}$ = 9.9 Hz), 127.4 (t, $^2J_{CF}$ = 28.0 Hz), 127.9, 128.0, 128.9, 136.4, 162.6 (t, $^2J_{CF}$ = 30.0 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −100.8 (d, J_{FH} = 11.6 Hz, 2F). HRMS: calcd for (M^+) $C_{11}H_{10}BrF_2NO$ 288.9914, found 288.9919.

General Procedure for the Preparation of Asymmetric Dimers 7. To a solution of the corresponding diene **2** (0.1 mmol) in anhydrous THF (0.1 M) at 0 °C was added dropwise a solution of sodium alkoxide (0.25 mmol, 0.5 M solution of MeONa/MeOH or 21 wt % EtONa/EtOH), and the mixture was allowed to reach room temperature. The solution was stirred for an additional 6−10 h at rt, hydrolyzed with water (5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and purified after solvent evaporation by means of flash chromatography with hexanes/ethyl acetate 3:1 as eluent.

(3*Z*,4*Z*)-N^1,N^6-Dibenzyl-3-(chloromethylene)-2,2,5,5-tetrafluoro-4-(methoxymethylene)hexanediamide (7a). Following the general procedure described above, 28 mg of **7a** (94%) was obtained as a colorless oil starting from 30 mg of **2a**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.61 (s, 3H), 4.49 (d, J = 5.8 Hz, 2H), 4.50 (d, J = 5.7 Hz, 2H), 6.45 (s, 1H), 6.66 (s, 1H), 6.86 (br s, 1H), 6.98 (br s, 1H), 7.29−7.38 (m, 10H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 43.5, 43.7, 61.7, 106.8 (t, $^2J_{CF}$ = 27.6 Hz), 112.6 (t, $^1J_{CF}$ = 255.8 Hz), 113.0 (t, $^1J_{CF}$ = 252.9 Hz), 127.7, 127.8, 127.9, 128.0, 128.5 (t, $^3J_{CF}$ = 5.2 Hz), 136.6, 137.2, 155.4 (t, $^3J_{CF}$ = 6.3 Hz), 162.9 (t, $^2J_{CF}$ = 29.8 Hz), 163.9 (t, $^2J_{CF}$ = 31.0 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −110.0 (s, 2F), −111.1 (s, 2F). HRMS: calcd for (M^+) $C_{23}H_{21}ClF_4N_2O_3$ 485.1255, found 485.1254.

General Procedure for the Preparation of Compounds 8 and 9. A solution of CuI (4 mg, 0.02 mmol, 20 mol %), Cs_2CO_3 (98 mg, 0.3 mmol), and the corresponding 1,3-diene **2** (0.10 mmol) in anhydrous toluene (0.09 M) was heated in a sealed tube at 80 °C during 15 h. The reaction mixture was then quenched with distilled water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. After complete evaporation of solvent, the reaction mixture was purified by flash column chromatography in *n*-hexane/ethyl acetate (5:1).

1,1′-Dibenzyl-4,4,4′,4′-tetrafluoro-1*H*,1′*H*-3,3′-bipyrrole-5,5′-(4*H*,4′*H*)-dione (8b). Following the general procedure described above, 17 mg of **8b** (47%) was obtained as a yellow solid starting from 50 mg of **2b**. Mp: 198−200 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.63 (s, 4H), 6.68 (t, J_{HF} = 1.3 Hz, 2H), 7.21−7.41 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz): 46.4, 106.1 (t, $^2J_{CF}$ = 20.9 Hz), 111.9 (t, $^1J_{CF}$ = 251.7 Hz), 127.8, 128.6, 129.3, 132.5 (t, $^3J_{CF}$ = 8.2 Hz), 134.1, 164.6 (t, $^2J_{CF}$ = 28.7 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): −115.8 (t, J_{HF} = 1.3 Hz, 4F). HRMS: calcd for $C_{22}H_{16}F_4N_2O_2$ 416.1148, found 416.1146.

