Asymmetric Synthesis

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Regio- and Enantioselective Aminofluorination of Alkenes**

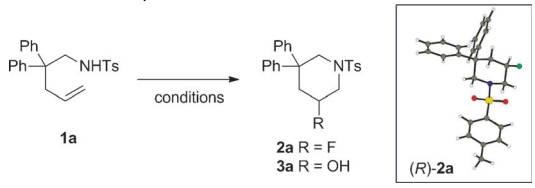
*Wangqing Kong, Pascal Feige, Teresa de Haro, and Cristina Nevado**

Compounds containing a C–F bond present improved properties (i.e. hydrophobicity, solubility, metabolic stability) compared to their corresponding C–H counterparts, thus explaining why approximately 25% of the current preclinical drugs contain at least one fluorine atom.[1,2] In this context, molecules that contain a vicinal aminofluorine moiety play a relevant role, as they constitute key building blocks for the synthesis of anticancer,[3] anticholinergic, and anti-inflammatory drugs,[4] as well as therapeutic β-peptides.[5] However, in spite of their importance, few methods are currently available to generate β-aminofluorinated compounds,[6] particularly in a stereocontrolled manner. Organocatalysis has been applied in this context[7] although reactivity always relies on the α-fluorination of carbonyl compounds through their enol forms.[8] Recently, Lewis base[9] and anionic phase-transfer[10] catalysts in combination with Selectfluor have been successfully employed in the stereocontrolled fluorination of nitrogen-containing activated olefins, such as indoles and enamides, respectively. The Ritter-type amidofluorination of styrenes is a prototype example of the use of electrophilic fluorine sources (e.g. Selectfluor) to activate alkenes towards the attack of nitrogen-nucleophiles, although the reaction scope is rather limited.[11] Other metal-free methods have also been recently developed for the intramolecular aminofluorination of unactivated olefins.[12] In addition, palladium catalysis in combination with strong oxidants has been successfully applied in both the intra- and intermolecular aminofluorination of alkenes.[13] These processes rely on the oxidation of Pd^{II} to Pd^{IV} species to facilitate the C–F bond formation.[14] However, to the best of our knowledge, an asymmetric variant of these transformations is not yet reported.

Our group has recently combined the unique carbophilicity of gold complexes with Selectfluor to trigger the formation of C_{sp^3} and C_{sp^2}–F bonds.[15] In addition we showed that gold can catalyze the selective oxidative difunctionalization of alkenes to give 1,2-aminoalcohols, aminoethers, and aminoamides.[16] We envisaged that this protocol could also be applied to the synthesis of 1,2-aminofluoro compounds under the right set of conditions.

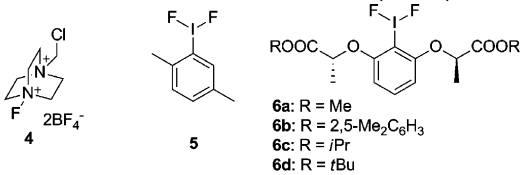
Initially, we studied the reaction of *N*-tosyl-2,2-diphenyl-4-pentenyl amine (**1a**) with a catalytic amount of $[(Ph_3P)AuNTf_2]$ in the presence of Selectfluor (**4**).[17] The starting material was partially converted into a complex mixture of products, but the desired fluoropiperidine **2a** could not be detected (Table 1, entry 1). Inspired by the Pd-catalyzed alkene aminofluorination reported by Liu and coworkers,[13] we attempted the reaction in the presence of $PhI(OPiv)_2$ as oxidant and silver fluoride as external source of fluorine. In this case, aminoalcohol **3a** was obtained, probably owing to the presence of adventitious water in the reaction (Table 1, entry 2). We then decided to use a phenyl difluoro-

Table 1: Discovery and optimization of the intramolecular metal-free aminofluorination of pentenamines.[17]