(*Z*)-*N*-Benzyl-3-(1-benzyl-4,4-difluoro-5-oxo-4,5-dihydro-1*H*-pyrrol-3-yl)-2,2-difluoro-4-methoxybut-3-enamide (9b). Following the general procedure described above, starting from 20 mg of **7b**, 11 mg of **9b** was obtained as a yellow oil (65%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.61 (s, 3H), 4.49 (d, J = 6 Hz, 2H), 4.60 (s, 2H), 6.64 (s, 1H), 6.66 (br s, 1H), 6.73 (t, J_{HF} = 2.1 Hz, 1H), 7.22−7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz): 43.6, 46.3, 61.8, 103.6 (t, $^2J_{CF}$ = 25.3 Hz), 108.7 (t, $^2J_{CF}$ = 21.8 Hz), 112.7 (t, $^1J_{CF}$ = 251.6 Hz), 114.3 (t, $^1J_{CF}$ = 251.6 Hz), 127.8, 127.9, 127.9, 128.4, 128.8, 129.1, 133.6 (t, $^3J_{CF}$ = 7.8 Hz), 134.5, 137.1, 151.6 (t, $^3J_{CF}$ = 6.4 Hz), 163.6 (t, $^2J_{CF}$ = 29.6 Hz), 164.6 (t, $^2J_{CF}$ = 29.6 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): −100.9 (s, 2F), −113.7 (s, 2F). HRMS: calcd for $C_{23}H_{20}F_4N_2O_3$ 448.1410, found 448.1415.

General Procedure for the Preparation of Compounds 10. A solution of $ZnBr_2$ (34 mg, 0.15 mmol) and the corresponding 1,3-diene **7** (0.10 mmol) in anhydrous dichloromethane (0.1 M) was heated in a sealed tube at 90 °C for 2 h. The reaction was then quenched with distilled water (5 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. After complete evaporation of solvent, the reaction mixture was purified by flash column chromatography in *n*-hexane/ethyl acetate (3:1).

(*Z*)-*N*-Benzyl-3-(1-benzyl-4-fluoro-2-methoxy-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-4-chloro-2,2-difluorobut-3-enamide (10a). Following the general procedure described above, starting from 50 mg of **7a**, 34 mg of **10a** were obtained as a colorless oil (70%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.04 (s, 3H), 4.13 (d, J = 14.5 Hz, 1H), 4.52 (d, J = 5.6 Hz, 2H), 4.96 (d, J = 14.5 Hz, 1H), 5.4 (d, J = 6.2 Hz, 1H), 6. 74 (br s, 1H), 6.92 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 43.8, 43.7, 49.8, 83.3 (dt, $^3J_{CF}$ = 5.9 Hz, $^4J_{CF}$ = 2 Hz), 112.9 (t, $^1J_{CF}$ = 257.7 Hz), 119.0 (td, $^3J_{CF}$ = 1.8 Hz, $^4J_{CF}$ = 0.6 Hz), 125.9 (td, $^2J_{CF}$ = 26.4 Hz, $^3J_{CF}$ = 4.9 Hz), 127.9, 128.0, 128.1, 128.6, 128.8, 128.9, 130.4 (dt, $^2J_{CF}$ = 6.4 Hz, $^3J_{CF}$ = 5.2 Hz), 135.6, 136.3, 149.5 (d, $^1J_{CF}$ = 293.7 Hz), 161.0 (d, $^2J_{CF}$ = 31.6 Hz), 161.7 (t, $^2J_{CF}$ = 29 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): −99.1 (dd, J_{FF} = 279.3 Hz, J_{FF} = 17.2 Hz, 1F), −100.8 (dd, J_{FF} = 279.3 Hz, J_{FF} = 17.2 Hz, 1F), −128.1 (ddd, J^1_{FF} = J^2_{FF} = 17.2 Hz, J_{FH} = 6.2 Hz). HRMS: calcd for $C_{23}H_{20}ClF_3N_2O_3$ 464.1114, found 464.1108.