Entry	Conditions	Product (yield [%])[a]	*ee* [%][b]
1	$[(Ph_3P)AuNTf_2]$ (5 mol%), **4** (2 equiv), $MeNO_2$, 80°C, 17 h	[c]	–
2	$[(Ph_3P)AuNTf_2]$ (5 mol%), $PhI(OPiv)_2$ (2 equiv), AgF (2 equiv), $MeNO_2$, 80°C, 17 h	**3a**	–
3	$PhI(OAc)_2$ (2 equiv), TBAF (2 equiv), $NaHCO_3$ (1 equiv), CH_3CN, 80°C, 17 h	**1a**	–
4	$[(Ph_3P)AuNTf_2]$ (5 mol%), **5** (2 equiv), $MeNO_2$, 80°C, 1.5 h	**2a**/**3a** 1:1[d]	–
5	**5** (2 equiv), CH_2Cl_2, M.S. (4 Å), 25°C, 17 h	**2a** (93)	–
6	(*R*,*R*)-**6a** (2.5 equiv), CH_2Cl_2, 25°C, 17 h	**2a** (76)	56
7	(*R*,*R*)-**6a** (2.5 equiv), toluene, 25°C, 17 h	**2a** (62)	67
8	(*R*,*R*)-**6b** (2.5 equiv), toluene, 25°C, 17 h	**2a**	45
9	(*R*,*R*)-**6c** (2.5 equiv), toluene, 25°C, 17 h	**2a** (70)	62
10	(*R*,*R*)-**6d** (2.5 equiv), toluene, 25°C, 17 h	**2a** (71)	81 (99)

[a] The value in brackets is the yield after column chromatography on neutral alumina. [b] Determined by HPLC on a chiral stationary phase. The value in brackets corresponds to the *ee* value after crystallization. [c] A complex mixture of products was obtained together with some recovered **1a**. [d] Ratio determined by ^1H NMR spectroscopy. M.S. = molecular sieves, Piv = trimethylacetyl, TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.



[*] Dr. W. Kong, P. Feige, T. de Haro, Prof. Dr. C. Nevado
Organic Chemistry Institute, Universität Zürich (Switzerland)
E-mail: nevado@oci.uzh.ch

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iodonium salt generated in situ by treatment of phenyliodo-diacetate with TBAF. However, only starting material was recovered (Table 1, entry 3). As $PhIF_2$ is unstable, we decided to investigate the ability of a more stable analogue.[18] Iodoarene difluorides are well-recognized fluorinating agents of alkenes,[19] alkynes,[20] and ketones[21] and have only been used with moderate success in fluorocyclizations of alcohols and carboxylic acids in the presence of additional amine-HF complexes.[22] When *p*-xylene-iodoniumdifluoride (**5**) was used under the reaction conditions shown in entry 4, we observed, for the first time, the formation of amino-fluorination product **2a** together with alcohol **3a**. A control experiment in the absence of gold and in the presence of molecular sieves (4 Å) in dichloromethane at room temperature, showed the clean formation of the β-fluorinated piperidine **2a**, which could be isolated in 93% yield (Table 1, entry 5).

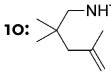
Notably, the reaction was highly regioselective affording exclusively the 6-*endo*-cyclization product. Inspired by the widespread use of chiral iodine(III) reagents,[23] and their recent successful application to the asymmetric functionalization of alkenes,[24] we decided to target an enantioselective version of this aminofluorocyclization. After some experimentation,[17] we found that the use of (*R*,*R*)-dimethyl lactate based hypervalent iodine (*R*,*R*)-**6a** afforded β-piperidine **2a** in 76% yield and 56% *ee* without the need of exhaustive anhydrous conditions (Table 1, entry 6). A slight increase in selectivity (67% *ee*) was observed when toluene was used as solvent (Table 1, entry 7). Oxidants (*R*,*R*)-**6b** and (*R*,*R*)-**6c,** bearing an *iso*-propyl and a 2,5-dimethylphenyl lactate unit, respectively, were tested but significant improvement in the selectivity was not achieved (Table 1, entries 8 and 9). Notably, the reaction of (*R*,*R*)-*tert*-butyl lactate iododifluoride ((*R*,*R*)-**6d**) gave **2a** in 71% yield with a significantly enhanced enantiomeric excess of 81%. Upon recrystallization, enantiomerically pure fluoropiperidine **2a** was obtained. The structure of (*R*)-**2a** was unequivocally assigned by X-Ray diffraction analysis.[25] It is worth mentioning that, although 2.5 equivalents of the chiral oxidant were used, 50–60% of the corresponding iodide precursor with the initial enantiomeric purity (99% *ee*) is recovered from the reaction mixture. To the best of our knowledge, our discovery not only represents one of the first examples of metal-free aminofluorination of nonactivated alkenes[12] but also the first breakthrough in the development of an asymmetric version of these highly demanded transformations.