4-(4,4-Difluoro-5-oxo-1-propyl)-4,5-dihydro-1*H*-pyrrol-3-yl)-3-fluoro-5-methoxy-1-propyl-1*H*-pyrrol-2(5*H*)-one (11). Following a two-step procedure, the CuI-mediated cyclization (preparation of compounds **8**) followed by $ZnBr_2$-mediated cyclization (preparation of compounds **10**), starting from 15 mg of **7h**, produced 8 mg of **11** as a yellow oil (66%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (t, J = 7.3 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H), 1.67 (m, 4H), 3.03 (s, 3H), 3.11 (ddd, J_1 = 14 Hz; J_2 = 8.4 Hz; J_3 = 6 Hz, 1H), 3.47 (ddd, J_1 = 21 Hz; J_2 = 14 Hz; J_3 = 7.1 Hz, 1H), 3.49 (ddd, J_1 = 21 Hz; J_2 = 14 Hz; J_3 = 7.2 Hz, 1H), 3.57 (ddd, J_1 = 15.8 Hz; J_2 = 8.4 Hz; J_3 = 7.1 Hz, 1H), 5.51 (d, J = 5.8 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.9, 11.3, 21.4, 21.8, 41.6, 44.7, 48.5, 82.6 (d, $^3J_{CF}$ = 6.9 Hz), 105.7 (td, $^2J_{CF}$ = 22.4 Hz; $^3J_{CF}$ = 6.8 Hz), 110.7 (t, $^1J_{CF}$ = 252.2 Hz), 114.2, 139.7 (td, $^3J_{CF}$ = 8.5 Hz; $^4J_{CF}$ = 8.5 Hz), 147.0

(d, $^{1}J_{CF}$ = 290.2 Hz), 161.8 (d, $^{2}J_{CF}$ = 29.7 Hz), 165.3 (t, $^{2}J_{CF}$ = 29.7 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −115.4 (ddd, J_{FF} = 13 Hz; J^{1}_{FH} = J^{2}_{FH} = 2.1 Hz, 2F), −133.4 (tdd, J_{FF} = 13 Hz; J^{1}_{FH} = 5.6 Hz; J^{2}_{FH} = 1.3 Hz, 2F). HRMS: calcd for $C_{15}H_{19}F_3N_2O_3$ 332.1348, found 332.1345.

(*Z*)-*N*1,*N*6-Dibenzyl-2,2,5,5-tetrafluoro-3,4-dimethylhex-3-dienamide (12). A solution of diene **2a** (20 mg, 0.1 mmol) in anhydrous methanol (5 mL) was introduced in a pressure reactor, and 0.4 mg of 10% Pd−C was added. The suspension was stirred at room temperature for 20 h under 15 atm of hydrogen. After this time, the pressure was released and the mixture filtered through a pad of Celite and washed with EtOAc (3 × 5 mL). Evaporation of the solvents rendered 15 mg of compound **12** (85%) as a white solid (without further purification). Starting from 20 mg of **2b**, 12.5 mg of **12** was obtained (85%). Mp: 168−170 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.92 (t, J = 2.2 Hz, 6H), 4.49 (d, J = 6.2 Hz, 4H), 7.22−7.37 (m, 10H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.4 (t, $^{3}J_{CF}$ = 4.4 Hz), 44.6, 117.3 (t, $^{1}J_{CF}$ = 253.6 Hz), 135.3 (t, $^{2}J_{CF}$ = 23 Hz), 129.0, 129.4, 130.3, 140.1, 164.9 (t, $^{2}J_{CF}$ = 31.3 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −122.247 (s, 4F). HRMS: calcd for $C_{22}H_{22}F_4N_2O_2$ 422.1617, found 422.1605.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.