We then set out to explore the scope of this reaction (Table 2). First, we decided to confirm that the product configuration is defined by that of the chiral oxidant. Indeed, (*S*,*S*)-**6d** afforded **2a** in comparable yield but opposite selectivity to that reported in Table 1 (Table 2, entry 1). We then evaluated the influence of the *N*-protecting group in the reaction. A series of different *N*-aromatic sulfonamides **1b**–**e** were converted into the corresponding β-fluoropiperidines **2b**–**e** in high yields, with complete regioselectivity and good levels of asymmetric induction (Table 2, entries 2–5). An *N*-methylsulfonamide substrate (**1f**) was also converted into the corresponding aminofluorinated product **2f** with moderate enantioselectivity (Table 2, entry 6). A carbobenzyloxy (Cbz) protected substrate (**1g**) proved to be amenable to the reaction conditions as well (Table 2, entry 7). In all these cases, high enantioselectivities (>90% *ee*) were obtained upon a single recrystallization of the products. We also examined the effect of substituents on the backbone of the aminopentene substrates. 2,2-Disubstituted substrates **1h**–**j** afforded aminofluorinated piperidines **2h**–**j** in good yields and selectivities (Table 2, entries 8–10). Substitution at the C1-position of the pentenamine substrate (**1k**) was also tolerated although the selectivity was slightly reduced (Table 2, entry 11). High levels of *cis*-diastereoselectivity were obtained in the reaction of **6d** with substrate **1l**; a result that is in sharp contrast to previous Pd-catalyzed examples (Table 2, entry 12).[13a] Our metal-free regioselective aminofluorination was applied to other pentenamine substrates (Table 2, entries 13–15 and additional examples in Table S3 of the Supporting Information); these results showed that terminal alkenes and aromatic substituents seem to be preferred for enantioselective induction.[17]

Owing to the widespread presence of azepane scaffolds in natural products as well as in synthetic bioactive molecules, we envisioned the extension of this method to the stereocontrolled synthesis of β-fluorinated azepane heterocycles (Table 3). *N*-(2,2-Diphenylhex-5-enyl)-4-tosyl amide **7a** was selected as benchmark substrate. To our surprise, under the

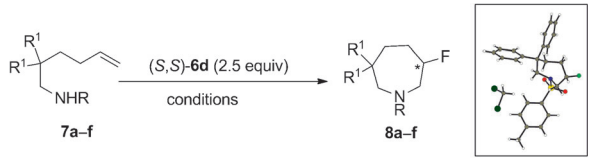
Table 2: Scope of the metal-free intramolecular aminofluorination reaction.[a]

1a–o **2a–o**

Entry	Substrate: R, R^1, $R^{2[b]}$	Product (Yield [%])[c]	*ee* [%][d]
1	**1a**: R = Ts, R^1 = Ph	(*S*)-**2a** (79)	81 (99)
2	**1b**: R = *o*-$MeC_6H_4SO_2$, R^1 = Ph	(*R*)-**2b** (72)	67 (90)
3	**1c**: R = *m*-$MeC_6H_4SO_2$, R^1 = Ph	(*R*)-**2c** (72)	79 (>99)
4	**1d**: R = $PhSO_2$, R^1 = Ph	(*S*)-**2d** (75)	77 (93)
5	**1e**: R = *p*-$OMeC_6H_4SO_2$, R^1 = Ph	(*S*)-**2e** (76)	76 (99)
6	**1f**: R = $MeSO_2$, R^1 = Ph	(*S*)-**2f** (75)	61 (98)[e]
7	**1g**: R = Cbz, R^1 = Ph	(*S*)-**2g** (69)	69[f]
8	**1h**: R = Ts, R^1 = *o*-MeC_6H_4	(*S*)-**2h** (73)	88
9	**1i**: R = Ts, R^1 = *p*-MeC_6H_4	(*S*)-**2i** (69)	74 (98)
10	**1j**: R = Ts, R^1 = *p*-$OMeC_6H_4$	(*S*)-**2j** (63)	72 (99)
11	**1k**: R = Ts, R^2 = Me	(*S*)-**2k** (70)	66
12	**1l**: R = Ts, R^1 = Ph, H	**2l** (71)[g]	–
13	**1m**: R = Ts, R^1 = Me[h]	**2m** (90)	–
14	**1n**: R = Ns, R^1 = Me[h]	**2n** (64)[i]	–
15	**1o**: 	**2o** (84)	–

[a] Reaction conditions: Same as Table 1, entry 10 with either (*R*,*R*)-**6d** or (*S*,*S*)-**6d**. Product configuration is indicated. [b] Unless otherwise stated R^x = H. [c] Yield after column chromatography on alumina. [d] Determined by HPLC on a chiral stationary phase. The value in brackets corresponds to the *ee* value after crystallization. [e] Reaction performed in chlorobenzene as solvent. [f] The *ee* value was determined upon Cbz removal and conversion into **2a**. [g] The *cis*/*trans* ratio of isomers was 20:1. A 6:1 d.r. was obtained in the reaction of **1l** with oxidant **5**. [h] Difluoride **5** was used as oxidant. [i] Reaction temperature = 50 °C.

Table 3: Optimization of the intramolecular aminofluorination of hexenamines.[17]



(*S*)-**8a**

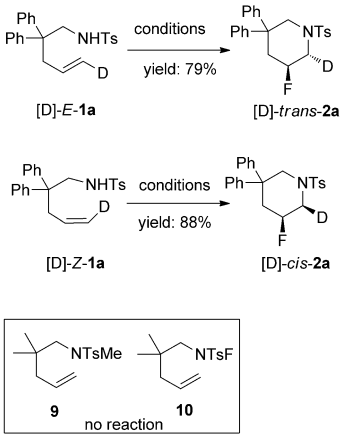
Entry	Substrate	Conditions	Product (yield [%])[a]	*ee* [%][b]
1	**7a** R = Ts, R^1 = Ph	toluene, RT, 7 days	**7a**	–
2	**7a**	[$(Ph_3P)AuNTf_2$] (5 mol%), CH_2Cl_2, RT, 2 days	**8a** (46)	61
3	**7a**	$HNTf_2$ (5 mol%), CH_2Cl_2, RT, 1 day	[c]	–
4	**7a**	$AgNTf_2$(5 mol%), CH_2Cl_2, RT, 7 days	[c]	–
5	**7a**	[2-PicAuNTf$_2$] (5 mol%), RT, CH_2Cl_2, 2 days	**8a** (62)	73 (99)
6	**7b** R = *m*-$MeC_6H_4SO_2$, R^1 = Ph	[2-PicAuNTf$_2$] (5 mol%), RT, CH_2Cl_2, 2 days	**8b** (59)	76 (91)
7	**7c** R = *p*-$OMeC_6H_4SO_2$, R^1 = Ph	[2-PinAuNTf$_2$] (5 mol%), RT, CH_2Cl_2, 2 days	**8c** (60)	77 (99)
8	**7d** R = $PhSO_2$, R^1 = Ph	[2-PicAuNTf$_2$] (5 mol%), RT, CH_2Cl_2, 2 days	**8d** (61)	77 (98)
9	**7e** R = Ts, R^1 = *m*-MeC_6H_5	[2-PicAuNTf$_2$] (5 mol%), RT, CH_2Cl_2, 4 days	**8e** (50)	75 (99)
10	**7f** R = Ts, R^1 = *p*-MeC_6H_5	[2-PicAuNTf$_2$] (5 mol%), RT, CH_2Cl_2, 4 days	**8f** (64)	72 (98)

[a] Yield after column chromatography on neutral alumina. [b] Determined by HPLC on a chiral stationary phase. The value in brackets corresponds to the *ee* value after crystallization. [c] A complex mixture of products was obtained. Pic = 2-pyridinecarboxylato.

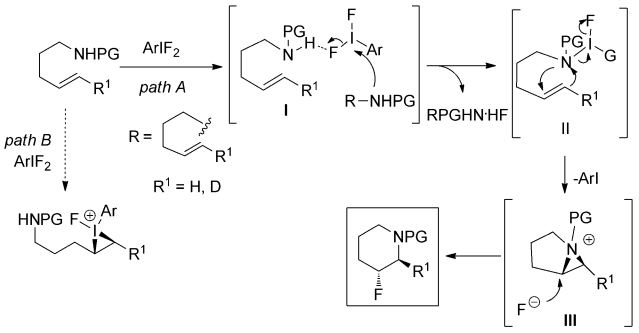
conditions used in Table 2, no conversion of the starting material was observed even after prolonged reaction times (Table 3, entry 1). We hypothesized that the 7-*endo-trig* cyclization might be a less favorable process, and thus the addition of a Lewis acid could facilitate the activation of the olefinic moiety.[17] Pleasingly, a catalytic amount of [$(Ph_3P)AuNTf_2$] was able to trigger the desired transformation to produce azepane **8a** in 46% yield and 61% *ee* (Table 3, entry 2). Control experiments with $AgNTf_2$ and $HNTf_2$ showed the need of gold for a successful transformation (Table 3, entries 3–4). Dichloro(pyridine-2-carboxylato)gold(III) complex in combination with $AgNTf_2$ proved to efficiently transform **7a** into **8a** with an increased the enantiomeric excess of 73% *ee* (Table 3, entry 5). Upon crystallization, the absolute configuration of enantiopure fluoroazepane **8a** was established to be *S* by X-Ray diffraction analysis.[25] As in the case of the penteneamine substrates, variations in the protecting group on the nitrogen atom (Table 3, entries 6–8) and on the substrate backbone (entries 9–10) were well-tolerated, so that the corresponding β-fluoroazepanes were obtained in synthetically useful yields and high enantiomeric purity upon crystallization of the reaction products.

To gain a deeper insight into the mechanism of these transformations the following control experiments were designed. First, deuterium labelled alkenes [D]-*E*- and [D]-*Z*-**1a** were prepared and subjected to the optimized reaction conditions from Table 1 (entry 5) to afford [D]-*trans*-**2a** and [D]-*cis*-**2a,** respectively, as single diastereoisomers (Scheme 1).[26] In addition, *N*,*N*-tosylmethyl and *N*,*N*-tosyl-fluoro-2,2-dimethyl-4-pentenyl amines **9** and **10** proved to be unreactive under the standard reaction conditions.

Based on these results, the fact that no 5-*exo* products were detected, and the observation of a faster reaction rate for the *N*-tosyl substrates compared to the *N*-nosyl one (Table 2, entries 13 vs. 14), we propose a reaction mechanism involving the oxidation of the sulfonamide in the first step (Scheme 2, path A) rather than an oxidation of the alkene (i.e. via cyclopropyl iodonium salt, path B).[24d] The lack of reactivity of **9** and **10** strongly suggests that activation of the aryliodofluoride reagent with the amine by H-bonding precedes the ligand exchange on the iodine(III) atom (intermediate **I**).[19,27] The aminofluoro iodonium intermediate **II** then reacts with the olefin to give aziridinium intermediate **III**, which undergoes nucleophilic attack by fluoride onto the more substituted carbon atom to give the *endo* cyclized products with *anti* selectivity.[28] The slower reaction observed for *N*-nosyl-substituted substrate **1n** versus the *N*-tosyl-substituted **1m**, strongly suggests that the nucleophilic attack of the nitrogen atom onto the olefin in **II** leading to **III** is the critical step in the reaction rather than the formation of **I**, which would be favored in the case of **1n** owing to the better H-bond donor properties of the nosyl-substituted N–H bond.



Scheme 1. Control experiments. For the reaction conditions see Table 1, entry 5.

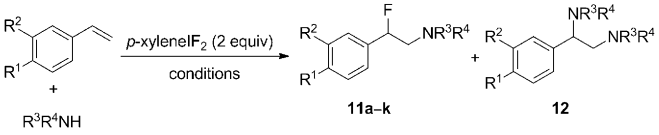


Scheme 2. Mechanistic proposal. PG = protecting group.

In line with this hypothesis, an intermolecular reaction with a monosubstituted olefin should deliver the fluoro group onto the internal carbon atom of the alkene. Such a regioselective reaction would provide access, for the first time, to 2-fluoro-2-phenylethanamines if styrenes were used as substrates. This class of compounds is currently not accessible, because previously reported electrophilic amidofluorinations of alkenes (metal or nonmetal catalyzed) provide 2-fluoro-1-phenylethanamines as a result of the carbocation stabilization at the benzylic position.[11,13] The realization of this hypothesis is summarized in Table 4. Mixing styrene and *N*-methyl-*N*-4-methylbenzenesulfonamide in a 2:1 ratio in the presence of 2 equivalents of iododifluoride **5** at 40 °C for two hours afforded the aminofluorinated product **11a** in 52% yield (71% based on recovered starting material) together with diamination product **12a** in 12% yield (Table 4, entry 1). By increasing the amount of styrene we were able to isolate the desired fluoroaminated product in 77% yield, and the excess of styrene could be almost completely recovered at the end of the reaction (Table 4, entry 2). 4-Trifluoromethyl, 4-fluoro, 4-chloro, and 4-bromo styrenes were transformed into the corresponding aminofluorinated products **11b–e** in good yields under the reaction conditions (Table 4, entries 3–6). Both, electron-withdrawing and electron-donating groups were tolerated at the 3-position of the aromatic ring as shown by examples summarized in entries 7 and 8.[29] Interestingly, the reaction of 3-methylstyrene gave the desired aminofluorinated product **11h** together with aziridinium intermediate **13**,[30] thus supporting the mechanistic proposal outlined in Scheme 2. We then decided to explore the substitution pattern on the amine counterpart by studying reactions with 1-fluoro-4-vinylbenzene. Under the optimized reaction conditions, a tosylamide afforded the product in **11i** in 53% yield (77% yield based on recovered starting material; Table 4, entry 10). 4-Methoxy-*N*-methylbenzenesulfonamide and *N*-methylmethanesulfonamide afforded the corresponding aminofluorinated products **11j** and **11k** in 80 and 68% yield, respectively (Table 4, entries 11 and 12). Diamination products **12** might arise from the competitive ring opening of the aziridinium **III** with free amine still present in the reaction media, as previously reported by Muñiz and co-workers.[24d]

In summary, we report here the first example of an intramolecular, metal-free regioselective aminofluorination of unactivated alkenes by using difluoroiodonium salts. In chiral form, these species provide access, for the first time, to 2-fluoropiperidines and azepanes in enantiomerically pure form. In addition, an intermolecular regioselective metal-free aminofluorination of styrenes has been developed enabling the synthesis of unprecedented 2-fluoro-2-phenylethanamines. This regioselective reaction nicely complements the previously available amidofluorination methods, which provide 2-fluoro-1-phenylethanamines, while expanding the scope on the amine counterpart, thus reflecting the synthetic utility of this method. Efforts towards an asymmetric variant of this transformation are currently underway in our laboratory.

Table 4: Scope of the metal-free intermolecular aminofluorination reaction.



Entry	Conditions[a]	Product: R^1, R^2, R^3, R^4	Yield [%][b,c]
1	A	**11a**: $R^1=R^2=H$, $R^3=Ts$, $R^4=Me$	52[d]
2	B	**11a**: $R^1=R^2=H$, $R^3=Ts$, $R^4=Me$	77
3	B	**11b**: $R^1=CF_3$, $R^2=H$, $R^3=Ts$, $R^4=Me$	68
4	B	**11c**: $R^1=F$, $R^2=H$, $R^3=Ts$, $R^4=Me$	68
5	B	**11d**: $R^1=Cl$, $R^2=H$, $R^3=Ts$, $R^4=Me$	66
6	B	**11e**: $R^1=Br$, $R^2=H$, $R^3=Ts$, $R^4=Me$	66
7	B	**11f**: $R^1=H$, $R^2=CF_3$, $R^3=Ts$, $R^4=Me$	72
8	B	**11g**: $R^1=H$, $R^2=F$, $R^3=Ts$, $R^4=Me$	70
9	B	**11h**: $R^1=H$, $R^2=CH_3$, $R^3=Ts$, $R^4=Me$	80
10	B	**11i**: $R^1=H$, $R^2=H$, $R^3=Ts$, $R^4=H$	53[e]
11	B	**11j**: $R^1=F$, $R^2=H$, $R^3=p$-$MeOC_6H_4SO_2$, $R^4=Me$	80
12	B	**11k**: $R^1=F$, $R^2=H$, $R^3=SO_2Me$, $R^4=Me$	68

[a] Conditions A: Alkene (2 equiv), amine (1 equiv), CH_2Cl_2, M.S. (4 Å), 60 °C, 2 h; conditions B: Alkene (6 equiv), amine (1 equiv), CH_2Cl_2, M.S. (4 Å), 60 °C, 17 h. [b] Yield of **11** after column chromatography on neutral alumina; [c] Diamines **12a–g** were isolated in less than 15% yield. [d] 71% yield based on recovered starting material. [e] 77% yield based on recovered starting material.

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[25] CCDC 905602 ((*R*)-**2a**) 905603 ((*S*)-**8a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

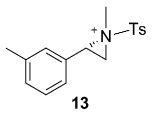
[26] Relative configuration was assigned based on NOE analysis. See Ref. [17] and Ref. [13a].

[27] As shown in Ref. [19], the activation of the iodonium difluoride salt can also be carried out by the HF-amine complex that was generated in the first step of the reaction.

[28] The role of gold in the reaction of hexenamines is not entirely clear, but we hypothesized that it might affect the conformation of the substrate upon coordination to the olefin enabling the formation of an aziridinium intermediate related to **III**.

[29] 4-Methoxystyrene underwent decomposition under these conditions. For further examples, see Ref. [17].

[30] Compound **13** could be characterized by ^{1}H NMR spectroscopy and HRMS–ESI. See Ref. [17].



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